Chapter 26

The Role of E-Cadherin-Catenin Complex in Prostate Cancer Progression

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1. Introduction

The genetic changes that promote progression of prostate adenocarcinomas are multifactorial and include alterations in several genes. The aberrations include those in genes that affect normal cell adhesion. The long arm of chromosome 16 (16q22.1) is deleted in 30% of primary prostatic tumors and more than 70% of metastatic prostate cancers. The E-cadherin gene is located in this region. E-cadherin is involved in maintaining homotypic cell-cell adhesion between normal prostatic glandular cells. The loss of E-cadherin expression is associated with metastatic progression of prostate cancer (Mason, 2002). Recent data suggests that abnormal expression of E-cadherin, leading to impaired adhesion, correlates with hematogenous spread of primary tumor cells in prostate cancer patients (Loric, 2001). The study further suggests that abnormal E-cadherin expression is a significant independent indicator of prostate cancer recurrence in patients.

Metastatic dissemination of prostate cancer cells occurs via the lymphatic system as well as the vascular system. This complex process of metastasis involves a series of steps starting with neoplastic transformation of prostate cells, tumor angiogenesis/lymphogenesis and cancer growth, loss of cell adhesion molecules and detachment of cancer cells from primary tumor, local invasion of stroma, dissemination of primary tumor cells via the lymphatics or vasculature, avoidance of tumor surveillance by the immune system, homing of primary prostate cancer cells to distant sites, establishment of tumor and growth of tumor at distant metastatic site (Arya et al., 2006). While the majority of metastic lesions are found in the obturator lymph nodes, lesions have also been detected in presacral, presciatic, as well as internal and external iliac nodes. Conversely, hematogenous spread of prostate cancer cells results in the formation of metastatic lesions in the bone, lung, liver and epidural space. Interestingly, in the majority of patients who die from prostate cancer, metastatic lesions have

been detected in the bone. One study shows that E-cadherin and β-catenin are downregulated in prostatic bone metastasis, but not in primary prostate tumors (Arya et al., 2006). The spine, femur, pelvis, rib cage, skull and humerus are frequent sites of metastatic prostate cancer lesions. The bone stroma apparently provides a microenvironment suitable for the growth of metastatic prostate cancer cells. While the molecular mechanisms associated with prostate cancer metastasis are not completely elucidated, potential markers of high-risk prostate cancer include the cadherins, catenins, focal adhesin kinase, connexins, integrins and metalloproteinases (Mol et al., 2007).

The E-cadherin-catenin complex and associated proteins have functional roles in cell-adhesion as well as in downstream signaling. It is well known that increased expression of cytoplasmic β-catenin is associated with increased translocation to the nucleus leading to transcriptional activation of β-catenin-TCF responsive genes. β-catenin, γ-catenin and $p120^{ctn}$ proteins are expressed in the nucleus, thereby suggesting that a complex system of checks and balances may exist in normal as well as in tumor cells.

2. Classical cadherins, type I

2.1. E-cadherin

The tight association of individual cells at junctional organelles and the polarized distribution of cytoplasmic and cell surface-components are the primary characteristics of normal epithelial tissues. As a result of this adhesion, normal epithelial cells are less mobile as compared to either cells of mesenchymal origin or to cancer cells of epithelial origin. Normal epithelial cells also have the ability to form selective permeability barriers, and to exhibit vectorial transport in tissues. Four organelles (tight junctions, desmosomes, gap junctions, zonula adherens junctions) are responsible for adhesion between two adjacent cells. In addition, distinct proteins are associated with each of these types of intracellular junctions, suggesting a specific role of each junction in normal cellular processes. First are the tight junctions, which have dual functions: maintenance of cell polarity and inhibition of uncontrolled exchange of small molecules, macromolecules, and water between two adjacent cells. Occludin and ZO-1 protein complexes are typically found in tight junctions in epithelial and endothelial cells (Schnittler et al., 1998). Second, desmosomes typify cells that have undergone epithelial differentiation. Desmosomes function in homophilic adhesion between adjacent cells and link desmosomal proteins to the cytoskeletal proteins called intermediate-sized filaments (Ifs). Desmoglein and desmocollin are pivotal components of desmosomal function (Schafer et al., 1996; Mertens et al., 1999). Third, gap junctions form intracellular channels that allow direct transfer of ions and metabolites. Connexin proteins form these gap junction channels (Dermietzel and Hofstadter, 1998; Windoffer et al., 2000). Zonula adherens junctions, the fourth type of organelles, are specialized structures containing the cell adhesion molecule E-cadherin.

The human E-cadherin gene, CDH1, is located on chromosome 16q22.1 (Rimm et al., 1994). It encodes a 135 kDa precursor form of E-cadherin. In essence, the precursor form cannot

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function in homophilic adhesion without undergoing N-terminal cleavage. The precursor E-cadherin protein is cleaved in the cytoplasm to form a mature 120 kDa protein containing the newly formed extracellular N-terminal domain. The extracellular domain or N-terminal end of E-cadherin is essential for homophilic calcium-dependent cell-cell adhesion. The mature form of E-cadherin, on the other hand, is transported to the basolateral surface of the epithelial cell where it can function in homophilic adhesion.

The mature E-cadherin contains three distinct domains: the highly conserved carboxy-terminal domain, a single pass transmembrane domain, and an extracellular domain (Figure 1). The extracellular domain consists of five tandem subdomain repeats that bind calcium, referred to as C1-C5 subdomains with the C1 domain being the most distal from the cell membrane. The C1 subdomain contains a histidine-alanine-valine sequence (HAV) that is speculated to be essential for the process of cell-cell adhesion. E-cadherin exists as a *cis* dimer on an individual cell when it is not adhering to an adjacent cell. Subsequent to calcium binding, a conformational change occurs in the HAV structure of the C1 subdomain, allowing the tryptophan-2 residue to move into a hydrophobic cavity. This conformational change allows E-cadherin to form a trans dimer 'zipper' between two adjacent cells. Subsequent linkage to the cytoskeleton stabilizes cell-cell adhesion. The cytoplasmic domain of E-cadherin is required for cadherin-catenin complex formation. The cytoplasmic tail of E-cadherin consists of two regions: the juxtamembrane region and the catenin-binding region. These regions are principally required for clustering of E-cadherin at cell-cell contacts (juxtamembrane) and as a major link to the actin cytoskeleton. These regions are known to stabilize E-cadherin clusters and participate in signal transduction processes via the catenin-binding region. The thirty-two amino acid, hydrophobic transmembrane region separates the extracellular domain from the highly conserved intracellular domain.

E-cadherin forms a complex with four catenin proteins, α-catenin (102 kDa), β-catenin (92 kDa), γ-catenin (83 kDa) and p120 catenin (75-120 kDa). The interaction of E-cadherin with cytoplasmic catenins, α, β, γ and p120 ($p120^{ctn}$) is required for the normal function of E-cadherin. The human genes for all four cadherin-associated catenins have been cloned and characterized; the genes are located on four different chromosomes. While α-Catenin is located on chromosome 5q31, β-catenin is located on chromosome 3p21, γ-catenin on chromosome 17q21, and $p120^{ctn}$ on chromosome 11q11 immediately adjacent to the centromere. All four catenins bind to E-cadherin, but exist as two distinct pools of E-cadherin-catenin complexes in the same cell. E-cadherin binds to either β-catenin or γ-catenin, but does not directly bind to α-catenin. α-catenin, however, binds to either β-catenin or γ-catenin. Therefore, in a single cell, one complex consists of E-cadherin with α− and β-catenin, and the other complex consists of E-cadherin with α and γ-catenin. E-cadherin-catenin complex formation begins shortly after biosynthesis, while still in the endoplasmic reticulum. The sequential order of cadherin-catenin complex formation begins with β-catenin interacting with E-cadherin. If E-cadherin fails to associate with β-catenin, E-cadherin is retained in the endoplasmic reticulum where it is subsequently degraded. A 30 amino-acid region within the cytoplasmic domain of E-cadherin is essential for β-catenin binding. E-cadherin and β-catenin are transported together in a bipartite fashion to the cell surface, where they associate with α-catenin.

The amino-terminal region of α-catenin binds to actin filaments in the cytoplasm, linking the cadherin-catenin complex to the cytoskeleton. Post-translational modification of $p120^{ctn}$ is associated with modulation of cadherin clustering and stablization of adhesion.In summary, a functional cadherin-catenin complex is important for maintaining cellular integrity.

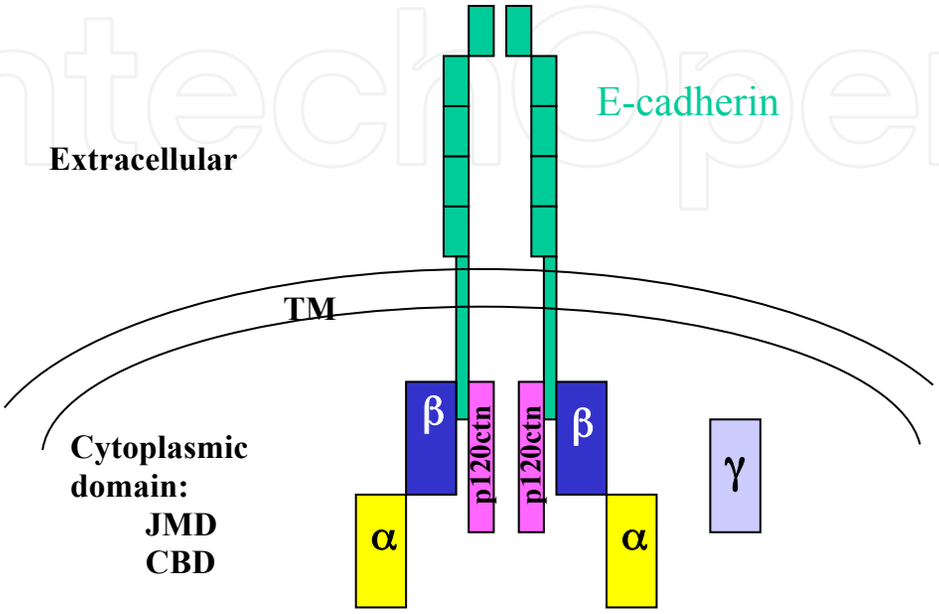

Figure 1. Schematic diagram of E-cadherin-catenin complex. The mature E-cadherin contains three distinct domains: the highly conserved cytoplasmic domain, a single pass transmembrane domain (TM), and an extracellular domain. The cytoplasmic tail of E-cadherin consists of two regions: the juxtamembrane domain (JMD) and the catenin-binding domain (CBD). β- and γ-Catenin bind to the CBD, and $p120^{ctn}$ binds to the JMD regions of E-cadherin. These regions are principally required for clustering of E-cadherin at cell-cell contact and as a major link to the actin cytoskeleton. E-cadherin forms a complex with four catenin proteins, α-catenin (102 kDa), β-catenin (92 kDa), γ-catenin (83 kDa), and p120 catenin (75-120 kDa). α, α-catenin; β, β-catenin; γ, γ-catenin; $p120^{ctn}$, p120 catenin.

2.2. Role of Cadherin in physiological and pathological processes

E-cadherin expression is regulated in both physiological and pathological processes, such as embryonic morphogenesis and tumorigenesis. Tissue and organ formation is regulated in a spatio-temporal manner involving cell proliferation, death, cell-cell adhesion, cell-substrate adhesion, polarization, and migration. One example of this highly regulated process is blastocyst differentiation. E-Cadherin has an essential function in the formation of the blastocyst during mouse embryonic development. Another example of the normal physiological processes associated with E-cadherin regulation is the formation of fluid space in development of murine cochlea. In this embryonic process, E-cadherin is downregulated on the lateral membranes of reticular lamina. This down-regulation allows the process of fluid space opening in the organ of Corti. Wound healing is a third example where a physiological event involves regulation of E-cadherin expression. Injury of the epithelial cell layer in the skin signals the release of cytokines and other factors, such as epidermal growth factor (EGF). These signals reduce cell adhesion and stimulate cell motility, allowing for wound re-

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pair. Subsequent to wound repair, cell adhesion is upregulated to restore the epithelial layer to its normal physiological state. Therefore, E-cadherin has to be highly regulated in the above normal physiological processes. Conversely, aberrant growth and differentiation result when E-cadherin is not tightly regulated, such as in cancer.

Association of E-cadherin with neighboring cells acts to inhibit cell mobility and to maintain normal epithelial cell phenotype. Tumorigenesis is an example of a pathological process that involves E-cadherin regulation. The loss or down-regulation of E-cadherin expression has been described in several tumors including stomach (Shino 1995; Tamura, 2000), colon (Van Aken, 1993; Dorudi, 1993), pancreas (Pignatelli, 1994), liver (Joo, 2002), prostate (Morton et al., 1993; Umbas et al., 1994; Ross et al., 1994; Bussemakers et al, 1994; Pan et al., 1998; Noe et al., 1999; Cheng et al., 1996), breast (Lim and Lee, 2002; Hiraguri et al, 1998; Moll et al., 1993; Palacios et al., 1995; Gamallo et al., 1993; Oka et al., 1993; Rasbridge et al., 1993; De Leeuw et al., 1997), uterus (Sakuragi et al., 1994), ovary (Veatch et al., 1994), thyroid (Brabant et al., 1993), and head and neck (Mattijssen et al., 1993). Recent reports suggest that poorly differentiated tumors exhibit reduced E-cadherin expression as a consequence of down-regulation or defects in catenins (Kadowaki et al., 1994; Kawanishi et al., 1995; Navarro et al., 1993; Oyama et al., 1994). Therefore, the results from these studies suggest that the degree of differentiation of tumors is related to the level of E-cadherin expression.

E-cadherin acts as an inhibitor of the invasive and metastatic phenotype of cancer cells. Since tumor invasion and metastasis is a multistep process, E-caderin may play a significant role in regulating invasion and metastasis at the initial steps in the process by promoting homotypic cell-cell adhesion. Numerous mechanisms affecting E-cadheirn-catenin complex formation are associated with a reduction in cell adhesion. While gene mutation is responsible for inactivating E-cadherin-mediated cell adhesion in some breast cancers and gastric adenocarcinomas (Berx et al., 1998a; Berx et al., 1998b), the exact mechanism of E-cadherin down-regulation in other highly invasive tumors is still under investigation. Mechanisms that regulate homophilic cell adhesion include reduction or loss of E-cadherin expression, reduced transcription of genes encoding catenin proteins, redistribution of E-cadherin to different sites within the cell, shedding of E-cadherin, cleavage of E-cadherin, and competition of proteins for binding sites on E-cadherin (Cavallaro and Christofori, 2004).

The proximal E-cadherin promoter contains multiple regulatory elements including three E-boxes, a single CCAAT box, and a GC-rich element. Therefore, the E-cadherin promoter contains more than one site for transcription factors to bind and regulate gene transcription in cancers. These factors include AP-2 (Batsche et al., 1998), SNAIL (Battle et al., 2000), SLUG (Hajra et al., 2002), dEF1/ZEB-1 (Grooteclaes and Frisch, 2000), SIP1/ZEB-2 (Comijn et al., 2001), E12/E47 (Perez-Moreno et al., 2001), and LEF/TCF (Huber et al., 1996). While the retinoblastoma gene and c-myc protooncogene products transactivate the E-cadherin promoter in epithelial cells through interaction with AP-2 transcription factors (Batsche et al., 1998), transcription of E-cadherin is down-regulated by overexpression of ErbB2 (D'Souza and Taylor-Papadimitriou, 1994). SNAIL and SLUG transcription factors have been shown to repress E-cadherin expression in breast cancer cell lines via all three

E-box elements, but particularly, via EboxA and EboxC, located in the proximal E-cadherin promoter (Hajra et al., 2002). Moreover, SLUG is a putative *in vivo* repressor of E-cadherin in breast cancer (Hajra et al., 2002). The E-cadherin promoter also contains binding sites for the lymphoid enhancer factor 1 (LEF1)-β-catenin transcription factor complex; this complex down-regulates E-cadherin expression (Huber et al., 1998). Overexpression of integrin-linked protein kinase ($p59^{ilk}$) stimulates LEF1-β-catenin signaling and causes down-regulation of E-cadherin expression with a concomitant decrease in cell adhesion (Novak et al., 1998). A single nucleotide polymorphism in the E-cadherin promoter has also been associated with a higher risk of prostate cancer in certain ethnic populations with a possible role in transcriptional regulation of E-cadherin gene expression in these individuals (Goto et al., 2007).

Gene transcription can also be regulated by epigenetic inactivation. Many cancer cells have been shown to use this mechanism to inactivate tumor-suppressor genes (Sidransky, 2002). Methylation of genes that encode p16 (cyclin-dependent kinase inhibitor), DAPK (death-associated protein kinase, apoptosis associated protein), and MGMT (a DNA repair protein, methyl O-guanine methyltransferase) has been implicated in lung, and head and neck cancer (Esteller et al., 1999; Sanchez-Cespedes et al., 2000). Aberrant methylation of the hMLH1 promoter has also been associated with microsatellite instability in colon cancer (Grady et al., 2001). Methylation of APC (Usadel et al., 2002), a key component in Wnt-β-catenin signaling, is associated with early-stage lung cancer and esophageal cancer (Kawakami, 2000). E-cadherin expression is downregulated in highly invasive prostate tumors as a result of transcriptional regulation (Morton et al., 1993; Kuczyk et al, 1998). Reduction in E-cadherin expression in prostate cancer cells has been attributed to hypermethylation of CpG islands in the E-cadherin gene promoter (Graff et al., 1995; Graff et al., 1997; Herman et al., 1996; Hirohashi, 1998; Li et al., 2001). This type of silencing of E-cadherin gene expression is also seen in cervical cancer cell lines and tumors (Chen et al., 2003). In summary, epigenetic inactivation of genes is an alternative mechanism used to regulate expression of certain genes in cancer cells. The significance and mechanism of gene inactivations associated with prostate cancer cell invasion remain to be determined.

Post-translational modification is an alternative mechanism to regulate E-cadherin-dependent homophilic cell adhesion (Hirohashi, 1998). Protein tyrosine kinases (PTKs) and phosphatases (PTPs), regulate intracellular phosphotyrosine levels, thereby regulating diverse cellular behaviors such as adhesion, growth and differentiation, and migration. Her2/Neu or ErbB2 tyrosine kinase, as well as transmembrane tyrosine phosphatases such as PTPμ, PTPκ, PTPλ and LAR, have been found to be associated with cadherin-catenin complexes in epithelial cells, suggesting opposing roles for these proteins in regulating cadherin-catenin association (Hellberg et al., 2002). Stimulation of growth factor receptors, i.e. EGF receptor (EGFR), can also regulate E-cadherin expression in tumor cells in a post-translational manner (Hazan and Norton, 1998; Moustafa et al, 1999). A reciprocal and reversible control of intercellular adhesion and cell proliferation occurs with increased expression of EGFR in several epithelial tumors (Jawhari et al, 1999). Restoration of E-cad-

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herin expression in human papilloma virus-transfected keratinocytes reversed the invasive phenotype and, interestingly, down-regulated EGFR expression (Wilding et al., 1996). An inverse relationship between EGFR activation and E-cadherin expression was also observed in lung cancer cells treated with neutralizing monoclonal antibody to EGFR (Moustafa et al., 1999). By blocking EGFR stimulation in lung cancer cells, E-cadherin expression is induced. Activation of Src can also induce tyrosine phosphorylation of E-cadherin and inhibit cell-cell adhesion. As a result of Src activation, the E-cadherin complex is ubiquitinated, leading to its endocytosis and thereby inhibiting homophilic cell adhesion (Fujita et al., 2002). Either transcriptional or post-translational modification of the cadherin-catenin complex can determine the integrity of the adherens junction, as well as regulating downstream signaling.

3. E-cadherin associated catenin proteins

3.1. α-catenin

The α-catenin gene encodes a 102kDa protein that links E-cadherin to the actin cytoskeleton. The amino terminus of α-catenin contains the actin-binding domain essential for linking the cadherin-catenin complex to the cytoskeleton (Beavon, 2000). The cytoplasmic components of the adherens junctions are necessary for linking cadherins to actin (Takeichi, 1991). The association of cadherins with the cytoskeleton is mediated via either α-actinin (Nieset et al., 1997; Knudsen et al., 1995) or vinculin (Hazan et al., 1997a; Weiss et al., 1998; Watabe-Uchida, 1998). α-Catenin is also known to interact with ZO-1 (Itoh et al., 1997). α-catenin associates with either β-catenin or γ-catenin in adherens junctions, but does not form a complex in desmosomes where γ-catenin is bound to desmosomal cadherins and desmoplakin, another desmosomal protein. Therefore, α-catenin links E-cadherin-catenin proteins to the cytoskeleton at adherens junctions, but not at desmosomes. This would suggest that α-cateinin may contribute to the stability of the E-cadherin-catenin complex in normal tissues. Recent studies have suggested that α-catenin is the best prognostic marker for prostate cancer specific survival (van Oort et al., 2007).

3.2. β-catenin

β-catenin is a 92 kDa multifunctional protein that belongs to the armadillo family of proteins, characterized by a central domain of 12 repeats of about 40 amino acids called arm repeats (Figure 2). The arm domain was originally described in armadillo, which is the *Drosophila* homologue of β-catenin (Kodama et al., 1999). β-catenin serves as a link between cadherins and the actin cytoskeleton. β-catenin also binds to numerous other proteins in cadherin-independent complexes (Behrens, 2002) such as APC, lymphoid enhancer factor and T-cell factor (LEF/TCF) transcription factors, RGS domain proteins axin/conductin (Kikuchi, 1999; Kikuchi, 2000; Von Kries et al., 2000; Akiyama, 2000) and prontin 52 (Bauer et al, 1998). β-catenin also associates with fascin, an actin-binding protein, in a cadherin independent manner (Tao et al., 1996).

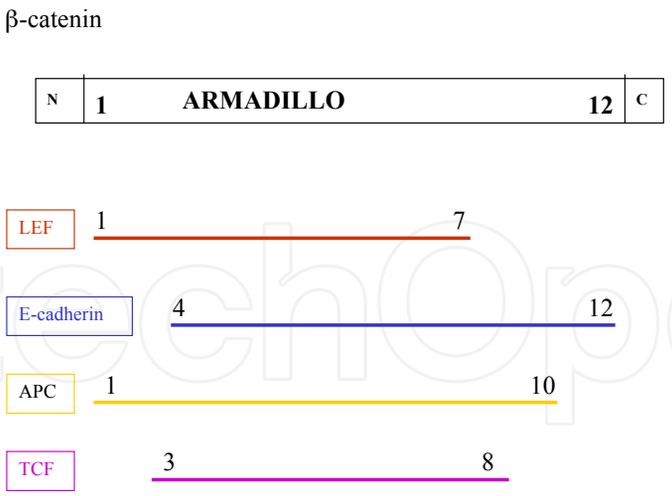

Figure 2. Diagram of the twelve armadillo repeats of β-catenin. The β-catenin protein consists of 12 armadillo repeats designated as 1-12. β-Catenin associates with specific proteins within the indicated region of the 12 repeats, in a mutually exclusive manner. Armadillo repeats 1-7 is designated as the LEF binding region; E-cadherin binds to repeats 4-12; APC binds to repeats 1-10; Tcf binds to repeats 3-8 of the β-catenin protein. Armadillo protein 12 has been shown to be involved in transactivation of Wnt-responsive genes. N, N-terminus; C, Carboxy-terminus; LEF, lymphoid enhancer-binding factor ; APC, adenomatous polyposis coli; TCF, T-cell Transcription factor.

In addition to its role in cell-adhesion, β-catenin is associated with Wnt signal transduction pathway (Figure 3). This pathway is important in regulating embryonic development, and generation of cell polarity. Wnt proteins are differentially expressed in tissues during mammalian development (Cadigan and Nusse, 1997). These proteins are particularly important in regulating tissue differentiation and organogenesis (Behrens, 2002; Parr and McMahon, 1994; Willert and Nusse, 1998; Brown and Moon, 1998; Bullions and Levine, 1998). When Wnt proteins are aberrantly activated, tumor formation ensues (Moon and Kimelman, 1998; Zeng et al., 1997; Wodarz and Nusse, 1998; Peifer and Polakis, 2000; Bienz and Clevers, 2000; Barker and Clevers, 2000). Wnt has also been demonstrated to play a role in cancer development by transmitting a signal via its cytoplasmic component, β-catenin protein (Lejeune et al., 1995; Shimizu et al., 1997; Polakis, 2001; Polakis, 2000; Polakis 1999; Eastman and Grosschedl, 1999; Cadigan and Nusse, 1997). Recent studies have suggested that Wnt proteins may have a role in tumor-induced osteoblastic activity, which is characterized by increased bone production as a result of prostate caner metastasis to the bone (Hall et al., 2006). Wnt proteins bind to cell surface receptors termed Frizzled (Fz). This interaction results in the activation of the cytoplasmic phosphoprotein disheveled (Dvl). Activated Dvl inhibits activation of axin and conductin proteins in the Wnt signaling cascade. Axin and its homolog, conductin (Axin2/Axil) form a multiprotein complex with APC and GSK3β; this activated complex catalyzes the phoshphorylation of β-catenin at specific residues in its N-terminal domain (Behrens, 2002; Ikeda et al., 1998). Axin and conductin act as scaffold proteins that directly bind several components of the Wnt signaling pathway, promoting the phosphorylation of β-catenin by GSK-3β (Jho et al., 2002; Ikeda et al., 1998; Fagotto et al., 1999; Itoh et al., 1998; Hsu et al., 1999; Julius et al., 2000). Four ser/thr residues in the N-terminal region of β-catenin are targets for GSK-3β phosphorylation. In the absence of a Wnt signal, GSK3β

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phosphorylates β-catenin, which is then targeted for ubiquitination and subsequently degraded by proteasomes. Interestingly, recent studies show that additional proteins are involved in priming β-catenin for phosphorylation by GSK3β. Casein kinase I, Casein kinase II and GSK3β act together in marking β-catenin for phosphorylation (Polakis, 2002; Amit et al., 2002; Liu et al., 2002; Yanagawa e al., 2002; Zhang et al., 2002).

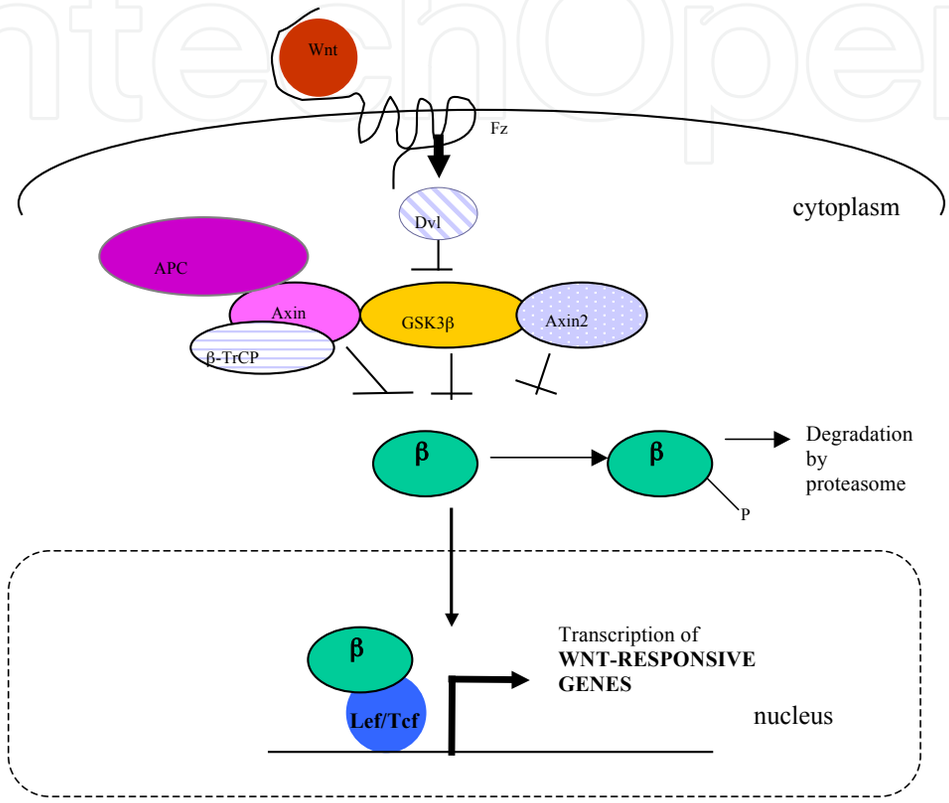

Figure 3. Diagram of Wnt signaling pathway. This schematic represents the Wnt-mediated signaling pathway that functions to stabilize cytoplasmic β-catenin. In the absence of Wnt signaling, β-catenin is degraded by the activity of glycogen synthase kinase 3β (GSK3β) in a complex with APC, axin, axin2 (conductin/Axil), and β-TrCP. The binding of Wnt proteins to its receptor, Frizzled (Fz) at the cell surface leads to the activation of Disheveled (Dvl) in the cytoplasm. Subsequently, GSK3β complex is inactivated and β-catenin accumulates in the cytoplasm, then enters the nucleus to interact with LEF/TCF proteins. β-Catenin-Tcf transcription factor activates the expression of Wnt responsive genes.

Regulation of β-catenin degradation is pivotal in downstream signaling. Several gene mutations have been reported in human cancers that render β-catenin resistant to GSK-3β mediated degradation. First, mutations in APC, a suppressor in human cancers, are associated with aberrant expression of β-catenin in colon cancers (Kawahara et al., 2000; Bienz and Clevers, 2000; Polakis 2000; Bright-Thomas and Hargest, 2002; Kawasaki et al., 2003). Second, oncogenic mutations have been identified in β-catenin at putative GSK-3β phosphorylation sites, which stabilize β-catenin in colorectal cancer and melanoma (Van Noort et al., 2002, Morin et al., 1997 and Korinek et al., 1997). Third, a mutation in human AXIN1 has been found to be associated with hepatocellular carcinoma (Satoh et al., 2000), while a mutation in AXIN2 (also called conductin) is found in colorectal and liver cancers

(Liu et al., 2000; Lustig et al., 2002). Conversely, constitutive Wnt signaling negatively regulates the ubiquitination and degradation of cytosolic β-catenin leading to its stabilization. In summary, stabilization of β-catenin in the cytosol is altered by three independent mechanisms: 1) gene mutation of any one of the degradation complex components: APC, axin, axin2 or GSK-3β, 2) gene mutation of β-catenin, or 3) constitutive Wnt signaling. As a result, the level of cytosolic β-catenin increases, and β-catenin translocates to the nucleus where it interacts with transcription factors of the LEF/TCF family. Several negative feedback loops could limit the duration or intensity of a Wnt-initiated signal. First, the F-box protein β-TrCP is an ubiquitin-ligase complex that has been shown to be involved in the proteasome mediated degradation of phosphorylated β-catenin (Chen et al., 1997; Behrens, 2002; Winston et al., 1999, Hart et al., 1999; Latres et al., 1999; Kitagawa et al., 1999). β-TrCP is post-transcriptionally induced by β-catenin/TCF signaling. As a result of this signal, β-catenin degradation is accelerated. Second, Tcf4/β-catenin signaling regulates transcription of the *Tcf1* gene in epithelial cells. While TCF1 does not bind β-catenin, TCF1 binds to transcriptional repressors such as groucho, which would allow TCF1 to serve as a feedback repressor of β-catenin/Tcf4 target genes (Roose et al., 1999; Polakis 2002). Third, axin2 (conductin) appears to downregulate β-catenin to normal levels after a Wnt signal in a negative feedback loop mechanism (Jho et al., 2002; Leung et al., 2002). This would suggest that, without precise regulation of Wnt-initiated signaling, β-catenin is aberrantly expressed. As a result, downstream target genes that might contribute to tumorigenesis are either up- or downregulated.

Increased concentration of β-catenin in the cytoplasm promotes its binding to LEF/TCF family of DNA-binding proteins. As a result, β-catenin translocates to the nucleus where it transcriptionally activates specific target genes. Although the exact mechanism of nuclear translocation of β-catenin has not been elucidated, association of β-catenin with several nuclear transport proteins, including importin/karyopherin and Ran (Wiechens and Fagotto, 2001; Fagotto et al., 1998), is not responsible. β-catenin lacks a classical nuclear localization sequence, but the armadillo repeats at the C-terminus are essential for nuclear translocation (Figure 2; Giannini et al., 2000; Funayama et al., 1995). Recent studies have suggested that, in prostate cancer cells, β-catenin can translocate into the nucleus as part of a complex with androgen receptor, AR, (Mulholland et al., 2002). This association of β-catenin with the androgen receptor is abrogated in the absence of armadillo repeat 6, further supporting the association of certain armadillo repeats with specific β-catenin functions. Armadillo repeats 4-12 are required for β-catenin to bind to E-cadherin (Hulsken et al., 1994; Orsulic 1996; Piedra et al., 2001). The expression of cadherin proteins could thus sequester β-catenin to the plasma membrane, preventing its nuclear translocation (Heasman et al., 1994; Fagotto et al., 1996; Weng et al., 2002). In the absence of sequestering proteins, β-catenin co-localizes with LEF/TCF in the nucleus to transactivate specific genes that contain LEF/TCF binding sites.

LEF-1 and TCF1-4 were first identified in immune cells (Clevers and van De Wetering, 1997). LEF-1 is a sequence-specific DNA-binding protein that is expressed in pre-B and pre-T lymphocytes of adult mice as well as in the neural crest, mesencephalon, tooth

germs and whisker follicles (Van Genderen et al., 1994). In addition to its role in organogenesis and embryogenesis, constitutive LEF/TCF/β-catenin transactivation is associated with oncogenesis in human colon carcinomas and melanomas (Korinek et al., 1997; Morin et al., 1997; Rubinfeld et al., 1997; Aoki et al., 1999). Although LEF/TCFs can bind directly to DNA through their HMG or DNA-binding domain, they are incapable of independently activating gene transcription (Polakis 2000; Polakis 2002, Behrens, 2002; Jiang and Struhl,1998; Kiatagawa et al., 1999; Hecht et al., 1999; Eastman and Grosschedl, 1999; Roose et al., 1999). Specific regions of β-catenin are required to interact with either LEF or TCF proteins. Armadillo repeats 1-7 of β-catenin interact with LEF while armadillo repeats 3-8 interact with TCF (Fig 1-3; Piedra et al., 2001; Sadot 1998; Behrens et al., 1996; Van de Wetering, 1997). β-catenin forms a complex with LEF/TCF proteins, depending on the amount of free β-catenin available. In this complex, LEF/TCF provides the DNA binding domain while β-catenin provides the transactivation domain. β-catenin binds specifically to sequences 1-51 of Tcf-4 (Miravet et al., 2002). Activation of this transcriptional complex between β-catenin and Tcf induces the expression of specific target genes (Mizushima et al., 2002; Behrens, 2002; Polakis 2002). Examples of these genes include ultrabithorax in *Drosophila*, nodal related 3 (McKendry et al., 1997), and siamois in *Xenopus* (Brannon et al., 1997), and c-myc (He 1998; Kolligs et al., 2000) and cyclin D1 (Tetsu and McCormick, 1999; Shtutman et al., 1999) in mammals. The list of target genes also include genes that regulate cellular functions other than stimulating cell growth, such as cyclooxygenase-2 (Howe et al., 2001); multi-drug resistance gene (Yamada et al., 2000); AF17 (Lin et al., 2001); metalloproteinase 7 (MMP-7) (Crawford et al., 1999; Brabletz et al., 1999); peroxisome proliferator-activated receptor δ (He 1999); laminin-5 γ2 (Hlubek 2001); c-jun/fra-1 (Mann et al., 1999) TCF-1 (Roose et al., 1999); axin2 (Jho et al., 2002; Leung et al., 2002); ITF-2 (Kolligs et al., 2002); E-cadherin (Huber et al., 1998; Novak et al., 1998); and mesenchymal genes (Huber et al., 1996; Miller and Moon, 1996; Novak and Dedhar, 1999).

3.3. Post-translational modification of β-catenin

The armadillo repeat domains of β-catenin are essential for binding to its many partners including E-cadherin, α-catenin and TCF-4. This association of β-catenin with various proteins is regulated by post-translational modification at specific sites of the arm repeats (Piedra et al., 2001). Sequences in central arm repeats 4-12 are required for β-catenin to associate with E-cadherin (Hulsken et al., 1994). Moreover, phosphorylation of tyrosine residue 654 (located in arm repeat 12) decreases association of β-catenin with E-cadherin (Roura et al., 1999). Simultaneously, phosphorylation of tyr-654 stimulates binding of β-catenin to the basal transcription factor TATA-binding protein (TBP). Phosphorylation of tyr-654 removes steric hindrance at the C-terminal allowing better access of key components of the transcriptional machinery, such as TBP. Since Tcf-4 binds to armadillo repeats 3-8, its association with β-catenin is not affected by phosphorylation of tyr-654 (arm repeat 12). β-Catenin binding to α-catenin is determined by a short 31 amino-acid sequence in the first armadillo repeat of β-catenin (Aberle et al., 1994). However, this association between β- and α-catenin is not affected by any known post-translational modifications of tyrosine residues.

3.4. γ-catenin

γ-Catenin and β-catenin are closely related and are members of the gene family that includes the Drosophila protein armadillo (Kodama et al., 1999; McCrea et al., 1991). γ-Catenin is identical to plakoglobin (Peifer et al., 1992; Knudsen and Wheelock, 1992). γ-Catenin and β-catenin share 80% sequence identity in the twelve arm repeat domains (Huber and Weis, 2001), but only share 29% and 41% sequence identity in the N- and C-terminal regions, respectively. There are two types of cell-cell junctions: adherens junctions and desmosomes (Takeichi, 1991; Cowin and Burke, 1996). While adherens junctions have one transmembrane component, E-cadherin, desmosomes have two transmembrane components, desmoglein and desmocollin (Buxton et al., 1993). Similar to β-catenin, γ-catenin binds directly to E-cadherin and α-catenin at adherens junctions (Aberle et al., 1994; Hulsken et al., 1994). γ-Catenin is the only component of both desmosome and adherens junctions, suggesting a pivotal role in cell-cell adhesion. In addition to forming a complex with E-cadherin, γ-catenin interacts with the cytoplasmic regions of desmoglein and desmocolin (Kowalczyk et al., 1994; Mathur et al., 1994; Troyanovsky et al., 1994a; Troyanovsky et al., 1994b; Wahl et al., 1996; Witcher et al., 1996). Arm repeats 1-4 of γ-catenin specifically interact with desmoglein. In contrast, γ-catenin arm repeats 11-12 are required for binding desmocolins, but not desmogleins (Witcher et al., 1996). A recent model proposes that the amino- and carboxy-terminal domains of γ-catenin form intramolecular interactions with the armadillo domain, inhibiting its association with desmoglein (Wahl, 2000). Classical cadherins, which include E- and N-cadherin, bind to the same site on γ-catenin as desmocolin (Hulsken et al., 1994; Sacco et al., 1995). Therefore, complexes consisting of E-cadherin, γ- and α-catenins are formed at adherens junctions, while γ-catenin, desmoglein and desmocolin complexes are formed at desmosomes in a mutually exclusive manner. γ-Catenin in adherens junctions and desmosomes may have a potential role in organizing cadherins into an adhesive zipper between two adjacent cells, thereby tightening the association between two cells. γ-Catenin is also found in the cytoplasm, where it forms a homodimer of unknown function (Cowin et al., 1986). The α-catenin binding region maps to the first repeat of γ-catenin, while N-cadherin binding region maps within repeats 7 and 8 (Sacco et al., 1995). γ-Catenin, like β-catenin (Ben Ze'ev and Geiger, 1998), interacts with several proteins, such as classical cadherins (Sacco et al., 1995), α-catenin (Nieset et al., 1997), fascin (Tao et al., 1996), axin (Ikeda et al., 1998; Behrens et al., 1998; Hart et al., 1999; Itoh et al., 1998), APC (Hulsken et al., 1994), and LEF/TCF transcription factors (Simcha et al., 1998; Huber et al., 1996). Tcf-4, however, contains two different sites for binding β- and γ-catenin. Interaction with γ-catenin inhibits transcription of downstream target genes (Miravet et al., 2002). β-Catenin binds to amino acids 1-50 of Tcf-4, whereas γ-catenin binds to residues 51-80. Tcf-4 specifically binds to γ-catenin in the region of arm repeats 1-6. Furthermore, *in vitro* kinase assays have suggested that phosphorylation of Tcf-4 negatively affects its interaction with γ-catenin without altering its association with β-catenin. Therefore, γ-catenin can contribute to homophilic cell-adhesion involving both adherens junctions and zonula adherens junctions.

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3.5. p120^{ctn}

p120Catenin (p120^{ctn}) was originally described as a tyrosine-phosphorylated protein in Src-transformed cells (Reynolds et al., 1992; Peifer et al., 1994; Mariner et al., 2000; Noren et al., 2000). Recent evidence suggests pleiotropic functions of p120^{ctn} such as cadherin clustering (Yap, 1998a; Yap et al., 1998b), cell motility (Chen et al., 1997), cadherin turnover at the cell surface (Davis et al., 2004), as well as regulation of neuronal outgrowth and of cadherin-catenin complex stability (Aono et al., 1999; Ohkubo and Ozawa, 1999). While α-, β- and γ-catenins bind to the catenin-binding domain (CBD) of the cadherin cytoplasmic tail, p120^{ctn} binds to the juxtamembrane domain (JMD). Unlike the other catenin proteins, p120^{ctn}does not interact with α-catenin, APC, or transcription factor Lef-1 (Daniel and Reynolds, 1995). Hence, p120^{ctn} does not directly modulate the actin cytoskeleton, implying a distinct role of p120^{ctn} in cadherin-catenin complex and downstream signaling.

p120^{ctn} is thought to indirectly regulate assembly and disassembly of adherens junctions via the Rho family of GTPases (Anastasiadis and Reynolds, 2000; Mariner et al., 2001; Anastasiadis et al, 2000; Grosheva et al., 2001). p120^{ctn} mediates cadherin-dependent activation of RhoA at nascent cell-cell contacts, thereby regulating cadherin clustering and cell junction formation (Anastasiadis et al., 2000). RhoA-GDP forms a complex with p120^{ctn} in the cytoplasm. Dissociation of GDP from RhoA is inhibited because of this trimer formation. In response to post-translational modification, such as tyrosine phosphorylation, p120^{ctn} forms a tighter complex with cadherin-catenin complexes at the cell membrane. The cadherin-bound p120^{ctn} dissociates from RhoA, resulting in the activation of RhoA by guanine nucleotide exchange factors (GEFs) such as Vav2. The exchange of GDP for GTP activates RhoA, which leads to downstream RhoA signaling events that promote cadherin clustering and junction formation. Therefore, cytoplasmic p120^{ctn} regulates specific signaling events at the cell membrane, but this does not preclude the role of nuclear p120^{ctn} in signal transduction.

In response to a putative external signal, p120^{ctn} translocates to the nucleus where it binds Kaiso transcription factor, suggesting that p120^{ctn} regulates transcriptional activity of unidentified target genes (Daniel and Reynolds, 1999; Van Hengel et al., 1999; Mariner et al., 2000). Kaiso interacts with p120, but does not form a complex with E-cadherin, α−catenin or β-catenin, suggesting a mutually exclusive interaction of p120^{ctn} with either Kaiso or E-cadherin. Kaiso is a DNA-binding protein that recognizes a specific consensus sequence and methylated CpG dinucleotides (Daniel et al., 2002; Prokhortchouk et al., 2001). Kaiso is ubiquitously expressed in a panel of cell lines that includes human breast cancer cell lines MCF-7 and MDA-MB-231. However, human prostate cancer cell lines have not yet been characterized with respect to Kaiso protein expression.

3.6. p120^{ctn} isoforms

Most cell types express alternatively spliced isoforms of p120^{ctn} (Anastasiadis and Reynolds, 2000; Thoreson and Reynolds, 2002; Staddon et al., 1995). The following nomenclature is used to distinguish the multiple isoforms of p120^{ctn} (Figure 4). Four different ATG start sites at the N-terminal are used to generate p120 isoforms type 1, 2, 3 and 4. While all four isoforms contain a central armadillo domain with ten arm repeats, only p120 isoform 1 contains

a putative coiled-coil domain. The significance of this domain in tumorigenesis is not completely understood. All p120^{ctn} isoforms contain a loop in arm repeat 6, which is thought to act as a nuclear localization signal. C-terminal splicing of p120^{ctn}, where exons A, B, C or none of the C-terminal exons are present adds to the complexity of p120^{ctn} nomenclature. An additional A, B or C designation is included in p120^{ctn} nomenclatrure, based on which C-terminal exon is present. For example, p120^{ctn} 1BC refers to an isoform of p120^{ctn} that is spliced at start site 1 in the N-terminus and contains exons B and C at the C-terminus. These four p120^{ctn} isoforms are differentially expressed based on cell type, suggesting that each isoform may have a specific cellular function. For instance, macrophages and fibroblasts make N-cadherin and express the p120^{ctn} 1A isoform, whereas epithelial cells make E-cadherin and express smaller isoforms such as p120^{ctn} 3A (Anastasiadis and Reynolds, 2000). Based on alternative splicing, possible occurrence of up to 32 isoforms of p120^{ctn} were found in human cells (Anastasiadis and Reynolds, 2000). As discussed above, it is well established that p120^{ctn} interacts with E-cadherin, RhoA and the Kaiso transcription factor. However, the size and specific isoform(s) involved in these interactions remains to be determined. Delineation of the sub-cellular distribution (cytoplasmic vs nuclear) of p120^{ctn} isoforms may provide some insight into the specific function of each.

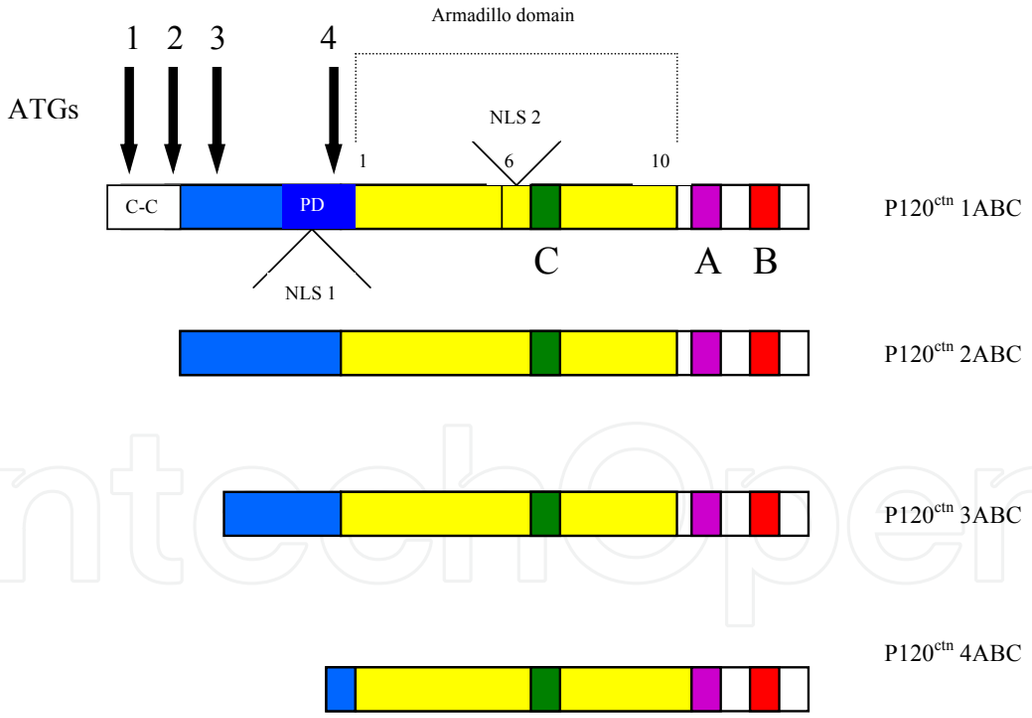

Figure 4. Diagrammatic representations of the multiple isoforms of p120 catenin. Cell-type-specific alternative splicing events result in multiple isoforms of p120 catenin. Four N-terminal ATG start sites generate p120 isoforms 1, 2, 3, and 4. p120 isoform 1 contains a putative coiled-coil domain (C-C), which is absent from isoforms 2-4. Additional alternative splicing generates p120 isoforms using alternative exons in the C-terminal region, exons A, B and C. Isoforms are designated p120^{ctn} 1-4, depending on the N-terminal start site. The A, B, and/or C designations refer to the exons present in the p120 catenin isoform. If none of the C-terminal exons are present, the letter N (for none) is used in the nomenclature (e.g. p120^{ctn}1N). PD, phosphorylation domain; NLS, Nuclear localization sequence.

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Similar to the situation with β and γ-catenin, increased levels of $p120^{ctn}$ in the cytoplasm may direct translocation of $p120^{ctn}$ to the nucleus where a downstream signaling cascade is initiated. Although the mechanism of nuclear translocation and the molecular basis for $p120^{ctn}$ isoform specificity has not been described, post-translational modification of $p120^{ctn}$ may be one means of directing $p120^{ctn}$ into either the cytoplasmic or the nuclear compartments. Specific sites of Src-initiated phosphorylation have been identified in murine p120, isoform 1A (Mariner et al., 2001). All of the Src-stimulated phosphorylation sites are present in the amino terminus of $p120^{ctn}$, whereas the tyrosine residues in the armadillo repeat regions are not phosphorylated. Six of these phosphorylated sites cluster in a short-region upstream of the first arm repeat and fourth ATG start site. The significance of Src phosphorylation at these sites remains to be determined. Nonetheless, post-translational modification of $p120^{ctn}$ may be involved in regulating cell-type specific expression patterns, cellular distribution, and/or downstream signaling.

4. N-cadherin

N-cadherin is a member of the classical cadherin family of transmembrane glycoproteins involved in homotypic cell adhesion (Takeichi, 1995). The extracellular domain of N-cadherin consists of five cadherin domains with residues that allow homophilic binding in the first extracellular domain (ECD) (Shan et al., 1999; Koch et al., 1999).In neuronal cells, N-cadherin is involved in the control of axonal growth, synapse formation and synaptic plasticity (Matsunaga et al., 1988; Riehl et al., 1996; Fannon and Colman, 1996; Inoue and Sanes, 1997; Tang et al., 1998; Bozdagi et al., 2000). While it is known that N-cadherin is important in homotypic cell adhesion, there is some evidence that N-cadherin may also be involved in signaling cascades that promote axonal growth (Utton et al., 2001). N-cadherin has been shown to have a role in bone formation (Marie, 2002). In contrast to E-cadherin, which is primarily expressed on cells of epithelial origin, N-cadherin is expressed on mesenchymal cells, such as neuronal tissues, stromal fibroblasts, muscle endothelium and in pleural mesothelial cells (Hazan et al., 1997b).

N-cadherin expression is also altered in pathological processes, such as metastasis of highly invasive cancer cells to regional lymph nodes and bone.The metastatic process is multifactorial, with possible transition of cells from an epithelial to a mesenchymal phenotype promoting migration of cells to distant sites. For example, breast cancer cell lines that have de-differentiated (more primitive) to a mesenchymal phenotype have reduced expression of E-cadherin with concomitant up-regulation of N-cadherin (Hazan et al., 1997b). The de-differentiated breast cancer cells are capable of interacting with surrounding stromal tissues, supporting the invasive phenotype of the breast cancer cells. The epithelial to mesenchymal transition (EMT) is also seen in prostate cancer cell lines, and is correlated with the increased invasive capacity of these cells (Tran et al., 1999). The more invasive prostate cancer cell lines (i.e., JCA-1[1]) and prostate stromal fibroblasts express N-cadherin, with a loss of E-cadherin expression. This would

1 JCA-1 and TsuPr1 have now been identified as derivatives of T24 Bladder Carcinoma cells and are not of prostatic origin (Van Bokhoven et al., 2001). However, JCA-1 and TsuPr1 remain relevant to our theoretical model of cancer cell invasion due to their urogenital origin and therefore, are included in this thesis. JCA-1 and TsuPr1 are indicated with * to emphasize the known origin of these cell lines.

suggest that mutually exclusive expression of either E-cadherin or N-cadherin would establish an epithelial or mesenchymal phenotype, respectively. Homotypic adhesion between prostate cancer cells and stromal fibroblasts (encapsulating the prostate gland) could promote prostate cancer cell invasion and extracapsular metastasis. The loss of E-cadherin and concomitant expression of N-cadherin would allow prostate cancer cells to undergo an epithelial to mesenchymal transition allowing the cells to now become highly invasive.

5. Classical cadherins, Type II

5.1. Cadherin 11

Type II cadherins, cadherins 5, 6, 7, 8, 9, 10, 11, and 12, have structural features similar to Type I cadherins, but differ in amino acid sequence. Type II mesenchymal cadherins are normally expressed on stromal cells and osteoblasts. A mesenchymal cadherin, cadherin 11, and its truncated variant are expressed on highly invasive breast cancer cell lines (Pishvaian et al., 1999), but not on non-invasive cell lines. Previous studies have shown that cadherin 11 is expressed in embryonic mesenchymal tissues, and restricted to certain regions of neural tube (Kimura et al., 1995; Hoffman and Balling, 1995). As tumor cells become more invasive and less differentiated, with concomitant loss of E-cadherin expression, there is an increase in mesenchymal cadherin expression. This pattern would suggest an epithelial to mesenchymal transition of highly invasive, poorly differentiated tumor cells. Although little is known about the expression pattern and function of Type II cadherins in prostate cancer cell lines, expression of cadherin 11 may facilitate metastasis of cancer cells and form distant lesions, particularly in the bone (Bussemakers et al., 2000; Tomita et al., 2000). It is important to note that patients with advanced lung, breast or prostate cancers develop bone metastasis (Mundy, 2002; Soos et al., 1997). In humans, prostate cancer cells invade Batson's vertebral veins, allowing metastatic cancer cells to reach and colonize distant sites within the bone (Geldof, 1997; Oesterling et al, 1997; Lehr and Pienta, 1998). Therefore, successive E-cadherin down-regulation, expression of metalloproteinases, and expression of mesenchymal cadherins allow prostate cancer cells to follow a defined metastatic pathway. The prostate cancer cells may disassociate, invade the basement membrane, metastasize, and colonize distant sites in the bone with concomitant expression of mesenchymal cadherin 11. This type of cancer cell-stromal cell interaction mediated by cadherin 11 is seen in invasive gastric cancers (Shibata et al., 1996). It is possible that E-cadherin acts as a tumor suppressor in cancer progression, while cadherin 11 regulates invasion and formation of metastatic lesions in the bone. This would warrant further investigation of the expression pattern and function of cadherin 11, as well as its role in signalling metastatic progression of prostate cancer cell lines.

6. Matrix metalloproteinases

6.1. Structural motifs

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that consist of more than 21 human MMPs. MMPs are divided into eight distinct structural

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groups, five of which are secreted and three of which are membrane-localized MMPs, MT-MMPs (Table 1). The existence of multiple MMPs suggests that each MMP subfamily has a specific function that is cell-type specific. Understanding the structural composition of each of the MMP subfamilies may provide some insight into their differential expression and function (Figure 5). MMPs contain an amino-terminal signal sequence (pre) that directs them to the endoplasmic reticulum, a propeptide (pro) sequence with a zinc-interacting thiol group that is cleaved upon activation, and a catalytic domain with a zinc-binding site. Classification of MMPs into the eight subclasses is based on their structural motifs. For example, Group 1 MMPs containing only the pre-, pro- and catalytic domains only, are called the minimal-domain MMP (Sternlicht and Werb, 2001; Egelblad and Werb, 2002). Group 2 MMPs are simple hemopexin-domain containing MMPs with a hemopexin-like domain in addition to the pre-, pro- and catalytic domains found in the minimal-domain MMPs. This additional domain is involved in interactions with tissue inhibitors of metalloproteinases (TIMPS), as well as with their proteolytic substrates. A hinge region connects the catalytic and hemopexin domains. The function of the hinge region is not known, but molecular modeling studies suggest that this region interacts with triple helical collagen (Nagase and Woessner, 1999). Six of the eight structural groups contain the hemopexin domain with the exception of Group 1, minimal- domain MMPs and Group 8, the Type II transmembrane MMPs. While the specific mechanism of proteolytic cleavage is not known, the hemopexin domain is essential for collagenases to cleave triple helical interstitial collagens (Bode, 1995). Note, however, that MMPs have substrate specificity distinct from that of hemopexin domain (Clark and Cawston, 1989). Cell-surface activation of pro-MMP2 requires the presence of hemopexin-domain of MMP-2 (Murphy et al., 1992; Strongin et al., 1995). In addition, recent *in vitro* studies have suggested that the hemopexin domain may assist tumor cells in evasion of immune surveilance. The hemopexin C-terminal domain of MT1-MMP has been suggested to modulate the levels of complement component (gC1qR) in the tumor cell microenvironment (Rozanov et al., 2002). C1q is a subcomponent of the C1 complex of the classical pathway of complement activation. Active MT1-MMP can reduce the levels of soluble gC1qR in the tumor vicinity via proteolytic cleavage. Interestingly, the hemopexin-like C-terminal domain is involved in proteolytic cleavage of gC1qR. These *in vitro* studies imply that tumor cells can evade immune surrveilance by hemopexin domain mediated cleavage of complement components. Group 3 encompasses gelatin-binding MMPs containing fibronectin-like repeats that are associated with binding collagen (FI) and gelatin (Egeblad and Werb, 2002; Allan et al., 1995; Steffensen et al., 1995). Groups 4-8 contain a motif between the propeptide and catalytic domains that is recognized by intracellular furin-like serine proteinases (FU). These MMPs are intracellularly activated by furin-initiated proteolytic cleavage at this site. Groups 5 MMPs contain a vitronectin-like insert in addition to the FU recognition motif. MMPs that are associated with the membrane include the membrane-type MMPs (Group 6) and the glycosylphosphatidylinositol (GPI)-anchored MMPs (Group 7). Membrane-type MMPs (MT-MMPs) have a carboxy-terminal, single-span transmembrane domain (TM) and a very short cytoplasmic domain (Cy). In contrast to the MT-MMPs, the GPI-anchored MMPs are tethered to the membrane by a GPI component at the C-terminal. Group 8 represents the type II transmembrane MMPs with an N-terminal signal anchor (SA)

that targets the MMP to the cell membrane. MMP-23 is identified as a type II transmembrane MMPs with unique cysteine array (CA) and immunoglobulin (Ig)-like domains at the C-terminus. The functional significance of these domains has not yet been established.

MMP subfamily	Structural Group	MMP number	MMP name	Substrates
Collagenases	2	1	Interstitial collagenase	Collagens I, II, III and VI, gelatins, aggrecan, entactin
	2	8	Neutrophil collagenase	Collagens I, II, III, aggrecan
	2	13	Collagenase-3	Collagens I, II, III
Gelatinases	3	2	72 kDa Type IV gelatinase	Gelatin, collagens I, IV, V, VII, X, XI, fibronectin, laminin, vitronectin
	3	9	92 kDa Type IV gelatinase	Gelatins, collagens IV, V, XIV, aggrecan, elastin, entactin, vitronectin
Stromelysins	2	3	Stromelysin-1	Aggrecan, gelatins, fibronectin, laminin, collagen III, IV, IX, X, vitronectin
	2	10	Stromelysin-2	Aggrecan, fibronectin, laminin, collagen IV
	4	11	Stromelysin-3	Fibronectin, laminin, collagen IV, aggrecan, gelatins
	2	18	Putative MMP	Collagen I
Membrane-type MMPs	6	14	MT1-MMP	Pro-MMP2, avb3 integrin, CD44, proMMP13, fibronectin, laminin, vitronectin, collagens I, II, III
	6	15	MT2-MMP	Not identified
	6	16	MT3-MMP	ProMMP-2
	7	17	MT4-MMP	Not identified
	6	24	MT5-MMP	Not identified
	7	25	MT6-MMP	Not identified
Other MMPs	1	7	Matrilysin (PUMP-1)	Aggrecan, fibronectin, laminin, collagen IV, elastin, entactin, vitronectin
	2	12	Macrophage elastase	Elastin
	2	19	Rheumatoid arthritis-associated MMP	Not identified
	2	20	Enamelysin	Amelogenin
	5	21	Homologue of *Xenopus* XMMP	
	2	22	CMMP	
	8	23	Cysteine array MMP	
	1	26	Endometase, matrilysin-2	Fibronectin, vitronectin, fibrinogen, type IV collagen, MMP9, gelatin
	2	27	Unkown	
	4	28	Epilysin	

Table 1. Classification and Nomenclature of Human MMPs. MMP superfamily is classified into eight structural groups. While five of these groups are secreted, three groups are membrane-bound. The MMP subfamily, structural group number, corresponding MMP number and the common name are shown in the table. Substrates for each enzyme are also listed in the table (Vincenti, 2000; Nagase and Woessner, 1999; Egelblad and Werb, 2002). MMP Structural Groups: Group 1, Minimal-domain; Group 2, Simple hemopexin-domain-containing; Group 3, Gelatin-binding; Group 4, Furin-activated secreted; Group 5, Vitronectin-like insert; Group 6, Transmembrane; Group 7, GPI-anchored; Group 8, Type II Transmembrane.

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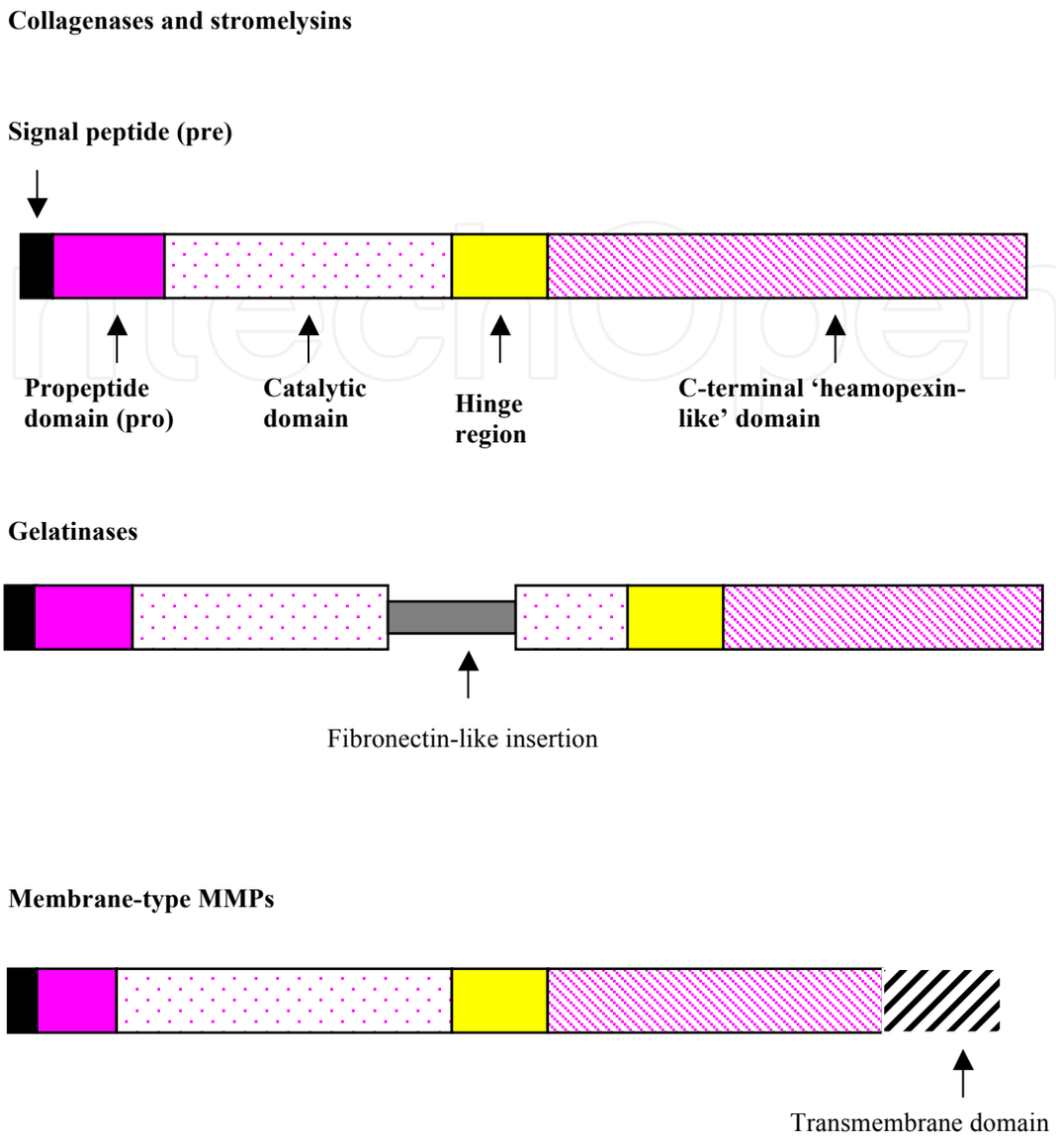

Figure 5. Structure of the matrix metalloproteinase. MMPs contain the following domains: signal peptide (pre-peptide), propeptide, catalytic domain, hinge region, and hemopexin-like domain. The cleavage of N-terminal propeptide domain of the latent MMP yields the active form of the enzyme. The gelatinases contain a fibronectin-like region within their catalytic domain. The membrane-type MMPs are characterised by a C-terminal transmembrane domain. The hemopexin-like repeat is absent in matrilysin (MMP-7).

Common names are also used to distinguish substrate specificity for each of the MMP groups described above. For example, interstitial collagenases, such as MMP-1 (structural group 2), have high specificity for fibrillar collagen types I, II, and III. In contrast, gelatinases, MMP-2 and MMP-9 (structural group 3), have a greater propensity to cleave denatured collagen products, as well as basement membrane components such as collagen type IV. Stromelysins, such as MMP-3 (structural group 2), cleave extracellular components and have the ability to activate other MMPs. Recently, a new subfamily of membrane-tethered or membrane-type MMPs, MT-MMPs (Group 6) has been included in the MMP family. Five enzymes: MT1-, MT2-, MT3-, MT4- and MT5- (Sato et al., 1996; Takino

et al., 1995; Will and Hinzmann, 1995; Puente et al., 1996; Pei, 1999) have been identified as members of this group.

MMPs are synthesized as inactive zymogen requiring proteolytic cleavage of the N-terminus in order to be activated. A cysteine-sulphydryl group in the propeptide domain interacts with a zinc ion bound to the catalytic domain. Proteolytic cleavage removes the propeptide domain, leading to the activation of latent MMP (Cao et al., 1998). Generally, MMPs are activated by either serine proteinases or other activated MMPs outside of the cell. In contrast, MMP-11, MMP-28 and MT-MMPs are activated by intracellular furin-like serine proteinases before they are associated with the cell membrane. MMP activity is regulated at three levels: transcription, activation, and inhibition/deactivation.

6.2. Transcriptional regulation of MMPs

Increased MMP expression in tumors is primarily associated with transcriptional changes rather than genetic alterations, although translocation of MMP23 genes in neuroblastoma and amplification of MMP24 gene have been reported (Llano, 1999). Transcriptional regulation of MMP mRNA expression is subject to influences by several chemical reagents, neurohormones, and cytokines (Liotta et al., 1983; Unemori and Werb, 1988; Galis et al., 1994; Werb et al., 1989; Matrisian and Hogan, 1990). For example, tumor necrosis factor alpha (TNF-α) and interleukin-1 can stimulate the production of MMP-1, MMP-3, and MMP-9 (MacNaul et al., 1990). While the pathways by which these factors regulate MMP transcription remain to be determined, it is known that the MMP promoter regions contain response elements that transcriptionally regulate expression. Tumor response element (TRE) and activation protein-1 (AP-1) binding sites are present in MMP-1, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12 and MMP-13 (Benbow and Brinkerhoff, 1997). Transcriptional regulation can be further influenced either by genetic polymorphisms or by growth factor-activated transcription factors. MMP-1 protein expression is influenced by polymorphisms in MMP-1 gene promoter. Promoters of inducible MMPs and TIMPs have specific sites that bind AP-1 and Polyoma Enhancer A-binding Protein-3 (PEA-3), which is pivotal in transcriptional activation. While Fos and Jun families of transcription factors bind to AP-1 sites, PEA-3 binds to the Ets binding sites (EBS). The presence of two guanine nucleotides in the MMP-1 promoter creates a functional Ets-binding site adjacent to an AP-1 site, up-regulating the transcription of MMP-1 gene in multiple cancers, including ovarian cancers (Kanamori, 1999). MMP transcription can also be downregulated in response to certain signals. For example, MMP-1 transcription can be repressed in the presence of the tumor suppressor p53 (Sun et al., 1999). Interestingly, p53 is also known to differentially regulate MMP-13 expression (Sun et al., 2000). Another example of transcriptional regulation of MMPs is the up-regulation of MMP-7 expression in colon tumors (Crawford, 2001). The PEA-3 subfamily of Ets transcription factors and the β-catenin-LEF-1 complex activate MMP-7 expression in colon tumors. These findings suggest that multiple regulatory elements in MMP promoter regions coordinately regulate tissue-specific and temporal expression of MMP.

6.3. Activation of MMPs

While transcriptional regulation is important in determining MMP synthesis, activation of MMPs is a key factor in regulating proteolysis of specific substrates. Newly synthesized MMPs are secreted into the extracellular space in zymogen form. Outside the cell, other MMPs, serine proteinases, growth factors, and chemical/physical reagents can activate the latent MMP. Proteolytic enzymes such as urokinase, plasmin, and cathepsins are known to activate MMPs. In addition, organomercurials (APMA) are used routinely to activate MMPs under experimental conditions. MMP activity *in vivo* has been associated with the interstitial form urokinase plasminogen activator (uPA). Recent evidence has shown that latent MMP-2 is activated at the cell surface in a highly regulated pathway involving tissue inhibitors of metalloproteinases-2 (TIMP-2) and MT1-MMP (Hernandez-Barrantes et al., 2000). TIMP-2 binds MT1-MMP at its N-terminus and proMMP-2 at its C-terminus. Another free MT1-MMP molecule cleaves the bound proMMP-2, leading to partial activation of MMP-2. Another fully activated MMP-2 is required to remove a residual portion of the MMP-2 propeptide (Deryugina, 2001). At low concentrations, TIMP-2 stimulates proMMP-2 activation; at high concentrations, it inhibits MMP-2 activation.

6.4. Inhibition of MMP activity

Inhibition/deactivation of MMPs can be accomplished by several factors including α-2-macroglobulin, tissue inhibitors of metalloproteinases (TIMPs), small molecules with TIMP-like domains, and the membrane-bound inhibitor RECK (reversion-inducing cysteine-rich protein with kazal motifs) (Sasahara et al., 2002). In tissue fluids, α2-macroglobulin forms a complex with MMPs that can bind to a scavenger receptor. Endocytosis removes the trimeric complex, α2-macroglobulin-MMP-scavenger receptor, in an irreversible manner. The activity of MMPs is regulated by the presence of endogenous protein inhibitors, Tissue Inhibitors of Metalloproteinases (TIMP). Four TIMPs (TIMPs1-4) have been identified, each with a specific function (Gomez et al., 1997). TIMPs inhibit tumorigenesis, cell invasion, metastasis and angiogenesis. A fine balance between MMPs and TIMPs regulates tumor progression. TIMP binds to the active site of MMP, leading to a conformational change in the enzyme. The ratio of MMP to its specific TIMP determines the metastatic potential of a tumor cell. Recent evidence suggests that an increase in MMP2 to TIMP2 ratio is associated with high-grade and high-stage prostate tumors (Still et al., 2000).

6.5. Normal and pathological processes involving MMP expression

MMPs are involved in normal embryonic development (Alexander et al., 1996b; Lelongt et al., 1997), renal organogenesis (Lelongt et al., 1997), and invasion and metastasis of cancer (Stetler-Stevenson et al., 1993). There are several examples of normal embryonic development that require MMP expression, including trophoblast implantation, embryonic growth, and tissue morphogenesis. In addition, MMPs are required for normal wound repair. As part of the wound repair process, development of new tissue at the site of injury involves a series of highly regulated events. MMPs degrade several components of the extracellular matrix (ECM), followed by migration of new cells to the site leading to formation of new

ECM at the injured site. The level as well as the tissue-specificity of MMPs can determine the degree of wound repair. For example, MMP-7 is the only MMP expressed by lung epithelial cells under conditions of tracheal damage (Dunsmore et al., 1998). In contrast, more than one MMP is required for epithelial cell migration during normal wound repair (Sudbeck et al., 1997). While different levels of MMP-1, -2, and –9 have been detected at the wound site, neutrophil-derived MMP-8 is the primary collagenase present in normal healing wounds. However, unregulated expression of MMP-8 is associated with chronic leg ulcers (Armstrong and Jude, 2002; Nwomeh et al., 1999). Mammary gland development and involution is another example of a physiological process that requires tightly regulated expression of MMPs (Lund et al., 1996). In summary, regulation of MMP expression and MMP activity is essential for normal cellular processes.

Pathological processes that are associated with aberrant MMP expression include cardiovascular disease (Libby, 1995; Thompson et al., 1995), interstitial fibrosis (Norman et al., 1995), glomerulosclerosis (Schaefer et al., 1997; Jacot et al., 1996), pulmonary emphysema (D'Armiento et al., 1992), and bullous pemphigoid (Liu et al., 1998), an autoimmune subepidermal blistering disease. MMPs are also associated with tumor progression and contribute to tumor invasion and metastasis. MMPs are associated with five principal processes promoting tumor progression (Egeblad and Werb, 2002). First, MMPs can promote cancer cell proliferation by three known mechanisms. These include release of cell-membrane-bound precursors of some growth factors, such as TGF-α, degradation of ECM proteins resulting in the release of peptide growth factors, or indirect proliferative signals through integrins. Second, MMPs regulate apoptosis as well as anti-apoptosis. MMP-3, -7, -9 and –11 are known to regulate apoptosis involving different signaling processes. Overexpression of MMP-3 is known to induce apoptosis in mammary epithelial cells by degrading laminin (Alexander et al., 1996a; Witty et al., 1995) and MMP-7 cleaves FAS ligand, a ligand for the death receptor FAS, from its membrane-bound precursor. As a result of this cleavage, a pro-apoptotic molecule is released into the surrounding microenvironment (Powell et al., 1999; Mitsiades et al., 2001). MMPs can also induce apoptosis of endothelial cells or epithelial cells by shedding the adhesion molecules VE-cadherin (Herren et al., 1998), PECAM-1 (Ilan et al., 2001) and E-cadherin (Steinhusen et al., 2001). Third, MMPs are positive regulators of angiogenesis, which is required for tumor growth. MMP-2, -9 and –14 and –19 have been shown to regulate angiogenesis by promoting the availability of factors involved in angiogenesis, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2) and TGF-β. These factors are required for endothelial cell proliferation and migration. Moreover, MMP-2 is required for transition to an angiogenic phenotype in a tumor model (Fang et al., 2000), suggesting that MMPs are important for maintenance of tumor growth and proliferation. Fourth, MMPs allow cancer cells to evade immune surveillance. For example, MMP-9 can cleave interleukin-2 receptor-a (IL-2Ra) from the surface of activated T lymphocytes, thereby suppressing their proliferation (Sheu et al., 2001). As a result of this suppression, tumor-specific T lymphocytes cannot infiltrate tumor cells. MMP-11 also generates a cleavage product that allows tumor cells to evade the tumor-targeted activity of natural killer cells. MMP-11 cleaves α1-proteinase-inhibitor, which decreases natural killer cell cytotoxicity (Kataoka et al., 1999). Active

membrane-type 1 MMP (MT1-MMP) has also been suggested to assist tumor cells in evasion of immune surveillance (Rozanov et al., 2002). Therefore, tumor cells escape immune surveillance leading to uncontrolled tumor growth. Fifth, MMPs degrade extracellular matrix components and allow tumor cells to migrate across epithelial basement membranes and metastasize to a new site. While the exact mechanism triggering MMP release by tumor cells is not yet completely understood, MMPs are the only enzymes known to degrade fibrillar collagen types I, II, III and IV. MMP-2, -3, -13 and –14 promote invasion of cell lines in *in vitro* models of invasion (Lochter et al., 1997; Belien et al., 1999; Deryugina et al., 1997; Polette and Birembaut, 1998). Furthermore, MMP-2 and MMP-14 cleave laminin-5 leading to cell motility (Koshikawa et al., 2000). Proteolytic cleavage of CD44 as well as integrin αv subunit by MMP-14 promotes cell migration (Kajita et al., 2001; Deryugina, 2001). Recently, MT-MMP1 has been identified as a downstream target of the β-catenin/Tcf4 complex in colorectal cancers, suggesting that E-cadherin-catenin signaling is important in regulating MT-MMP1 expression (Takahashi et al., 2002). Interestingly, MMP-14 has recently been shown to function as an integrin convertase promoting cell adhesion, migration and focal adhesion kinase phosphorylation of breast cancer cells (Ratnikov et al., 2002). These findings suggest that MMP-14 may be important in regulating cross-talk between integrin and cell-adhesion molecules. MMP-3 as well as MMP-7 cleaves E-cadherin leading to tumor progression (Noe et al., 2001). The newly released E-cadherin cleavage product could interfere with another unprocessed E-cadherin molecule such that E-cadherin function is impaired and, as a result, tumor-cell invasion ensues. Taken together, MMPs are important in many aspects of tumor progression in addition to tumor cell migration and invasion.

6.6. Role of MMP in prostate cancer

Growth factors and receptor kinases can also influence transcriptional regulation of MMPs. MMPs have been shown to play a significant role in prostate cancer metastasis (Wood et al., 1997; Sehgal et al, 1998; Pajouh et al, 1991; Powell et al, 1993). Moreover, recent evidence suggests an increase in MMP-2 and TIMP-2 ratio is associated with high-grade and high-stage prostate tumors (Still et al., 2000). MMP expression could be induced by two possible mechanisms. First, prostate stromal cells could secrete growth factors such as epidermal growth factor (EGF) and induce expression of downstream effectors such as metalloproteinases. Growth factors and their receptors have been shown to be key components of tumor development and progression (Sundareshan et al., 1999). Epidermal growth factor receptor (EGFR) expression in bladder cancer cells, for example, is associated with high tumor stage and grade (Nutt et al., 1998). EGF has been shown to induce the AP-1 transcriptional regulatory complex, which transcriptionally activates MMP-1 expression and MMP-3 expression in fibroblasts. EGFR stimulation promotes both breast cancer cell migration (Price et al., 1999) and induces MMP-1 expresssion (Nutt and Lunec, 1996). Second, MMP expression is also regulated by E-cadherin expression (Nawrocki-Raby et al., 2003). Restoration of E-cadherin expression in E-cadherin negative Dunning rat prostate tumor cells inhibits *in vitro* invasion and MMP-2 activity in these cells (Luo et al., 1999).

7. Concluding remarks

The cellular localization of E-cadherin and the catenin proteins has a significant role in regulating cancer progression. β-, γ- and $p120^{ctn}$ proteins are important components of the E-cadherin-catenin signal transduction pathway. Elucidating the mechanisms of nuclear localization or nuclear retention of β-, γ- and $p120^{ctn}$ proteins, may help us to understand the role of these catenins in regulating E-cadherin downstream signaling events associated with prostate cancer invasion.

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References

[1] Aberle, H., Butz, S., Stappert, J., Weissig, H., Kemler, R., & , H. Hoschuetzky ((1994). Assembly of the cadherin-catenin complex in vitro with recombinant proteins. Journal of Cell Science, 107, 3655-3663.

[2] Aberle, H., Bauer, A., Stappert, J., Kispert, A., & Kemler, R. (1997). catenin is a target for the ubiquitin-proteasome pathway." EMBO Journal, 16(13), 3797-3804.

[3] Akiyama, T. (2000). Wnt/b-catenin signaling. *Cytokine and Growth Factor Reviews*, 11, 273-282.

[4] Alexander, C. M., Howard, E. W., Bissell, M. J., & Werb, Z. (1996a). Rescue of mammary epithelial cell apoptosis and entactin degradation by a tissue inhibitor of metalloproteinase-1 transgene. Journal of Cell Biology, 135, 1669-1677.

[5] Alexander, C. M., Hansell, E. J., Behrendtsen, O., Flannery, M. L., Kishnani, N. S., Hawkes, S. P., & , Z. Werb ((1996b). Expression and function of matrix metalloprotei-

nases and their inhibitors at the maternal-embryonic boundary during mouse embryo implantation. Development , 122, 1723-1736.

[6] Allan, J. A., Docherty, A. J. P., Barer, P. J., Huskisson, N. S., Reynolds, J. J., & , G. Murphy ((1995). Binding of gelatinases A and B to type-1 collagen and other matrix components."Biochemistry Journal , 309, 299-306.

[7] Amit, S., Hatzubai, A., Birman, Y., Andersen, J. S., Ben-Shushan, E., Mann, M., Ben-Neriah, Y., & Alkalay, I. (2002). Axin-mediatedCKI phosphorylation of beta-catenin at Ser 45: a molecular switch for the Wnt pathway." Genes and Development , 16, 1066-1076.

[8] Anastasiadis, P.Z. and A.B. Reynolds (2000). "The p120 catenin family: complex roles in adhesion, signaling and cancer." Journal of Cell Science 113: 1319-1334.

[9] Anastasiadis, P.Z., S.Y. Moon, M.A. Thoreson, D.J. Mariner, H.C. Crawford, Y. Zheng and A.B. Reynolds (2000)."Inhibition of RhoA by p120 catenin."Nature Cell Biology 2(9): 637.

[10] Aoki, M., Hecht, A., Kruse, U., Kemler, R., & , P. K. Vogt ((1999). Nuclear endpoint of Wnt signaling: Neolastic transformation induced by transactivating lymphoid-enhancing factor 1." Proceedings of the National Academy of Sciences , 96(1), 139-144.

[11] Aono, S., S. Nakagawa, A.B. Reynolds and M. Takeichi (1999). "$P120^{ctn}$ acts as an inhibitory regulator of cadherin function in colon carcinoma cells." Journal of Cell Biology 145: 551-562.

[12] Armstrong, D.G. and E.B. Jude(2002). The role of matrix metalloproteinases in wound healing. American Podiatric Medical Association , 92(1), 12-8.

[13] Arya, M., Bott, S. R., Shergill, I. S., Ahmed, H. U., Williamson, M., & , H. R. Patel ((2006). The metastatic cascade in prostate cancer. Surgical Oncology, 15, 117-128.

[14] Barker, N., & , H. Clevers ((2000). Catenins.Wnt signaling and cancer."Bioessays, 22, 961-965.

[15] Batsche, E., Muchardt, C., ehrens, J., & , H. C. Hurst and C.Cremisi ((1998). RB and c-Myc activate expression of the E-cadherin gene in epithelial cells through interaction with transcription factor AP-2. Molecular and Cellular Biology, 18(7), 3647-3658.

[16] Battle, E., Sancho, E., Franci, C., Dominguez, D., Monfar, M., Baulida, J., & , A. Garcia de Herreros ((2000). The transcription factor Snail is a repressor of E-cadherin gene expression in epithelial tumour cells." Nature Cell Biology , 2, 84-89.

[17] Bauer, A., Otmar, H., & Kemler, R. (1998). Pontin52, an interaction partner of β-catenin, binds to the TATA box binding protein." Proceedings of the National Academy of Sciences , 95, 14787-14792.

[18] Beavon, I.R.G(2000). The E-cadherin-catenin complex in tumour metastasis: structure, function and regulation. European Journal of Cancer , 36, 1607-1620.

[19] Behrens, J., Von, J. P., Kries, M., Kuhl, L., Bruhn, D., Wedlich, R., Grosschedl, , & , W. Bichmeier ((1996). Functional interaction of β-catenin with the trnscription factor Lef1."Nature , 382, 638-642.

[20] Behrens, J., Jerchow, B. A., Wurtele, M., Grimm, J., Asbrand, C., Wirtz, R., Kuhl, M., Wedlich, D., & Birchmeier, W. (1998). Functional interaction of an Axin homolog, conductin, with β-catenin, APC, and GSK3β." Science , 280, 596-599.

[21] Behrens, J. (2002). Control of beta-catenin signaling in tumor development. Annals ofNew York Academy of Sciences , 910, 21-35.

[22] Belien, A. T., Paganetti, P. A., & Schwab, M. E. (1999). Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. Journal of Cell Biology , 144(2), 373-384.

[23] Benbow, U., & Brinkerhoff, C. (1997). The AP-1 site and MMP gene regulation: what is all the fuss about? Matrix Biology , 15, 519-526.

[24] Ben, Ze'ev. A., & , B. Geiger ((1998). Differential molecular interactions of beta-catenin and plakoglobin in adhesion, signaling and cancer. Current Opinion in Cell Biology, 10(5), 629-639.

[25] Berx, G., Staes, K., Hengel, J. V., Molemans, F., Bussemakers, M. J. G., Bokhoven, A. V., & , F. and Roy ((1995). Cloning and Characterization of the Human invasion Suppressor Gene E-cadherin (CDH1). Genomics, 26, 281-289.

[26] Berx, G., Becker, K. F., Hofler, H., & van Roy, F. (1998a). Mutations of the human E-cadherin (CDH1) gene. *Human Mutation*, 12(4), 226-237.

[27] Berx, G., Nollet, F., & van Roy, F. (1998b). Dysregulation of the E-cadheirn/catenin complex by irreversible mutations in human carcinomas."Cell Adhesion and Communication 6(2-3): 171-184.

[28] Bienz, M., & , H. Clevers ((2000). Linking colorectal cancer to Wnt signaling. Cell, 103(2), 311-320.

[29] Bode, W. (1995). A helping hand for collagenases: the haemopexin-like domain. Structure , 3, 527-530.

[30] Bozdagi, O., Shan, W., Tanaka, H., Benson, D. L., & Huntley, G. W. (2000). Increasing numbers of synaptic puncta during late-phase LTP: N-cadherin is synthesized, recruited to synaptic sites, and required for potentiation. *Neuron*, 28(1), 245-259.

[31] Brabant, G., Hoang-Vu, C., Cetin, Y., Dralle, H., Scheumann, G., Molne, J., Hansson, G., Jansson, S., Ericson, L. E., & Nilsson, M. (1993). E-cadherin: a differentiation marker in thyroid malignancies. *Cancer Research*, 53(20), 4987-4993.

[32] Brabletz, T., Jung, A., Dag, S., Hlubek, F., & Kirchner, T. (1999). Beta-catenin regulates the expression of the matrix metalloproteinase-7 in human colorectal cancer. American Journal of Pathology, 155(4), 1033-1038.

[33] Bracke, M. E., & , F. M. Van Roy and M. Mareel ((1996). The E-cadherin/catenin complex in invasion and metastasis. Current Topics in Microbiology and ImmunologyPt 1):, 123 EOF-61 EOF.

[34] Brannon, M., Gomperts, M., Sumoy, L., Moon, R. T., & Kimelman, D. (1997). A beta-catenin/XTcf-3 complex binds to the siamois promoter to regulate dorsal axis specification in Xenopus. Genes and Development , 11, 2359-2370.

[35] Bright-Thomas, R. M., Hargest, R., & (2002).", A. P. (2002). APC, β-catenin and hTCF-4; an unholy trinity in the genesis of colorectal cancer."European Journal of Surgical Oncology , 29, 107-117.

[36] Brown, J.D. and R.T. Moon. (1998). Wnt signaling: why is everything so negative? *Current Opinion in Cell Biology*, 10, 182-187.

[37] Bryden, A.A.G., J. A. Hoyland, A.J. Freemont, N.W. Clarke, D.S. Wismayer and N.J.R. George (2002). "E-cadherin and β-catenin are downregulated in prostatic bone metastases." British Journal of Urology International 89(4): 400.

[38] Bukholm, I. K., Nesland, J. M., Karesen, R., & , U. Jacobsen and A.-L.Borresen-Dale ((1998). E-cadherin and α-, β-, and γ-catenin protein expression in relation to metastasis in human breast carcinoma."Journal of Pathology , 185, 262-266.

[39] Bullions, L. C., & , A. Levine ((1998). The role of beta-catenin in cell adhesion, signal transduction, and cancer. Current Opinion in Oncology, 10, 81-87.

[40] Bussemakers, M. J. G., Giroldi, L. A., & , A. van Bokhoven and J.A. Schalken ((1994). Transcriptional regulation of the human E-cadherin gene in human prostate cancer cell lines: characterization of the human E-cadherin gene promoter. Bio.Biophy. Res. Com. , 203(2), 1284-1290.

[41] Bussemakers, M. J. G., Van Bokhoven, A., Tomita, K., Jansen, C. F. J., & , J. A. Schalken ((2000). Complex cadherin expression in human prostate cancer cells. InternationalJournal of Cancer85: , 446 EOF-50 EOF.

[42] Butz, S., & , R. Kemler ((1994). Distinct cadherin-catenin complexes in Ca^{2+} dependent cell-cell adhesion."*FEBS Letters* . , 355, 195-200.

[43] Buxton, R. S., Cowin, P., Franke, W. W., Garrod, D. R., Green, K. J., King, I. A., Koch, P. J., Magee, A. I., Rees, D. A., Stanley, J. R., & Steinberg, M. S. (1993). Nomenclature of the desmosomal cadherins. Journal of Cell Biology , 121, 481-483.

[44] Cadigan, K. M., & Nusse, R. (1997). Wnt singnaling: a common theme in animal development." Genes and Development , 11, 3286-3305.

[45] Cao, J., Drews, M., Lee, H. M., Conner, C., Bahou, W. F., & Zucker, S. (1998). The propeptide domain of membrane type 1 matrix metalloproteinase is required for binding of tissue inhibitor of metalloproteinases and for activation of pro-gelatinase A. Journal of Biological Chemistry , 273(52), 34745-34752.

[46] Cavallaro, U., & , G. Christofori ((2004). Cell adhesion and signaling by cadherins and Ig-CAMs in cancer."*Nature Reviews Cancer*. Cancer , 4, 118-132.

[47] Chen, H., Paradies, N. E., Fedor-Chaiken, M., & Brackenbury, R. (1997). E-cadherin mediates adhesion and suppresses cell motility via distinct mechanisms. *Journal of Cell Science*, 110, 345-356.

[48] Chen, C., , L., Liu, S. S., , S., Ip, M., Wong, L. C., Ng, T. Y., & Ngan, H. Y. S. (2003). E-cadherin expression is silenced by DNA methylation in cervical cancer cell lines and tumours. European Journal of Cancer, 39, 517-523.

[49] Cheng, L., Nagabhushan, M., & Pretlow, T. P. (1996). Expression of E-cadherin in primary and metastatic prostate cancer. American Journal of Pathology 148: , 1375 EOF-80 EOF.

[50] Clark, I. M., & , T. E. Cawston ((1989). Fragments of human fibroblast collagenase. Purification and characterization. Biochemistry Journal , 263, 201-206.

[51] Clevers, H., & , M. van De Wetering ((1997). TCF/LEF factors earn their wings. Trends in Genetics, 13, 485-489.

[52] Comijn, J., Berx, G., Vermassen, P., Verschueren, K., Van Grunsve, L., Bruyneel, E., Mareel, M., Huylebroeck, D., & van Roy, F. (2001). The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion. *Molecular Cell*, 7, 1267-1278.

[53] Cowin, P., , H., Kapprell, P., Franke, W. W., Tamkum, J., & Hynes, R. O. (1986). Plakoglobin: a protein common to different kinds of intercellular adhering junctions. *Cell*, 46, 1063-1073.

[54] Cowin, P., & , B. Burke ((1996). Cytoskeleton-membrane interactions. Current Opinion in Cell Biology, 8, 56-65.

[55] Crawford, H. C., Fingleton, B. M., Rudolph-Owen, L. A., Goss, K. J., Rubinfeld, B., Polakis, P., & Matrisian, L. M. (1999). The metalloproteinase matrilysin is a target of beta-catenin transactivation in intestinal tumors. *Oncogene*, 18(18), 2883-2891.

[56] Crawford, H. C., Fingleton, B., Gustavson, M. D., Kurpios, N., Wagenaar, R. A., Hassell, J. A., & Matrisian, L. M. (2001). The PEA3 subfamily of Ets transcription factors synergizes with β-catenin-LEF-1 to activate matrilysin transcription in intestinal tumors." Mol. Cell Biol., 21, 1370-1383.

[57] D'Armiento, J., Dalal, S. S., Okada, Y., Berg, R. A., & Chada, K. (1992). Collagenase expression in the lungs of transgenic mice causes pulmonary emphysema. *Cell*, 71, 955-961.

[58] D'Souza, B., & Taylor-Papadimitriou, J. (1994). Overexpression of ERBB2 in human mammary epithelial cells signals inhibition of transcription of the E-cadherin gene. Proceedings of the National Academy of Sciences, 91, 7202-7206.

[59] De Leeuw, W. J. G., Berx, C. B., Vos, J. L., Peterse, M. J., Van de Vijver, S., Litvinov, F., Van Roy, C. J., Corneliss, A. M., & Cleton-Jansen, . (1997). Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. Journal of Pathology , 183, 404-411.

[60] Daniel, J.M. and A.B. Reynolds (1995). "The tyrosine kinase substrate p120cas binds directly to E-cadherin but not to the adenomatous polyposis coli protein or alpha-catenin." Molecular Cellular Biology 15: 4819-4824.

[61] Daniel, J.M. and A.B. Reynolds (1999). "The Catenin p120^{ctn} interacts with Kaiso, a novel BTB/POZ domain zinc finger transcription factor." Molecular Cellular Biology 19(5): 3614-3623.

[62] Daniel J.M., C.M. Spring, H.C. Crawford, A.B. Reynolds and A. Baig (2002). "The p120ctn-binding partner Kaiso is a bi-modal DNA-binding protein that recognizes both a sequence-specific consensus and methylated CpG dinucleotides." Nucleic Acids Research 30(13): 2911-2919.

[63] Davis, M.A., Ireton, R.C. and A.B. Reynolds (2003). "A core function of p120-catenin in cadherin turnover." Journal of Cell Biology 163(3): 525-534.

[64] Dermietzel, R., & , F. Hofstadter ((1998). Gap junctions in health and disease. Virchows Arch , 432, 177-186.

[65] Deryugina, E. I., Luo, G. X., Reisfeld, R. A., Bourdon, M. A., & Strongin, A. (1997). Tumor cell invasion through matrigel is regulated by activated matrix metalloproteinase-2. *Anticancer Research*, 17, 3201-3210.

[66] Deryugina, E.I(2001). MT1-MMP initiates activation of proMMP-2 and integrin avb3 promotes maturation of MMP-2 in breast carcinoma cells." Experimental Cell Research , 263, 209-223.

[67] Dorudi, S., Sheffield, J. P., Poulsom, R., Northover, J. M., & , I. R. Hart ((1993). E-cadherin expression in colorectal cancer. An immunocytochemical and in situ hybridization study. American Journal of Pathology , 142(4), 981-986.

[68] Dunsmore, S. E., Saarialh-Kere, U. K., Roby, J. D., Wilson, C. L., Matrisian, L. M., Welgus, H. G., & Parks, W. C. (1998). Matrilysin expression and function in airway epithelium. Journal of Clinical Investigations , 102, 1321-1331.

[69] Eastman, Q., & Grosschedl, R. (1999). Regulation of LEF-1/TCF transcription factors by Wnt and other signals. *Current Opinion in Cell Biology*, 11, 233-240.

[70] Egelblad, M., & , Z. Werb ((2002). New functions for the matrix metalloproteinases in cancer progression."Nature Reviews Cancer , 2(3), 161-174.

[71] Esteller, M. M., Sanchez-Cespedes, R., Rosell, D., Sidransky, S. B., Baylin, , & , J. G. Herman ((1999). Detection of aberrant promoter hyermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients."Cancer Research , 59, 7-70.

[72] Fagotto, F., Funayama, N., Gluck, U., & Gumbiner, B. M. (1996). Binding to cadherins antagonizes the signaling activity of beta-catenin during axis formation in Xenopus. Journal of Cell Biology , 132(6), 1105-1114.

[73] Fagotto, F., Gluck, U., & , B. M. Gumbiner ((1998). Nuclear localization signal-independent and importin/karyopherin-independent nuclear import of β-catenin."Current Biology , 8, 181-190.

[74] Fagotto, F., E-h, Jho. L., Zeng, T., Kurth, T., Joos, C., Kaufmann, , & Costantini, F. (1999). Domains of Axin involved in protein-protein interactions, Wnt pathway inhibition, and intracellular localization. Journal of Cell Biology , 145(4), 741-756.

[75] Fang, J., Shing, Y., Wiederschain, D., Yan, L., Butterfield, C., Jackson, G., Harper, J., Tamvakopoulos, G., & Moses, M. A. (2000). Matrix metalloproteinase-2 is required for the switch to the angiogenic phenotype in a tumor model. Proc. Natl. Acad. Sci. USA , 97, 3884-3889.

[76] Fannon, A. M., & Colman, D. R. (1996). A model for central synaptic junctional complex formation based on the differential adhesive specificities of the cadherins. *Neuron*, 17(3), 423-434.

[77] Fujita, Y., Krause, G., Scheffner, M., Zechner, D., Leddy, H. E. M., Behrens, J., Sommer, T., & Birchmeier, W. (2002). Hakai, a c-Cbl-like protein, ubiquitinates and induces endocytosis of the E-cadherin complex." Nature Cell Biology , 4, 222-231.

[78] Funayama, N. F., Fagotto, P., Mc Crea, , & Gumbiner, B. M. (1995). Embryonic axis induction by the armadillo repeat domain of β-catenin: evidence for intracellular signaling." Journal of Cell Biology , 128(5), 959-968.

[79] Galis, Z. S., Sukhova, G. K., Lark, M. W., & Libby, P. (1994). Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. Journal of Clinical Investigations , 94(6), 2493-503.

[80] Gamallo, C., Palacios, J., Suarez, A., , A., Pizarro, M., Quintanilla, , & Cano, A. (1993). Correlation of E-cadherin expression with differentiation grade and histological type in breast carcinoma. American Journal of Pathology , 142, 987-993.

[81] Geldof, A. A. (1997). Models for cancer skeletal metastasis: A reappraisal of Batson's Plexus. *Anticancer Research*, 17, 1535-1540.

[82] Giannini, A. L., M.d, M., Vivanco, , & Kypta, R. M. (2000). Analysis of β-catenin aggregation and localization using GFP fusion proteins: nuclear import of α-catenin by the β-catenin/Tcf complex." Experimental Cell Research , 255(2), 207-220.

[83] Gomez, D. E., Alonso, D. F., Yoshiji, H., & Thorgeirsson, U. P. (1997). Tissue inhibitors of metalloproteinases: structure, regulation and biological functions. *European Journal of Cell Biology*, 74, 111-122.

[84] Goto, T., Nakano, M., Ito, S., Ehara, H., Yamamoto, N., & , T. Deguchi ((2007). Significance of an E-cadherin gene promoter polymorphism for risk and disease severity of prostate cancer in a Japanese population. Urology, 70(1), 127-30.

[85] Grady, W. M., Rajput, A., Lutterbaugh, J. D., & , S. D. Markowitz ((2001). Detection of aberrantly methylated hMLH1 promoter DNA in the serum of patients with microsatellite unstable colon cancer. Cancer Research, 61, 900-902.

[86] Graff, J. R., Herman, J. G., & Lapidus, R. G. (1995). E-cadherin expression is silenced by DNA hypermethylation in human breast and prostate carcinomas. *Cancer Research*, 5195 EOF-9 EOF.

[87] Graff, J. R., Herman, J. G., Myohanen, S., Baylin, S. B., & Vertino, P. M. (1997). Mapping Patterns of CpG Island Methylation in Normal and Neoplastic Cells Implicates Both Upstream and Downstream Regions in de Novo Methylation. Journal of Biological Chemistry , 272(35), 22322-22329.

[88] Grooteclaes, M. L., & , S. M. Frisch ((2000). Evidence for a function of CtBP in epithelial gene regulation and anoikis. Oncogene, 19, 3823-3828.

[89] Grosheva, I., M. Shtutman, M. Elbaum and A.D. Bershadsky (2001). "p120 catenin affects cell motility via modulation of activity of Rho-family GTPases: a link between cell-cell contact formation and regulation of cell locomotion." Journal of Cell Science 114: 695-707.

[90] Hajra, K. M., -S, D. Y., Chen, , & Fearon, E. R. (2002). The SLUG Zinc-finger protein represses E-cadherin in Breast Cancer. *Cancer Research*, 62, 1613-1618.

[91] Hall, C. L., Kang, S., Mac, O. A., & Dougald, E. T. Keller ((2006). Role of Wnts in Prostate Cancer Bone Metastases. Journal of Cellular Biochemistry , 97, 661-672.

[92] Hart, M., -P, J., Concordet, I., Lassot, I., Albert, R., del los, Santos. H., Durand, C., Perret, B., Rubinfeld, F., Margottin, R., Benarous, , & Polakis, P. (1999). The F-box protein β-TrCP associates with phosphorylated β-catenin and regulates its activity in the cell." Current Biology , 9, 207-210.

[93] Hazan, R. B., Kang, L., Roe, S., Borgen, P. I., & Rimm, D. L. (1997a). Vinculin is associated with the E-cadherin adhesion complex. Journal of Biological Chemistry , 272(51), 32448-32453.

[94] Hazan, R. B., Kang, L., Wooley, B. P., & Borgen, P. I. (1997b). N-cadherin promotes adhesion between invasive breast cancer cells and the stroma. *Cell Adhesion and Communication*, 4(6), 399-411.

[95] Hazan, R. B., & Norton, L. (1998). The Epidermal Growth Factor Receptor Modulates the interaction of E-cadherin with the Actin Cytoskeleton. Journal of Biological Chemistry, 273(15), 9078-9084.

[96] He, T. C., Sparks, A. B., Rago, C., Hermeking, H., Zawel, L., Da, L. T., Costa, P. J., Morin, B., Vogelstein, , & Kinzler, K. W. (1998). Identification of c-MYC as a target of the APC pathway. Science , 281, 1509-1512.

[97] He, T. C., Chan, T. A., Vogelstein, B., & Kinzler, K. W. (1999). PPARdelta is an APC-regulated target of nonsteroidal anti-inflamatory drugs." Cell , 99(3), 335-345.

[98] Heasman, J., Crawford, A., Goldstone, K., Garner-Hamrick, P., Gumbiner, B., Mc Crea, P., Kintner, C., Noro, C. Y., & Wylie, C. (1994). Overexpression of cadherins and underexpression of beta-catenin inhibit dorsal mesoderm induction in early Xenopus embryos. *Cell*, 79(5), 791-803.

[99] Hecht, A., Litterst, C. M., Huber, O., & Kemler, R. ((1999). Functional characterization of multiple transactivating elements in β-catenin, some of which interact with the TATA-binding protein in vitro."Journal of Biological Chemistry , 274, 18017-18025.

[100] Hellberg, C. B., Burden-Gulley, S. M., Pietz, G. E., & Brady-Kalnay, S. M. (2002). Expression of the receptor protein-tyrosine phosphatase, PTPm, restores E-cadherin-dependent adhesion in human prostate carcinoma cells.". Journal of Biological Chemistry , 277(13), 11165-11173.

[101] Herman, J. G., Graff, J. R., Myohanen, S., Nelkin, B. D., & Baylin, S. B. (1996). Methylation-specific PCR: A novel PCR assay for methylation status of CpG islands. Proceedings of the National Academy of Sciences , 93, 9821-9826.

[102] Hernandez-Barrantes, S., Toth, M., Bernardo, M. M., Yurkova, M., Gervasi, D. C., Raz, Y., Sang, Q. A., & Fridman, R. (2000). Binding of Active 57kDa Membrane Type 1-Matrix metalloproteinase (MT1-MMP) to tissue inhibitor of metalloproteinase (TIMP-2) regulates MT1-MMP processing and proMMP-2 activation." Journal of Biological Chemistry , 275(16), 12080-12089.

[103] Herren, B., Levkau, B., Raines, E. W., & Ross, R. (1998). Cleavage of beta-catenin and plakoglobin and shedding of VE-cadherin during endothelial apoptosis: evidence for a role for caspases and metalloproteinases. Molecular Biology Cell , 9(6), 1589-1601.

[104] Herrenknecht, K., Ozawa, M., Eckerskorn, C., Lottspeich, F., Lenter, M., & Kemler, R. (1991). The uvomorulin-anchorage protein α catenin is α vinculin homologue." Proceedings of the National Academy of Sciences , 88, 9156-9160.

[105] Hinck, L., Nathke, I. S., Papkoff, J., & Nelson, W. J. (1994). Dynamics of cadherin/catenin complex formation: novel protein interactions and pathways of complex assembly. Journal of Cell Biology , 125, 1327-1340.

[106] Hiraguri, S., Godfrey, T., Nakamura, H., Graff, J., Collins, C., Shayesteh, L., Doggett, N., Johnson, K., Wheelock, M., Herman, J., Baylin, S., Pinkel, D., & Gray, J. (1998). Mechanisms of inactivation of E-cadherin in breast cancer cell lines. *Cancer Research*, 58, 1972-1977.

[107] Hirohashi, S., & (1998).", . (1998). Inactivation of the E-cadherin-mediated cell adhesion system in human cancers. American Journal of Pathology, 153(2), 333-339.

[108] Hlubek, F., Jung, A., Kotzor, N., Kirchner, T., & Brabletz, T. (2001). Expression of the invasion factor laminin γ2 in colorectal carcinomas is regulated by β-catenin." Cancer Research , 61, 8089-8093.

[109] Hoffmann, I., & Balling, R. (1995). Cloning and expression analysis of a novel mesodermally expressed cadherin. *Developmental Biology*, 169, 337-346.

[110] Howe, L., Crawford, H. C., Subbaramaiah, K., Hassell, J. A., Dannenberg, A. J., & Brown, A. M. C. (2001). PEA3 is up-regulated in response to Wnt1 and activates the expression of cyclooxygenase-2. Journal of Biological Chemistry , 276(23), 20108-20115.

[111] Hsu, W., Zeng, L., & , F. Costantini((1999). Identification of a domain of axin that binds to the serine/threonine protein phosphatase 2A and a self-binding domain. Journal of Biological Chemistry , 274, 3439-3445.

[112] Huber, O., Korn, R., & Mc Laughlin, R. (1996). Nuclear localization of beta-catenin by interaction with transcription factor LEF-1. *Mechanisms of Development*, 3 EOF-10 EOF.

[113] Huber, O., Bierkamp, C., & , R. Kemler ((1998). Cadherins and Catenins in development. Current Opinion in Cell Biology, 8, 685-691.

[114] Huber, A.H. and W.I. Weis(2001). The structure of the β-catenin/E-cadherin complex and the molecular basis of diverse ligand recognition by β-catenin."Cell , 105, 391-402.

[115] Hulsken, J., Birchmeier, W., & Behrens, J. (1994). E-cadherin and APC compete for the interaction with β-catenin and the cytoskeleton." Journal of Cell Biology , 127, 2061-2069.

[116] Ikeda, S., Kishida, S., Yamamoto, H., , H., Murai, S., Koyama, , & Kikuchi, A. (1998). Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK3β and β-catenin and promotes GSK3β-dependent phosphorylation of β-catenin." EMBO Journal , 17(5), 1371-1384.

[117] Ilan, N., Mohsenin, A., Cheung, L., & Madri, J. A. (2001). PECAM-1 shedding during apoptosis generates a membrane-anchored truncated molecule with unique signaling characteristics. FASEB Journal, 15, 362-372.

[118] Inoue, A., & Sanes, J. R. (1997). Lamina-specific connectivity in the brain: regulation by N-cadherin, neurotrophins, and glycoconjugates. Science , 276, 1428-1431.

[119] Itoh, M., Nagafuchi, A., Moroi, S., & , S. Tsukita ((1997). Involvement of ZO-1 in cadherin-based cell adhesion through its direct binding to alpha-catenin and actin filaments. Journal of Cell Biology , 138, 181-192.

[120] Itoh, K., Krupnik, V. E., & Sokol, S. Y. (1998). Axis determination in Xenopus involves biochemical interactions of axin, glycogen synthase kinase 3 and β-catenin." Current Biology , 8, 591-594.

[121] Jacot, T. A., Striker, G. E., Stetler-Stevenson, M., & Striker, L. J. (1996). Mesangial cells from transgenic mice with progressive glomerlosclerosis exhibit stable, phenotypic changes including undetectable MMP-9 and increased type IV collagen." Laboratory Investigations , 75, 79-799.

[122] Jawhari, A. U., Farthing, M. J. G., & Pignatelli, M. (1999). The E-cadherin/Epidermal Growth Factor Receptor Interaction: A Hypothesis of Reciprocal and Reversible Control of Intercellular Adhesion and Cell Proliferation. Journal of Pathology , 187, 155-157.

[123] Jho-H, E., Zhang, T., Domon, C., -K, C., Joo-N, J., Freund, , & Costantini, F. (2002). Wnt-β-catenin/Tcf signaling induces the transcription of Axin2, a negative regulator of the signaling pathway." Molecular and Cellular Biology , 22(4), 1172-1183.

[124] Jiang, J., & , G. Struhl ((1998). Regulation of the hedgehog and wingless signaling pathways by the F-box/WD40-repeat protein slimb."*Nature.* , 391, 493-496.

[125] Joo, Y. E., Rew, J. S., Park, C. S., & Kim, S. J. ((2002). Expression of E-cadherin, alpha- and beta-catenins in patients with pancreatic adenocarcinomas."Pancreatology , 2(2), 129-137.

[126] Joseph-Silverstein, J., & Silverstein, R. L. (1998). Cell Adhesion Molecules: An Overview. *Cancer Investigation*, 16(3), 176-182.

[127] Jou, T. S., Stewart, D. B., & , J. Stappert ((1995). Genetic and biochemical dissection of protein linkages in the cadherin-catenin complex. Procedings of the National Academy of Sciences , 92, 5067-5071.

[128] Julius, M. A., Schelbert, B., Hsu, W., Fitzpatrick, E., Jho, E., Fagotto, F., Costantini, F., & Kitajewski, J. (2000). Domains of axin and disheveled required for interaction and function in Wnt signalins." Biochemical and Biophysical Research Communications , 276, 1162-1169.

[129] Kadowaki, T., Shiozaki, H., Inoue, M., Tamura, S., Oka, H., Doki, Y., Iihara, K., Matsui, S., Iwazawa, T., & Nagafuchi, A. (1994). E-cadherin and alpha-catenin expression in human esophageal cancer. *Cancer Research*, 54, 291-296.

[130] Kajita, M., Itoh, Y., Chiba, T., Mori, H., Okada, A., Kinoh, H., & Seiki, M. (2001). Membrane-tye 1 matrix metalloproteinase cleaves CD44 and promotes cell migration." Journal of Cell Biology , 153(5), 893-904.

[131] Kanamori, Y. (1999). Correlation between expression of the matrix metalloproteinase-1 gene in ovarian cancers and an insertion/deletion polmorphism in its promoter region." Cancer Research , 59, 4225-4227.

[132] Kataoka, H., Uchino, H., Iwamura, T., Seiki, M., Nabeshima, K., & , M. Koono ((1999). Enhanced tumor growth and invasiveness in vivo by a carboxyl-terminal fragment of a1-proteinase inhibitor generated by matrix metalloproteinases: a possible modulatory role in natural killer cytotoxicity." American Journal of Pathology , 154(2), 457-468.

[133] Kawahara, K., Morishita, T., Nakamura, T., Hamada, F., Toyoshima, K., & Akiyama, T. (2000). Down-regulation of β-catenin by the colorectal tumor suppressor APC requires association with axin and β-catenin." Journal of Biological Chemistry , 275(12), 8369-8374.

[134] Kawakami, K. (2000). Hypermethylated APC DNA in plasma and prognosis of patients with esophageal adenocarcinoma. Journal of National Cancer Institute , 92, 1805-1811.

[135] Kawasaki, Y., Sato, R., & Akiyama, T. (2003). Mutated APC and Asef are involved in the migration of colorectal tumour cells. *Nature Cell Biology*, 5, 211-215.

[136] Kawanishi, J., Kato, J., Sasaki, K., Fujii, S., Watanabe, N., & , Y. Niitsu ((1995). Loss of E-cadherin-dependent cell-cell adhesion due to mutation of the β-catenin gene in a human cancer cell line, HSC-39." Molecular and Cellular Biology , 15(3), 1175-1181.

[137] Kikuchi, A. (1999). Roles of axin in the Wnt signaling pathway.". Cell Signaling , 11(11), 777-788.

[138] Kikuchi, A. (2000). Regulation of beta-catenin signaling in the Wnt pathway. *Biochemical and Biophysical Research Communications*, 268(2), 243-248.

[139] Kimura, Y., Matsunami, H., Inoue, T., Shimamura, K., Uchida, N., Ueno, T., & , T. Miyazaki and M.Takeichi ((1995). Cadherin 11 Expressed in association with mesenchymal morphogenesis in the head, somite, and limb bud of early mouse embryos." Developmental Biology, 169, 347-358.

[140] Kitagawa, M., Hatekeyama, S., Shirane, M., Matsumoto, M., Ishida, N., Hatori, K., Nakamichi, I., Kikuchi, K., & Nakayama, K. (1999). An F-box protein, FWD1, mediates ubiquitin-dependent proteolysis of beta-catenin." EMBO Journal , 18, 2401-2410.

[141] Knudsen, K., & Wheelock, M. (1992). Plakoglobin, or an 83-kDa homologue distinct from β-catenin, interacts with E-cadherin and N-cadherin." Journal of Cell Biology , 118, 671-679.

[142] Knudsen, K. A., Solar, A. P., Johnson, K. R., & , M. J. Wheelock ((1995). Interaction of alpha-actinin with the cadherin/catenin cell-cell adhesion complex via alpha-catenin. Journal of Cell Biology , 130, 67-77.

[143] Koch, A. W., Bozic, D., Pertz, O., & , J. Engel ((1999). Homophilic adhesion by cadherins. Current Opinion in Structural Biology, 9(2), 275-281.

[144] Kodama, S., Ikeda, S., Asahara, T., Kishida, M., & Kikuchi, A. (1999). Axin directly interacts with plakoglobin and regulates its stability. Journal of Biological Chemistry , 274(39), 27682-27688.

[145] Kolligs, F. T., Kolligs, B., Hajra, K. M., Hu, G., Tani, M., Cho, K. R., & Fearon, F. R. (2000). Gamma-catenin is regulated by the APC tumor suppressor and its oncogenic activity is distinct from that of β-catenin." Genes and Development , 14(11), 1319-1331.

[146] Kolligs, F. T., Nieman, M. T., Winer, I., Hu, G., Van Mater, D., Feng, Y., Smith, I. M., Wu, R., Zhai, Y., Cho, K. R., & Fearon, E. R. (2002). ITF-2, a downstream target of the Wnt/TCF pathway, is activated in hum. an cancers with beta-catenin defects and promotes neoplastic transformation." Cancer Cell , 1(2), 145-155.

[147] Korinek, V., Barker, N., Morin, P. J., Van Wichen, D., de Weger, R., Kinzler, K. W., Vogelstein, B., & Clevers, H. (1997). Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma. Science , 275, 1784-1787.

[148] Koshikawa, N. G., Giannelli, V., Cirulli, K., Miyazaki, , & , V. Quaranta ((2000). Role of cell surface metalloprotease MT-MMP in epithelial cell migration over laminin-5." Journal of Cell Biology , 148(3), 615-624.

[149] Kowalczyk, A. P., Palka, H. L., Luu, H. H., Nilles, L. A., Anderson, J. E., Wheelock, M. J., & , K. J. Green ((1994). Posttranslational regulation of plakoglobin expression. Influence of the desmosomal cadherins on plakoglobin metabolic stability. Journal of Biological Chemistry , 269, 31214-31223.

[150] Kraus, C., T. Liehr, J. Hulsken, J. Behrens, W. Birchmeier, K.-H.Grzeschik and W.G. Ballhausen (1994). "Localization of the human ▪ -catenin gene (CTNNB1) to 3p21: A region implicated in tumor development." Genomics 23: 272-274.

[151] Kuczyk, M., Serth, J., Machtens, S., Bokemeyer, C., Bathke, W., Stief, C., & Jonas, U. (1998). Expression of E-cadherin in primary prostate cancer: correlation with clinical features." British Journal of Urology , 81, 406-412.

[152] Larue, L., Ohsugi, M., Hirchenhain, J., & Kemler, R. (1994). E-cadherin null mutant embryos fail to form a trophectoderm epithelium." Procedings of the National Academy of Sciences , 91, 8263-8267.

[153] Latres, E., Chiaur, D. S., & Pagano, M. (1999). The human F box protein β-Trcp associates with the Cul1/Skp1 complex and regulates the stability of β-catenin." Oncogene , 18(4), 849-854.

[154] Lehr, J.E. and K.J. Pienta(1998). Preferential adhesion of prostate cancer cells to a human bone marrow endothelial cell line." Journal of National Cancer Institute, 90, 118-23.

[155] Lejeune, S., Huguet, E. L., Hamby, A., Poulson, R., Haris, A. L., & (1995).", . (1995). Wnt5a cloning, expression, and up-regulation in human primary breast cancers." Clinical Cancer Research , 1(2), 215-222.

[156] Lelongt, B., Trugnan, G., Murphy, G., & Ronco, P. M. (1997). Matrix metalloproteinases MMP2 and MMP9 are produced in earl stages of kidney morphogenesis but only MMP9 is required for renal organogenesis in vitro." Journal of Cell Biology , 136, 1363-1373.

[157] Leung, J. Y., Kolligs, F. T., Wu, R., Zhai, Y., Kuick, R., Hanash, S., Cho, K. R., & , E. R. Fearon ((2002). Activation of AXIN2 expression by beta-catenin-T cell factor.A feed-

back repressor pathway regulating Wnt signaling." Journal of Biological Chemistry , 277(24), 21657-21665.

[158] Li-C, L., Zhao, H., Nakajima, K., Oh, B. R., Filho, L. A. R., Carroll, P., & Dahiya, R. (2001). Methylation of the E-cadherin gene promoter correlates with progression of prostate cancer." Journal of Urology , 166, 705-709.

[159] Libby, P. (1995). Molecular bases of the acute coronary syndromes." Circulation , 91, 2844-2850.

[160] Lickert, H., Bauer, A., Kemler, R., & Stappert, J. (2000). Casein Kinase II Phosphorylation of E-cadheirn increases E-cadherin/β-catenin interaction and strengthens cell-cell adhesion." Journal of Biological Chemistry , 275(7), 5090-5095.

[161] Lim, S. C., & , M. S. Lee ((2002). Significance of E-cadherin/beta-catenin and cyclin D1 in breast cancer." Oncology Reports , 9(5), 915-28.

[162] Lin-M, Y., Ono, K., Satoh, S., Ishiguro, H., Fujita, M., Miwa, N., Tanaka, T., Tsunoda, T., , K., Yang, C., Nakamura, Y., & , Y. Furukawa ((2001). Identification of AF17 as a downstream gene of the β-catenin/T-Cell Factor pathway and its involvement in colorectal carcinogenesis." Cancer Research , 61, 6345-6349.

[163] Liotta, L. A., Rao, C. N., & , S. H. Barskey ((1983). Tumor invasion by the extracellular matrix." Lab Investigation , 49, 636-649.

[164] Liu, Z., Shipley, J. M., Vu, T. H., Zhou, X., Diaz, L. A., Werb, Z., & Senior, R. M. (1998). Gelatinase B-deficient mice are resistant t experimental bullous pemphigoid." Journal of Experimental Medicine , 188, 475-482.

[165] Liu, W., Dong, X., Mai, M., Seelan, R. S., Taniguchi, K., Krishnadath, K. K., Halling, K. C., Cunningham, J. M., Boardman, L. A., Qian, C., Christensen, E., Schmidt, S. S., Roche, P. C., Smith, D. I., & Thibodeau, S. N. (2000). Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating beta-catenin/TCF signaling." Nature Genetics , 26(2), 146-147.

[166] Liu, C., Li, Y., Semenov, M., Han, C., Baeg, G. H., Tan, Y., Zhang, Z., Lin, X., & , X. He ((2002). Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism."Cell , 108, 837-847.

[167] Llano, E. (1999). Identification and characterization of human MT5-MMP, a new membrane-bound actiator of progelatinase A overexpressed in brain tumors." Cancer Research , 59, 2570-2576.

[168] Lochter, A., Galosy, S., Muschler, J., Freedman, N., Werb, Z., & Bissell, M. J. (1997). Matrix metalloproteinase stromelysin-1 triggers a cascade of molecular alterations that leads to stable epithelial-to-mesenchymal conversion and a remalignant phenotype of mammary epithelial cells." Journal of Cell Biology , 139(7), 1861-1872.

[169] Loric, S., Paradis, V., , J., Gala, L., Berteau, P., Bedossa, P., Benoit, G., & Eschwege, P. (2001). Abnormal E-cadherin expression and prostate cell blood dissemination as

markers of biological recurrence in cancer." European Journal of Cancer , 37, 1475-1481.

[170] Lund, L. R., Romer, J., Thomasset, N., Solberg, H., Pyke, C., Bissell, M. J., Dano, K., & Werb, Z. (1996). Two distinct phases of apoptosis in mammary gland involution: Proteinase-independent and dependent pathways." Development , 122, 181-193.

[171] Luo, J., Lubaroff, D. M., & , M. J. C. Hendrix ((1999). Suppression of Prostate Cancer Invasive Potential and Matrix Metalloproteinase Activity by E-cadherin Transfection."Cancer Research , 59, 3552-3556.

[172] Lustig, B., Jerchow, B., Sachs, M., Weiler, S., Pietsch, T., Karsten, U., van de Wetering, M., Clevers, H., Schlag, P. M., Birchmeier, W., & Behrens, J. (2002). Negative feedback loop of Wnt signaling through upregulation of conductin/axin2 in colorectal and liver tumors." Molecular and Cellular Biology , 22(4), 1184-1193.

[173] Mac, Naul. K. L., Chartrain, N., Lark, M., Tocci, M. J., & Hutchinson, N. I. (1990). Discordinate expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases-1 in rheumatoid human synovial fibroblasts: synergistic effects of interlekin-1 and tumor necrosis factor-a on stromelysin expression." Journal of Biological Chemistry , 265, 17238-17245.

[174] Mann, B., Gelos, M., Siedow, A., Hanski, M. L., Gratchev, A., Ilyas, M., Bodmer, W. F., Moyer, M. P., Riecken, E. O., Buhr, H. J., & Hanski, C. (1999). Target genes of β-catenin-T cell-factor/lymphoid-enhancer factor signaling in human colorectal carcinomas." Procedings of the National Academy of Sciences, 96, 1603-1608.

[175] Marie, P.J(2002). Role of N-cadherin in Bone Formation." Journal of Cellular Physiology , 190, 297-305.

[176] Mariner, D.J., J. Wang and A.B. Reynolds (2000). "ARVCF localizes to the nucleus and adherens junction and is mutually exclusive with p120(ctn) in E-cadherin complexes." Journal of Cell Science 113(Pt 8): 1481-90.

[177] Mariner, D.J., P. Anastasiadis, H. Keilhack, F-D., Bohmer, J. Wang, and A.B. Reynolds (2001). "Identification of Src Phosphorylation sites in the catenin p120." Journal of Biological Chemistry 276(30): 28006-28013.

[178] Mason, M. D., Davies, G., & , W. G. Jiang ((2002). Cell adhesion molecules and adhesion abnormalities in prostate cancer."Critical Reviews in Oncology/Hematology , 41, 11-28.

[179] Mathur, M., Goodwin, L., & Cowin, P. (1994). Interactions of the cytoplasmic domain of the desmosomal cadherin Dsg1 with plakoglobin."Journal of Biological Chemistry , 269, 14075-14080.

[180] Matrisian, L.M. and B.L.M. Hogan(1990). Growth factor regulated proteases and extracellular matrix remodeling during mammalian development." Current Topics in Developmental Biology , 24, 219-259.

[181] Matsunaga, M., Hatta, K., Nagafuchi, A., & , M. Takeichi ((1988). Guidance of optic nerve fibres by N-cadherin adhesion molecules."Nature , 334, 62-64.

[182] Mattijssen, V., Peters, H. M., Schalkwijk, L., Manni, J. J., van Hof-Grootenboer, B., & , P. H. de Mulder and D.J. Ruiter ((1993). E-cadherin expression in head and neck squamous-cell carcinoma is associated with clinical outcome." International Journal of Cancer , 55(4), 580-585.

[183] Mc Crea, P. D., Turck, C. W., & Gumbiner, B. (1991). A homolog of the armadillo protein in Drosohila (plakoglobin) associated with E-cadherin." Science , 254, 1359-1361.

[184] Mc Kendry, R., Hsu, S. C., Harland, R. M., & Grosschedl, R. (1997). LEF-1/TCF proteins mediate wnt-inducible transcription from the Xenopus nodal-related 3 promoter." Developmental Biology , 192, 420-431.

[185] Mertens, C., Kuhn, C., Moll, R., Schwetlick, I., & , W. W. Franke ((1999). Desmosomal plakophilin 2 as a differentiation marker in normal and malignant tissues."Differentiation , 64, 277-290.

[186] Miller, J.R. and R.T. Moon(1996). Signal transduction through beta-catenin and specification of cell fate during embrogenesis." Genes and Development , 10, 2527-2539.

[187] Miravet, S., Piedra, J., Miro, F., Itarte, E., & , A. G. de Herreros and M. Dunach ((2002). The transcriptional factor Tcf-4 contains different binding sites for β-catenin and plakoglobin." Journal of Biological Chemistry , 277(3), 1884-1891.

[188] Mitsiades, N., , W., Yu, H., Poulaki, V., Tsokos, M., & Stamenkovic, I. (2001). Matrix metalloproteinase-7-mediated cleavage of fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity." Cancer Research , 61, 577-581.

[189] Mizushima, T., Nakagawa, H., Kamberov, Y. G., Wilder, E. L., Klein, P. S., & Rustgi, A. K. (2002). Wnt-1 but not Epidermal Growth factor induces β-catenin/T-Cell factor-dependent transcription in Esophageal Cancer Cells." Cancer Research , 62, 277-282.

[190] Mol, , , A. J. M., Gelfof, A. A., Meijer, G. A., & , H. G. van der Poel and R.J.A. van Moorselaar ((2007). New experimental markers for early detection of high-risk prostate cancer: role of cell-cell adhesion and cell-migration." Journal of Cancer Research and Clinical Oncology , 133(10), 687-695.

[191] Moll, R., Mitze, M., Frixen, U. H., & , W. Birchmeier ((1993). Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas." American Journal of Pathology , 143, 1731-1742.

[192] Moon, R. T., & , D. Kimelman ((1998). From cortical rotation to organizer gene expression, toward a molecular explanation of axis specification in Xenopus."Bioessays , 20, 536-545.

[193] Morin, P., Sparks, A., Korinek, V., Barker, N., Clevers, H., Vogelstein, B., & Kinzler, K. (1997). Activation of β-catenin-Tcf signaling in colon cancer by mutations in β-catenin or APC."Science , 275, 1787-1790.

[194] Morton, R. A., Ewing, C. M., Nagafuchi, A., Tsukita, S., & , W. B. Isaacs ((1993). Reduction of E-cadherin levels and deletion of the α-catenin gene in human prostate cancer cells."Cancer Research , 53, 3585-3590.

[195] Moustafa-E, A., Yansouni, D., Alaoui-Jamali, M. A., & O'Connor Mc, M. O'Connor-McCourt ((1999). Up-Regulation of E-Cadherin by an Anti-Epidermal Growth Factor Receptor Monoclonal Antibody in Lung Cancer Cell Lines."Clinical Cancer Research , 5, 681-686.

[196] Mulholland, D. J., Cheng, H., Reid, K., Rennie, P. S., & Nelson, C. C. (2002). The Androgen Receptor can promote β-catenin nuclear translocation." Journal of Biological Chemistry , 277(20), 17933-17943.

[197] Mundy, G. R. (2002). Metastasis to bone: causes, consequences and therapeutic opportunities." Nature Reviews Cancer , 2, 584-593.

[198] Murphy, G., , F., Willenbrock, R. V., Ward, M. I., Cockett, D., Eaton, D., & Docherty, A. J. P. (1992). The C-terminal domain of 72 kDa gelatinase A is not required for catalysis, but is essential for membrane activation and modulates interactions with tissue inhibitors of metalloproteinases." Biochemistry Journal , 283, 637-641.

[199] Nagase, H., Woessner, J. F., & Jr , . (1999). Matrix Metalloproteinases."Journal of Biological Chemistry , 274(31), 21491-21494.

[200] Nathke, I. S., Hinck, L., Swedlow, J. R., Papkoff, J. R., & , W. J. Nelson ((1994). Defining interactions and distributions of cadherin and catenin complexes in polarized epithelial cells." Journal of Cell Biology , 125, 1341-1352.

[201] Navarro, P., Lozano, E., & Cano, A. (1993). Expression of E- or P-cadherin is not sufficient to modify the morphology and the tumorigenic behavior of murine spindle carcinoma cells." Journal of Cell Science , 105, 923-934.

[202] Nieset, J., Redfield, A., Jin, F., Knudsen, K., , K., Johnson, M., & Wheelock, . (1997). Characterization of the interactions of alpha-catenin with alpha-catenin and beta-catenin/plakoglobin."Journal of Cell Science , 110, 1013-1022.

[203] Noe, V., Chastre, E., Bruyneel, E., Gespach, C., & Mareel, M. (1999). Extracellular regulation of cancer invasion: the E-cadherin-catenin and other pathways." Biochemical Society Symposium , 65, 43-62.

[204] Noe, V., Fingleton, B., Jacobs, K., Crawford, H. C., Vermeulen, S., Steelant, W., Bruyneel, E., Matrisian, L. M., & Mareel, M. (2001). Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1." Journal of Cell Science, 114, 111-118.

[205] Noren, N.K., B.P. Liu, K. Burridge and B. Kreft (2000). "P120 Catenin regulates the actin cytoskeleton via Rho family GTPases." Journal of Cell Biology 150:567-580.

[206] Norman, J. T., Gatti, L., Wilson, P. D., & , M. Lewis ((1995). Matrix metalloproteinases and tissue inhigitor of matrix metalloproteinases expression by tubular epithelia and

interstitial fibroblasts in the normal kidney and in fibrosis."Experimental Nephrology , 3, 88-89.

[207] Novak, A., Hsu, S. C., Leung-Hagesteijn, C., Radeva, G., Papkoff, J., Montesano, R., Roskelley, C., Grosschedl, R., & Dedhar, S. (1998). Cell adhesion and the integrin-linked kinase regulate the LEF-1 and beta-catenin signaling pathways." Proceedings of the National Academy of Sciences , 95(8), 4374-4379.

[208] Novak, A. and S. Dedhar (1999)."Signaling through beta-catenin and Lef/Tcf."Cellular and Molecular Life Sciences 56(5-6): 523-537.

[209] Nawrocki-Raby, B., Gilles, C., Polette, M., Martinella-Catusse, C., Bonnet, N., Puchelle, E., , J., Foidart, M., & , F. van Roy and P. Birembaut ((2003). E-cadherin mediates MMP down-regulation in highly invasive bronchial tumor cells. "American Journal of Pathology , 163(2), 653-661.

[210] Nutt, J. E., & , J. Lunec ((1996). Induction of metalloproteinase (MMP-1) expression by epidermal growth factor (EGF) receptor stimulation and serum deprivation in human breast tumour cells."European Journal of Cancer 32A: , 2127-2135.

[211] Nutt, J. E., Mellon, J. K., Qureshi, K., & Lunec, J. (1998). Matrix Metalloproteinase-1 is induced by epidermal growth factor in human bladder tumour cell lines and is detectable in urine of patients with bladder tumours." British Journal of Cancer , 78(2), 215-220.

[212] Nwomeh, B. C., , H., Liang, X., Cohen, I. K., & Yager, D. R. (1999). MMP-8 is the predominant collagenase in healing wounds and nonhealing ulcers." Journal of Surgical Research , 81, 189-195.

[213] Oesterling, J., Fuks, Z., Lee, C. T., & , H. L. Scher ((1997). Cancer of the prostate. In: Devita, Hellman, Rosenberg eds. Cancer Principles and Practice of Oncology Philadelphia: lippincott-Raven , 2, 1322-1386.

[214] Ohkubo, T and M. Ozawa (1999). "$P120^{ctn}$ binds to the membrane-proximal region of the E-cadherin cytoplasmic domain and is involved in modulation of Adhesion activity." Journal of Biological Chemistry 274(30): 21409-21415.

[215] Ohsugi, M. L., Larue, H., Schwarz, , & , R. Kemler ((1997). Cell-junctional and cytoskeletal organization in mouse blastocysts lacking E-cadherin." Developmental Biology , 185, 261-271.

[216] Oka, H., Shiozaki, H., Kobayashi, K., Inoue, M., Tahara, H., Kobayashi, T., Takatsuka, Y., Matsuyoshi, N., & , S. Hirano and M.Takeichi ((1993). Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis." Cancer Research , 53, 1696-1701.

[217] Orsulic, S., Huber, O., Aberle, H., Arnold, S., & Kemler, R. (1999). E-cadherin binding prevents beta-catenin nuclear localization and beta-catenin/LEF-1-mediated transactivation." Journal of Cell Science , 112(8), 1237-1245.

[218] Oyama, T., Kanai, Y., Ochiai, A., Akimoto, S., Oda, T., Yanagihara, K., Nagafuchi, A., Tsukita, S., Shibamoto, S., & Ito, F. (1994). A truncated beta-catenin disrupts the interaction between E-cadherin and alpha-catenin: a cause of loss of intercellular adhesiveness in human cancer cell lines." Cancer Research , 54, 6282-6287.

[219] Ozawa, M., Baribault, H., & Kemler, R. (1989). The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species." EMBO Journal , 8, 1711-1717.

[220] Ozawa, M., & , R. Kemler ((1998). Altered Cell Adhesion Activity by Pervanadate Due to the Dissociation of α-Catenin from the E-cadherin-Catenin Complex."Journal of Biological Chemistry , 273(11), 6166-6170.

[221] Ozawa, M. (2002). Lateral Dimerization of the E-cadherin extracellular domain is necessary but not sufficient for adhesive activity." Journal of Biological Chemistry , 277(22), 19600-19608.

[222] Pajouh, M. S., Nagle, R. B., Breathnach, R., Finch, J. S., Brawer, M. K., & , G. T. Bowden ((1991). Expression of metalloproteinase genes in human prostate cancer."Journal of Cancer Research and Clinical Oncology , 117(2), 144-150.

[223] Palacios, J., Benito, N., Pizarro, A., , A., Suarez, J., Espada, A., Cano, , & Gamallo, C. (1995). Anamalous expression of P-cadherin in breast carcinoma. Correlation with E-cadherin expression and pathological features."American Journal of Pathology , 146, 605-612.

[224] Pan, Y., Matsuyama, H., Wang, N., Yoshihiro, S., Haggarth, L., Li, C., Tribukait, B., Ekman, P., & Bergerheim, U. S. R. (1998). Chromosome 16q24 Deletion and decreased E-cadherin expression: possible association with metastatic potential in prostate cancer." Prostate , 36, 31-38.

[225] Parr, B. A., & Mc , A. P. McMahon ((1994). Wnt genes and vertebrate development."Current Opinion in Genetics and Development , 4(4), 523-528.

[226] Pei, D. (1999). Identification and characterization of the fifth membrane-type matrix metalloproteinase MT5-MMP."Journal of Biological Chemistry , 274(13), 8925-8932.

[227] Peifer, M., Mc Crea, P. D., Green, K. J., Wieschaus, E., & Gumbiner, B. M. (1992). The vertebrate adhesive junction proteins β-catenin and plakoglobin and the Drosophila segment polarity gene armadillo form a multigene family with similar properties." Journal of Cell Biology , 118, 681-691.

[228] Peifer, M., Berg, S., & Reynolds, A. B. (1994). A repeating amino acid motif shared by proteins with diverse cellular roles." Cell , 76, 789-791.

[229] Peifer, M., & , P. Polakis ((2000). Wnt signaling in oncogenesis and embryogenesis-a look outside the nucleus."Science , 287, 1606-1609.

[230] Perez-Moreno, M. A., Locasciao, A., Rodrigo, I., Dhondt, G., Portillo, F., Nieto, M. A., Cano, A., & (2001)."", . (2001). A new role for E12/E47 in the repression of E-cadherin

expression and epithelial-mesenchymal transitions."Journal of Biological Chemistry , 276, 27424-27431.

[231] Pertz, O., Bozic, D., Koch, A. W., Fauser, C., Brancaccio, A., & Engel, J. (1999). A new crystal structure, Ca2+ dependence and mutational analsis reveal molecular details of E-cadherin homoassociation." EMBO Journal , 18(7), 1738-47.

[232] Piedra, J., Martinez, D., Castano, J., Miravet, S., Dunach, M., & , G. Garcia de Herreros ((2001). Regulation of β-catenin structure and activity by tyrosine phosphorylation."Journal of Biological Chemistry , 276(23), 20436-20443.

[233] Pignatelli, M., Ansari, T. W., Gunter, P., Liu, D., Hirano, S., Takeichi, M., Kloppel, G., & Lemoine, N. R. (1994). Loss of membranous E-cadherin expression in pancreatic cancer: correlation with lymph node metastasis, high grade, and advanced stage." Journal of Pathology , 174(4), 243-248.

[234] Pishvaian, M. J., Feltes, C. M., Thompson, P., Bussemakers, M. J., Schalken, J. A., & Byers, S. W. (1999). Cadherin 11 is expressed in invasive breast cancer cell lines." Cancer Research , 59, 947-952.

[235] Pokutta, S., Drees, F., Takai, Y., Nelson, W. J., & , W. I. Weis ((2002). Biochemical and structural definition of the 1-afadin- and actin-binding sites of α-catenin."Journal of Biological Chemistry , 277(21), 18868-18874.

[236] Polakis, P. (1999). The oncogenic activation of beta-catenin."Current Opinion in Genetics , 9, 15-21.

[237] Polakis, P. (2000). Wnt signaling and cancer." Genes and Development , 14, 1837-1851.

[238] Polakis, P. (2001). More than one way to skin a catenin."Cell , 105(5), 563-566.

[239] Polakis, P. (2002). Casein Kinase 1: a Wnt'er of disconnect." Current Biology 12: RR501., 499.

[240] Polette, M., & , P. Birembaut ((1998). Membrane-type metalloproteinases in tumor invasion."International Journal of Biochemistry and Cell Biology , 30(11), 1195-1202.

[241] Powell, W. C., Knox, J. D., Navre, M., Grogan, T. M., Kittelson, J., Nagle, R. B., & Bowden, G. T. (1993). Expression of the metalloproteinase matrilysin in DU145 cells increases their invasive potential in severe combined immunodeficient mice." Cancer Research , 53, 417-422.

[242] Powell, W. C., Fingleton, B., Wilson, C. L., Boothby, M., & Matrisian, L. M. (1999). The metalloproteinase matrilysin proteolytically generates active soluble fas ligand and potentiates epithelial cell apoptosis." Current Biology , 9, 1441-1447.

[243] Price, J. T., Tiganis, T., Agarwal, A., Djakiew, D., & Thompson, E. W. (1999). Epidermal Growth Factor Promotes MDA-MB-231 Breast Cancer Cell Migration through a Phosphatidylinositol 3'-Kinase and Phospholipase C-dependent Mechanism." Cancer Research , 59, 5475-5478.

[244] Prokhortchouk, A., B. Hendrich, H. Jorgensen, A. Ruzov, M. Wilm, G. Georgiev, A. Bird and E. Prokhortchouk (2001). "The p120 catenin partner kaiso is a DNA methylation-dependent transcriptional repressor." Genes and Development 15: 1613-1618.

[245] Puente, X. S., Pendas, A. M., Llano, E., Velasco, G., & Lopez, C. Lopez-Otin ((1996). Molecular cloning of a novel membrane-type matrix metalloproteinase from a human breast carcinoma." Cancer Research, 56, 944-949.

[246] Rasbridge, S. A. C. E., Gillett, S. A., Sampson, F. S., Walsh, R. R., & Millis, . (1993). Epithelial (E-) and placental (P-) cadherin cell adhesion molecule expression in breast carcinoma." Journal of Pathology , 169(2), 245-250.

[247] Ratnikov, B. I., Rozanov, D. V., Postnova, T. I., Baciu, P. G., Zhang, H., Di Scipio, R. G., Chestukhina, G. G., Smith, J. W., Deryugina, E. I., & Strongin, A. Y. (2002). An alternative processing of integrin av subuit in tumor cells by membrane type-1 matrix metalloproteinase." Journal of Biological Chemistry , 277(9), 7377-7385.

[248] Reima, I. E., Lehtonen, I., & Virtanen, J. E. Flechon ((1993). The cytoskeleton and associated proteins during cleavage, compaction and blastocyst differentiation in the pig." Differentiation , 54(1), 34-45.

[249] Reynolds, A.B., L. Herbert, J.L. Cleveland, S.T. Berg and J.R. Gaut (1992). "P120, a novel substrate of protein tyrosine kinase receptors and of p60v-src, is related to cadherin-binding factors beta-catenin, plakoglobin and armadillo." Oncogene 7: 2439-2445.

[250] Reynolds, A.B., N.A. Jenkins, D.J. Gilbert, N.G. Copeland, D.N. Shapiro, J.Wu and J.M. Daniel (1996). "The gene encoding p120cas, a novel catenin, localizes on human chromosome 11q11 (CTNND) and mouse chromosome 2 (Catns)." Genomics 31(1): 127-9.

[251] Reynolds, A.B., and J.M. Daniel (1997). "$P120^{ctn}$, a Src-substrate turned catenin." In P. Cowin and M. Klymkowsky (ed.), Cytoskeletal-membrane interactions and signal transduction,vol. 3. Georgetown: Landes Bioscience, p31.

[252] Riehl, R., Johnson, K., Bradley, R., Grunwald, G. B., Cornel, E., Lilienbaum, A., & Holt, C. E. (1996). Cadherin function is required for axon outgrowth in retinal ganglion cells in vivo." Neuron , 17, 837-848.

[253] Rimm, D.L. and J.S. Morrow(1994). Molecular Cloning of Human E-cadherin Suggests a Novel Subdivision of the Cadherin Superfamily." Biochemical and Biophysical Research Communications , 200(3), 1754-1761.

[254] Roczniak-Ferguson, A. and A.B. Reynolds (2003)."Regulation of p120-catenin nucleocytoplasmic shuttling activity."Journal of Cell Science 116: 4201-4212.

[255] Roose, J., Huls, G., Van Beest, M., Moerer, P., Van der Horn, K., Goldschmeding, R., Logtenberg, T., & Clever, H. (1999). Synergy between tumor suppressor APC and the beta-catenin-Tcf target Tcf1." Science , 285, 1923-1926.

[256] Ross, J. S., Figge, H. L., & Bui, H. X. (1994). E-cadherin expression in prostatic carcinoma biopsies: correlation with tumor grade, DNA content, pathologic stage, and clinical outcome." Modern Pathology 7: 835.

[257] Roura, S., Miravet, S., Piedra, J., & , A. Garcia de Herreros and M. Dunach ((1999). Regulation of E-cadherin/catenin association by tyrosine phosphorylation."Journal of Biological Chemistry , 274, 36734-36740.

[258] Rozanov, D. V., Ghebrehiwet, B., Postnova, T. I., Eichinger, A., Deryugina, E. I., & Strongin, A. Y. (2002). The hemopexin-like C-terminal domain of membrane type 1 matrix metalloproteinase regulates proteolysis of a multifunctional protein, gC1qR." Journal of Biological Chemistry , 277(11), 9318-9325.

[259] Rubinfeld, B., Robbins, P., El -Gamil, M., Albert, I., Porfiri, E., & , P. Polakis ((1997). Stabilization of β-catenin by genetic defects in melanoma cell lines."Science , 275, 1790-1792.

[260] Sacco, P. A., Mc Granahan, T. M., Wheelock, M. J., & Johnson, K. R. (1995). Identification of plakoglobin domains required for association with N-cadherin and alpha-catenin." Journal of Biological Chemistry , 270, 20201-20206.

[261] Sadot, E., Simcha, I., Shtutman, M., Ben-Ze'ev, A., & , B. Geiger ((1998). Inhibition of β-catenin-mediated transactivation by cadherin derivatives."Proceedings of the National Academy of Sciences , 95, 15339-15344.

[262] Sakuragi, N., Nishiya, M., Ikeda, K., Ohkouch, T., Furth, E. E., Hareyama, H., Satoh, C., & Fujimoto, S. (1994). Decreased E-cadherin expression in endometrial carcinoma is associated with tumor dedifferentiation and deep myometrial invasion." Gynecologic Oncology, 53, 183-189.

[263] Sanchez-Cespedes, M., Esteller, M., Wu, L., Nawroz-Danish, H., Yoo, G. H., Koch, W. M., Jen, J., Herman, J. G., & Sidransky, D. (2000). Gene promoter hypermethlation in tumors and serum of head and neck cancer patients."Cancer Research , 60, 892-895.

[264] Sasahara, R. M., Brochado, S. M., Takahashi, C., Oh, J., Maria-Engler, S. S., Granjeiro, J. M., Noda, M., & Sogayar, M. C. (2002). Transcriptional control of the RECK metastasis/angiogenesis suppressor gene." Cancer Detection and Prevention , 26(6), 435-443.

[265] Sato, H., Kinoshita, T., Takino, T., Nakayama, K., & Seiki, M. (1996). Activation of a recombinant membrane type-1 matrix metalloproteinase (MT1-MMP) by furin and its interaction with tissue inhibitor of metalloproteinases (TIMP-2)" FEBS Letter , 393, 101-104.

[266] Satoh, S., Daigo, Y., Furukawa, Y., Kato, T., Miwa, N., Nishiwaki, T., Kawasoe, T., Ishiguro, H., Fuita, M., Tokino, T., & (2000).", A. X. I. (2000). AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1." Nature Genetics , 24, 245-250.

[267] Schafer, S., Stumpp, S., & , W. W. Franke ((1996). Immunological identification and characterization of the desmosomal cadherin Dsg2 in coupled and uncoupled epithelial cells and in human tissues."Differentiation , 60, 99-108.

[268] Schaefer, L., X. Han, C. August, F. Matzkies, T. Lorenz and R.M. Schaefer (1997)."Differential regulation of glomerular gelatinase B (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in obese Zucker rats."Diabetologia 40: 1035-1043.

[269] Schnittler, H., & , J. (1998). Structural and functional aspects of intercellular junctions in vascular endothelium."Basic Research Cardiology , 93, 30-39.

[270] Sehgal, G., Hua, J., Bernhard, E. J., Sehgal, I., Thompson, T. C., & , R. J. Muschel ((1998). Requirement for matrix metalloproteinase-9 (Gelatinase B) expression in metastasis by murine prostate carcinoma."American Journal of Pathology , 152(2), 591-596.

[271] Shan, W.S., A. Koch, J. Murray, D.R. Colman and L. Shapiro (1999)."The adhesive binding site of cadherins revisted."Biophysical Chemistry 82(2-3): 157-163.

[272] Sheu, B.-C., S-M.Hsu, H-N. Ho, H-C. Lien, S-C Huang, and R-H.Lin (2001)."A novel role of metalloproteinase in cancer-mediated immunosuppression." Cancer Research 61: 237-242.

[273] Shibata, T., Ochiai, A., Gotoh, M., Machinami, R., & Hirohashi, S. (1996). Simultaneous expression of Cadherin 11 in signet-ring cell carcinoma and stromal cells of diffuse-type gastric cancer."Cancer Letter , 99, 147-153.

[274] Shimizu, H., Julius, M. A., Giarre, M., Zheng, Z., Brown, A. M., & Kitajewski, J. (1997). Transformation by Wnt family proteins correlates with regulation of beta-catenin." Cell Growth and Differentiation , 8, 1349-1358.

[275] Shino, Y., Watanabe, A., Yamada, Y., Tanase, M., Yamada, T., Matsuda, M., Yamashita, J., Tatsumi, M., Miwa, T., & , H. Nakano ((1995). Clinicopathologic evaluation of immunohistochemical E-cadherin expression in human gastric carcinomas."Cancer , 76(11), 2193-2201.

[276] Shtutman, M., Zhurinsky, J., Simcha, I., Albanese, C., D'Amico, M., Pestell, R., & Ben, A. Ben-Ze'ev ((1999). The cyclin D1 gene is a target of the beta-catenin/Lef1 pathway." Proceedings of the National Academy of Sciences , 96, 5522-5527.

[277] Sidransky, D. (2002). Emerging Molecular Markers of Cancer."Nature Reviews Cancer , 2(3), 210-219.

[278] Simcha, I., Shtutman, M., Salomon, D., Zhurinsky, J., Sadot, E., Geiger, B., & Ben-Ze'ev, A. (1998). Differential nuclear translocation and transactivation potential of beta-catenin and plakoglobin." Journal of Cell Biology , 141, 1433-1448.

[279] Slagle, B. L., Zhou, Y. Z., Birchmeier, W., & , K. A. Scorsone ((1993). Deletion of the E-cadherin gene in hepatitis B virus-positive Chinese hepatocellular carcinomas." Hepatology , 18(4), 757-762.

[280] Soos, G., Jones, R. F., Haas, G. P., & Wang, C. Y. (1997). Comparative intraosseal growth of human prostate cancer cell lines LNCaP and PC-3 in the nude mouse." Anticancer Research, 17, 4253-4258.

[281] Staddon, J.M., C. Smales, C. Schulze, F.S. Esch and L.L. Rubin (1995)."p120, a p120-related protein (p100), and the cadherin/catenin complex."Journal of Cell Biology 130(2): 369-381.

[282] Stappert, J., & Kemler, R. (1994). A short core region of E-cadherin is essential for catenin binding and is highly phosphorylated." Cell Adhesion and Communication , 2(4), 319-327.

[283] Steffensen, B., Wallon, U. M., & Overall, C. M. (1995). Extracellular matrix binding properties of recombinant fibronectin type II-like modules of humna 72-kDa gelatinase/type IV collagenase." Journal of Biological Chemistry , 270, 11555-11566.

[284] Steinhusen, U., Weiske, J., Badock, V., Tauber, R., Bommert, K., & , O. Huber ((2001). Cleavage and Shedding of E-cadherin after Induction of Apoptosis."Journal of Biological Chemistry , 276(7), 4972-4980.

[285] Sternlicht, M. D., & Werb, Z. (2001). How matrix metalloproteinases regulate cell behavior." Annual Review of Cell Developmental Biology , 17, 463-56.

[286] Stetler-Stevenson, W.G., L.A. Liotta and D.E. Kleiner Jr(1993). Extracellular matrix 6: role of matrix metaloproteinases in tumor invasion and metastasis." FASEB Journal , 7, 1434-1441.

[287] Still, K., Robson, C. N., , P., & , M. C. Autzen ((2000). Robinson and F.C. Hamdy."Localization and quantification of mRNA for matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) in human benign and malignant prostatic tissue."Prostate , 42, 18-25.

[288] Strongin, A. Y., Collier, I., Bannikov, G., Marmer, B. L., Grant, G. A., & , G. I. Goldberg ((1995). Mechanism of cell surface activation of 72-kDa type IV collagenase."Journal of Biological Chemistry , 270(10), 5331-5338.

[289] Sudbeck, B. D., Pilcher, B. K., Welgus, H. G., & Parks, W. C. (1997). Induction and repression of collagenase-1 by keratinocytes is controlled by distinct components of different extracellular matrix components." Journal of Biological Chemistry , 272, 22103-22110.

[290] Sun, Y., Y. Sun, L. Wenger, J.L. Ruter, C.E. Brinckerhoff and H.C. Cheung (1999). "p53 Down-regulates human matrix metalloproteinase-1 (collagenase-1) gene expression." Journal of Biological Chemistry 274(17): 11535-11540.

[291] Sun, Y., J.M. Cheung, J. Martel-Pelletier, J.P. Pelletier, L. Wenger, R.D. Altman, D.S. Howell, and H.S. Cheung (2000). "Wild type and mutant p53 differentially regulate the gene expression of human collagenase-3 (hMMP-13). Journal of Biological Chemistry 275(15): 11327-11332.

[292] Sundareshan, P., Nagle, R. B., & Bowden, G. T. (1999). EGF Induces the expression of matrilysin in the human prostate adenocarcinoma line, LNCaP." The Prostate , 40, 159-166.

[293] Syrigos, K. N., Karayiannakis, A., Syrigou, E. I., Harrington, K., & Pignatelli, M. (1998). Abnormal expression of correlates with poor survival in patients with bladder cancer." European Journal of Cancer 34(13): 2037-2040., 120.

[294] Takahashi, M., Tsunoda, T., Seiki, M., Nakamura, Y., & Furukawa, Y. ((2002). Identification of membrane-type metalloproteinase-1 as a target of the β-catenin/Tcf4 complex in human colorectal cancers."Oncogene , 21, 5861-5867.

[295] Takeichi, M. (1991). Cadherin cell adhesion receptors as a morphogenetic regulator." Science , 251, 1451-1455.

[296] Takeichi, M. (1995). Morphogenetic roles of classic cadherins."Current Opinion in Cell Biology , 7(5), 619-627.

[297] Takino, T., Sato, H., Shinagawa, A., & , M. Seiki ((1995). Identification of the second membrane-type metalloproteinase (MT-MMP2) gene from a human placenta cDNA library. MT-MMPs form a unique membrane-type subclass in the MMP family." Journal of Biological Chemistry , 270(39), 23013-23030.

[298] Tamura, G., Yin, J., Wang, S., Fleisher, A. S., Zou, T., Abraham, J. M., Kong, D., Smolinski, K. N., Wilson, K. T., James, S. P., Silverberg, S. G., Nishizuka, S., Terashima, M., Motoyama, T., & Meltzer, S. J. (2000). E-cadherin gene promoter hypermethylation in primary human gastric carcinomas."Journal of National Cancer Institute , 92(7), 569-73.

[299] Tang, L., Hung, C. P., Schuman, E. M., & (1998)."", . (1998). A role for the cadherin family of cell adhesion molecules in hippocampal long-term potentiation."Neuron , 20(6), 1165-1175.

[300] Tao, Y. S., Edwards, R. A., Tubb, B., Wang, S., Bryan, J., & Mc Crea, P. D. (1996). Beta-catenin associates with the actin-bundling protein fascin in a noncadherin complex." Journal of Cell Biology , 134, 1271-1281.

[301] Tetsu, O., & Mc Cormick, F. (1999). Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells." Nature , 398, 422-426.

[302] Thompson, R. W., Mertens, R. A., Liao, S., Holmes, D. R., Mecham, R. P., Welgus, H. G., & Parks, W. C. (1995). Production and localization of 92 kDa gelatinase in abdominal aortic aneurysms: an elastolytic metalloproteinase expressed by aneurysm-infiltrating macrophages." Journal of Clinical Investigations , 96, 318-326.

[303] Thoreson, M.A. and A.B. Reynolds (2002)."Altered expression of the catenin p120 in human cancer: implications for tumor progression."Differentiation 70: 583-589.

[304] Tomita, K., Van Bokhaven, A., Van Leenders, G., Ruijter, E. T. G., Jansen, C. F. J., Bussemakers, M. J. G., & Schalken, J. A. (2000). Cadherin switching in human prostate cancer progression."Cancer Research 60: 3650.

[305] Tran, N. L., Nagle, R. B., Cress, A. E., & , R. L. Heimark ((1999). N-cadherin expression in human prostate carcinoma cell lines."American Journal of Pathology , 155, 787-798.

[306] Troyanovsky, S. M., Troyanovsky, L. G., Eshkind, L. G., Leube, R. E., & Franke, W. W. (1994a). Identification of amino acid sequence motifs in desmocollin, a desmosomal glycoprotein, that are required for plakoglobin binding and plaque formation." Proceedings of the National Academy of Sciences, 91, 10790-10794.

[307] Troyanovsky, S. M., Troyanovsky, R. B., Eshkind, L. G., Krutovskikh, V. A., Leube, R. E., & , W. W. Franke ((1994b). Identification of the plakoglobin-binding domain in desmoglein and its role in plaque assembly and intermediate filament anchorage."Journal of Cell Biology , 127, 151-160.

[308] Umbas, R., Isaacs, W. B., Breinguier, P. P., Schaafsma, H. E., Karthaus, H. F. M., Oosterhof, G. O. N., Debruyne, F. M. J., & Schalken, J. A. (1994). Decreased E-cadherin expression is associated with poor prognosis in patients with prostate cancer." Cancer Research , 54, 3929-3933.

[309] Unemori, E. N., & , Z. Werb ((1988). Collagenase expression and endogenous activation in rabbit synovial fibroblasts stimulated by the calcium ionophore A23187."Journal of Biological Chemistry , 263(31), 16252-16259.

[310] Usadel, H., Brabender, J., Danenberg, K. D., Jeronimo, C., Harden, S., Engles, J., Danenberg, P. V., Yang, S., & Sidransky, D. (2002). Quantitative adenomatous polyposis coli promoter methylation analysis in tumor tissue, serum and plasma DNA of patients with lung cancer."Cancer Research , 62, 371-375.

[311] Utton, M. A., Eickholt, B., Howell, F. V., Wallis, J., & Doherty, P. (2001). Soluble N-cadherin stimulates fibroblast growth factor receptor dependent neurite outgrowth and N-cadherin and the fibroblast growth factor receptor co-cluster in cells." Journal of Neurochemistry , 76, 1421-1430.

[312] Van Aken, J., Cuvelier, C. A., De Wever, N., Roels, J., Gao, Y., & Mareel, M. M. (1993). Immunohistochemical analysis of E-cadherin expression in human colorectal tumours."Pathology Research and Practice , 189, 975-978.

[313] Van Genderen, C., Okamura, R. M., Farinas, I., Quo, R. G., Parslow, T. G., Bruhn, L., & Grosschedl, R. (1994). Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice." Genes and Development , 8, 2691-2703.

[314] Van Hengel, J., Vanhoenacker, P., Staes, K., & Van Roy, F. (1999). Nuclear localization of the Armadillo-like catenin is counteracted by a nuclear export signal and by

E-cadherin expression." Proceedings of the National Academy of Sciences 96: 7980-7985., 120ctn.

[315] Van Noort, M., Meeldijk, J., Van der Zee, R., Deshee, O., & Clevers, H. (2002). Wnt Signaling controls the phosphorylation status of β-catenin." Journal of Biological Chemistry , 277(20), 17901-17905.

[316] Van Oort, I. M., Tomita, K., van Bokhoven, A., Bussemakers, M. J. G., Kiemeney, L. A., Karthaus, H. F. M., Witjes, J. A., & Schalken, J. A. (2007). The prognostic value of E-cadherin and the cadherin-associated molecules α-, β-, γ-catenin and in prostate cancer specific survival: a long-term follow-up study." Prostate 67: 1432-1438., 120ctn.

[317] Van de Wetering, M., Cavallo, R., Dooijes, D., van Beest, M., van Es, J., Loureiro, J., Ypma, A., Hursh, D., jones, T., Bejsovec, A., Peifer, M., Mortin, M., & Clevers, H. (1997). Armadillo coactivates transcription driven by the product of the Drosophila segment polarity gene dTCF." Cell , 88, 789-799.

[318] Veatch, A. L., Carson, L. F., & , S. Ramakrishnan ((1994). Differential expression of the cell-cell adhesion molecule E-cadherin in ascites and solid human ovarian tumor cells."International Journal of Cancer , 58(3), 393-399.

[319] Vincenti, M.P(2000). The Matrix Metalloprotienase (MMP) and Tissue inhibitor of metalloproteinase (TIMP) Genes." In: Matrix Metalloproteinase Protocols Totowa: Humana Press, , 122-123.

[320] Von, Kries. J. P., Winbeck, G., Asbrand, C., Schwarz-Romond, T., Sochnikova, N., Dell'Oro, A., Behrens, J., & Birchmeier, W. (2000). Hot spots in beta-catenin for interactions with LEF-1, conductin and APC."Nature Sructural Biology , 7(9), 800-7.

[321] Wahl, J., Sacco, P., Mc Granahan-Sadler, T., Sauppe, L., Wheelock, M., & , K. Johnson ((1996). Plakoglobin domains that define its association with the desmosomal cadherins and the classical cadherins: identification of unique and shared domains." Journal of Cell Science , 109, 1143-1154.

[322] Wahl, J. K., Nieset, J. E., Sacco-Bubulya, P. A., Sadler, T. M., Johnson, K. R., & Wheelock, M. J. (2000). The amino- and carboxyl-terminal tails of β-catenin reduce its affinity for desmoglein 2." Journal of Cell Science , 113, 1737-1745.

[323] Watabe-Uchida, M., Uchida, N., Imamura, Y., nagafuchi, A., Fujimoto, K., Uemura, T., Vermeulen, S., F.van, Roy. E. D., Adamson, , & Takeichi, M. (1998). A-catenin-vinculin interaction functions to organize the apical junctional complex in epithelial cells." Journal of Cell Biology , 142(3), 847-857.

[324] Weiss, E. E., Kroemker, M., , A., Rudiger, H., Jockusch, B. M., & Rudiger, M. (1998). Vinculin is part of the cadherin-catenin junctional complex: complex formation beteen alpha-catenin and vinculin." Journal of Cell Biology , 141, 755-784.

[325] Weng, Z., Xin, M., Pablo, L., Grueneberg, D., Hagel, M., Bain, G., Muller, T., & , J. Papkoff ((2002). Protection againsto anoikis and down-regulation of cadherin expres-

sion by a regulatable beta-catenin protein."Journal of Biological Chemistry , 277, 18677-18686.

[326] Werb, Z., Tremble, P. M., Behrendtsen, O., Crowley, E., & Camsk, C. H. (1989). Signal transduction through the fibronectin receptor induces collagenase and stromelysin gene expression." Journal of Cell Biology , 109, 877-889.

[327] Whitlon, D.S(1993). E-cadherin in the mature and developing organ of Corti of the mouse."Journal of Neurocytochemistry , 22, 1030-1038.

[328] Wiechens, N., Fagotto, F., & (2001).", C. R. (2001). CRM1- and Ran-independent nuclear export of β-catenin."Current Biology , 11, 18-27.

[329] Wilding, J., Vousden, K. H., Soutter, W. P., Mc Crea, P. D., & , R. Del Buono and M. Pignatelli ((1996). E-cadherin Transfection Down-regulates the Epidermal Growth Factor Receptor and Reverses the Invasive Phenotype of Human Papilloma Virus-transfected Keratinocytes." Cancer Research, 56, 5285-5292.

[330] Will, H., & Hinzmann, B. (1995). cDNA sequence and mRNA tissue distribution of a novel human matrix metalloproteinase with a potential transmembrane segment." European Journal of Biochemistry , 231, 602-608.

[331] Willert, K., & Nusse, R. (1998). Beta-catenin: a key mediator of Wnt signaling." Current Opinion in Genetics and Development , 8, 95-102.

[332] Windoffer, R., Beile, B., Leibold, A., Thomas, S., Wilhelm, U., & , R. E. Leube ((2000). Visualization of gap junction mobility in living cells."Cell Tissue Research , 299, 347-362.

[333] Winston, J. T., Strack, P., Beer-Romero, P., Chu, C. Y., Elledge, S. J., & Harper, J. W. (1999). The SCFb-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IκBα and β-catenin and stimulates IκBα ubiquitination in vitro." Genes and Development , 13, 270-283.

[334] Witcher, L. L., Collins, R., Puttogunta, S., Mechanic, S. E., Munson, M., Gumbiner, B., & Cowin, P. (1996). Desmosomal cadherin binding domains of plakoglobin."Journal of Biological Chemistry , 271(18), 10904-10909.

[335] Witty, J.P., T. Lempka, R.J. Coffey, Jr and L.M. Matrisian (1995). "Decreased tumor formation in 7, 12-dimethylbenzanthracene-treated stromelysin-1 transgenic mice is associated with alterations in mammary epithelial cell apoptosis." Cancer Research 55: 1401-1406.

[336] Wodarz, A., & , R. Nusse ((1998). Mechanisms of Wnt signaling in development."Annual Review of Cell and Developmental Biology , 14, 59-88.

[337] Wood, M., Fudge, K., Mohler, J. L., Frost, A. R., Garcia, F., Wang, M., & Stearns, M. E. (1997). In situ hybridization studies of metalloproteinases 2 and 9 and TIMP1 and TIMP2 expression in human prostate cancer." Clinical Experimental Metastasis , 15, 246-258.

[338] Yamada, T., Takaoka, A. S., Naishiro, Y., Hayashi, R., Maruyama, K., & , C. Maesawa ((2000). Transactivation of the Multidrug Resistance 1 gene by T-Cell Factor 4/β-catenin complex in early colorectal carcinogenesis."Cancer Research , 60, 4761-4766.

[339] Yanagawa, S., , Y., Matsuda, J., lee, H., Matsubayashi, S., Sese, T., Kadowaki, , & Ishimoto, A. (2002). Casein kinase 1 phosphorylates the Armadillo protein and induces its degradation in Drosophila." EMBO Journal , 21, 1733-1742.

[340] Yap, A.S(1998a). The morphogenetic role of cadherin cell adhesion molecules in human cancer: a thematic review." Cancer Investigation , 16(4), 252-261.

[341] Yap, A.S., C.M. Niessen, and B.M. Gumbiner (1998b)."The Juxtamembrane Region of the Cadherin Cytoplasmic Tail Supports Lateral Clustering, Adhesive Strengthening, and Interaction with $p120^{ctn}$."Journal of Cell Biology141(3): 779-789.

[342] Zhang, Y., Qiu, W. J., Chan, S. C., Han, J., He, X., & Lin, S. C. (2002). Casein kinase I and casein kinase II differentially regulate Axin function inWnt and JNK pathways." Journal of Biological Chemistry , 277, 17706-17712.

[343] Zeng, L., Fagotto, F., Zhang, T., Hsu, W., Vasicek, T. J., Perry, W. L., Lee, J. J., Tilghman, S. M., Gumbiner, B. M., & Costantini, F. (1997). The mouse fused locus encodes Axin, an inhibitor of the Wnt signaling pathway that regulates embryonic axis formation." Cell ., 90, 181-192.