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Brain Metastases Progression of Breast Cancer

Ala-Eddin Al Moustafa^{1,2,3}, Amber Yasmeen², Lina Ghabreau⁴,
Ali H. Mohamed⁴ and Amal Achkhar^{1,5}

¹*Syrian Research Cancer Centre of the Syrian Society against Cancer, Aleppo*

²*Oncology Department, Faculty of Medicine, McGill University, Montréal*

³*Department of Mechanical Engineering, Concordia University, Montréal*

⁴*Department of Pathology, Faculty of Medicine/University of Aleppo, Aleppo*

⁵*Faculty of Pharmacy, University of Aleppo, Aleppo*

^{1,4,5}*Syria*

^{2,3}*Canada*

1. Introduction

The development of brain metastases is one of the complications of breast cancer most feared by patients, having connotations of loss of identity and independence (Mayer, 2007). Clinically evident brain metastases occur in 20-30% of patients with metastatic breast cancer (Landis et al., 1999; Lin et al., 2004) and median survival of patients who develop breast cancer brain metastases (BCBMs) is generally poor, ranging from 2 to 9 months (Altundag et al., 2007; Lee et al., 2008; Ogawa et al., 2008). The treatment of metastasis to the brain is complicated by the unique characteristics of the brain. The blood-brain barrier (BBB), with its tight junctions and lack of lymphatic drainage, makes the delivery of chemotherapeutic agents difficult and represents a therapeutic haven from chemotherapy (Patchell, 2003; Ballabh et al., 2004; Nathoo et al., 2005). In addition, brain metastatic disease is the most poorly understood aspect of cancer progression. The potential of malignant cells to spread to distant organs including lung, bone and brain is the leading cause of death from breast cancer. Some breast cancer metastases display tissue-specific patterns to distant organs, such as the brain (Palmieri et al., 2006-2007; Sanna et al., 2007) and bone (Yang et al., 2007; Wang et al., 2007). The metastatic process is a complex phenomenon, and involves several genes. Recent studies recognize cell adhesion proteins especially E-cadherin and matrix metalloproteinases (MMPs), growth factor receptors such as EGF-R, ErbB-2, VEGF, and contributions from signal transduction pathways in addition to the activation of specific chemokines/cytokines, as major regulators of the metastatic process (Zeljko et al., 2011; Klein et al., 2009; Bos et al., 2009; Kennecke et al., 2010; Carotenuto et al., 2010; Hinton et al., 2010). Contrary to non-invasive breast cancer cells, malignant cells must display enhanced migratory behaviour and the ability to breach blood vessel walls and the dense collagenous matrix surrounding tumours. Additionally, metastatic cells must overcome the dynamics of a foreign microenvironment, to colonize and survive at a distant target site. Once metastasis has occurred, tumour growth is highly dependent on the ability of tumours to induce their own vascularization (Harlozinska, 2005; Hinton et al., 2008). There are key events to which malignant cells must adhere to complete their migration and angiogenesis: invasion of the

surrounding stromal tissue, intravasation, evasion of programmed cell death and growth within a new microenvironment (Kaplan et al., 2006). These events are governed by several important genes that can regulate cell cancer invasion to a specific organ such as lung, bone and brain. In this chapter, we will discuss the contributions of E-cadherin, MMPs EGF-R, ErbB-2, VEGF and chemokine genes, to the induction and progression of metastasis of breast cancer especially to the brain.

2. MMPs and E-cadherin in brain metastasis

Ecadherin and MMPs family proteins are heavily involved in the metastases of the brain (VanMeter et al., 2001; Lewis-Tuffin et al., 2010). MMPs are a broad family of zinc-dependent proteinases that play a key role in extracellular matrix (ECM) degradation in metastasis (Kessenbrock et al., 2010); their expression is regulated via cytokines, and the ECM metalloprotease inducer is found on the surface of tumour cells. MMP activity is known to correlate with invasiveness, metastasis, and poor prognosis (Murphy, 2008; Kessenbrock et al., 2010). Earlier study found that MMP-2 is present in all metastatic brain tumours tested regardless of the site of origin and that the level of activity inversely correlated with survival (Jäälinojä et al., 2000; Deryugina and Quigley, 2006). Meanwhile, although MMP-9 was found to be up-regulated in all brain metastases and primary brain tumours, there was an inability to correlate up-regulation with survival (Arnold et al., 1999). Furthermore, previous studies showed that MMPs might be involved in the metastases of breast cancer to the brain (Cheng and Hung, 2007). A breast cancer brain metastases rat model was derived from injection of a carcinogen-induced mammary adenocarcinoma cell line in the left ventricle of rat (Mendes et al., 2005). The micro-metastasis in the brain showed a significantly higher expression of MMP-2, -3 and -9 and an increase in MMP-2 and MMP-3 activity compared to the normal brain tissue (Deryugina and Quigley, 2006). Furthermore, the development of brain metastasis was significantly decreased by the treatment with a selective synthetic MMP inhibitor (Mendes et al., 2005). This phenomenon was confirmed by another study in which human breast cancer cells over-expressed with MMP2 were inoculated into the left ventricle, a higher incidence of metastasis to brain was observed (Tester et al., 2004). Another study also showed that brain seeking breast cancer cells have a higher total and active amount MMP-1 and MMP-9 with higher migration and invasion capacity, which could be decreased by the application of MMP-1 and/or MMP-9 inhibitor (Stark et al., 2007).

On the other hand, E-cadherin/catenin complex is vital for the maintenance of both normal and tumour cytoarchitecture as well as a necessary mediator of cell-cell adhesion. β -catenin, as well as plakoglobin (γ -catenin), associate directly with the highly conserved cytoplasmic domain of E-cadherin in a mutually exclusive manner (Yasmeen et al., 2006; Al Moustafa et al., 2008). The E-cadherin/ β -catenin complex is linked via α -catenin either directly or indirectly to the actin filament network via the actin-binding proteins α -actinin or vinculin (Yasmeen et al., 2006; Al Moustafa et al., 2008). The association of the E-cadherin/catenin complex with the cytoskeleton is essential for tight cell-cell adhesions. In the metastatic escape of a tumour, clone cells reduced intercellular adhesion and disrupted cytoarchitecture, and are thus prone to separation from the primary tumour mass (Al Moustafa et al., 2011). These clones are then free to invade both locally as well as to continue on to intravasation and further progress in the cascade (Nathoo et al., 2005).

Decreased expression of the E-cadherin/catenin complex has been correlated with invasion, metastasis, and unfavorable prognosis (Bremnes et al., 2002). Shabani et al. (2003) established a correlation between E-cadherin/catenin complex expression and an increased mindbomb homolog 1 (MIB1) index in metastatic adenocarcinomas. Further, E-cadherin is expressed in most meningiomas (Tohma et al., 1992; Figarella-Branger et al., 1994; Howng et al., 2002), and its loss may be associated with tumour progression (Schwechheimer et al., 1998). E-cadherin expression in glioblastoma multiforme or glioblastomas appears to be an exception to the epithelial-mesenchymal transition (EMT) rule, which is an important event in the progression cancer and metastasis (Lewis-Tuffin et al., 2010; Al Moustafa et al., 2011) (Figure 1). The molecular mechanisms underlying the contribution of E-cadherin to growth and/or invasiveness in glioblastomas are currently unknown. Although, the two main sources of brain metastasis - adenocarcinomas of the lung or the breast represent different models of the course of the disease (Bos et al., 2009); Zeljko et al. (2011) have showed that E-cadherin changes were frequent in metastases from both those malignancies. Moreover, Saad et al. (2008) demonstrated that loss of E-cadherin in patients with adenocarcinomas and squamous cell carcinomas of the lung is significantly associated to the increased risk of developing brain metastases. The results of other authors investigating E-cadherin involvement in brain metastasis (Arnold et al., 1999; Shabani et al., 2003; Prudkin et al., 2009) collectively demonstrate that E-cadherin is constantly expressed in metastatic deposits. Furthermore, our recent studies also demonstrated that E-cadherin-catenin complex is involved in cell migration and metastasis *in vivo* and *in vitro* (Yasmeen et al., 2007). In order to investigate the cooperation effect between ErbB-2 receptor and high-risk human papillomavirus (HPV) in breast carcinogenesis and metastasis, we generated double transgenic mice carrying ErbB-2 and E6/E7 of HPV type 16 under mouse mammary tumour virus (MMTV) and human keratin 14 (K14) promoters, respectively. Within six months, these double transgenic mice developed large and extensive invasive breast cancers to several vital organs including lung, bone and brain. Histological analysis of ErbB-2/E6/E7 transgenic mouse tumours revealed the presence of invasive breast carcinomas. However, breast tissues from ErbB-2 and E6/E7 singly transgenic mice showed only *in-situ* cancer and normal mammary phenotype, respectively (Yasmeen et al., 2007). In parallel, to assess the outcome of ErbB-2/E6/E7 cooperation in human breast carcinogenesis, we examined the effect of ErbB-2 and E6/E7 of HPV type 16 on the BT20 breast cancer cell lines. We found that ErbB-2/E6/E7 cooperate in the BT20 cell line to induce large colony formation and cell migration using soft agar and wound healing assays, respectively, in comparison with ErbB-2, E6/E7 and wild type cells. Moreover, we demonstrated that ErbB-2/E6/E7 cooperation induces a nuclear translocation of β -catenin in BT20 cells; regarding the mechanism of this translocation, we reported that ErbB-2/E6/E7 cooperation provokes a dissociation of E-cadherin/catenin complex by tyrosine phosphorylation of β -catenin through pp60(c-Src) kinase phosphorylation. Subsequently, the free β -catenin enters to the nucleus and modulates cell transcription via its association with the Tcf/Lef transcription factors (Yasmeen et al., 2007; Al Moustafa et al., 2008) (Figure 2). In conclusion, our *in vitro* and *in vivo* models demonstrated that the ErbB-2 tyrosine kinase receptor cooperates with E6/E7 of high-risk HPVs in breast tumorigenesis and metastasis via E-cadherin/catenin complex (Yasmeen et al., 2007; Al Moustafa et al., 2008). These studies provide evidence that MMPs and E-cadherin play an important role in brain metastases of breast cancer.

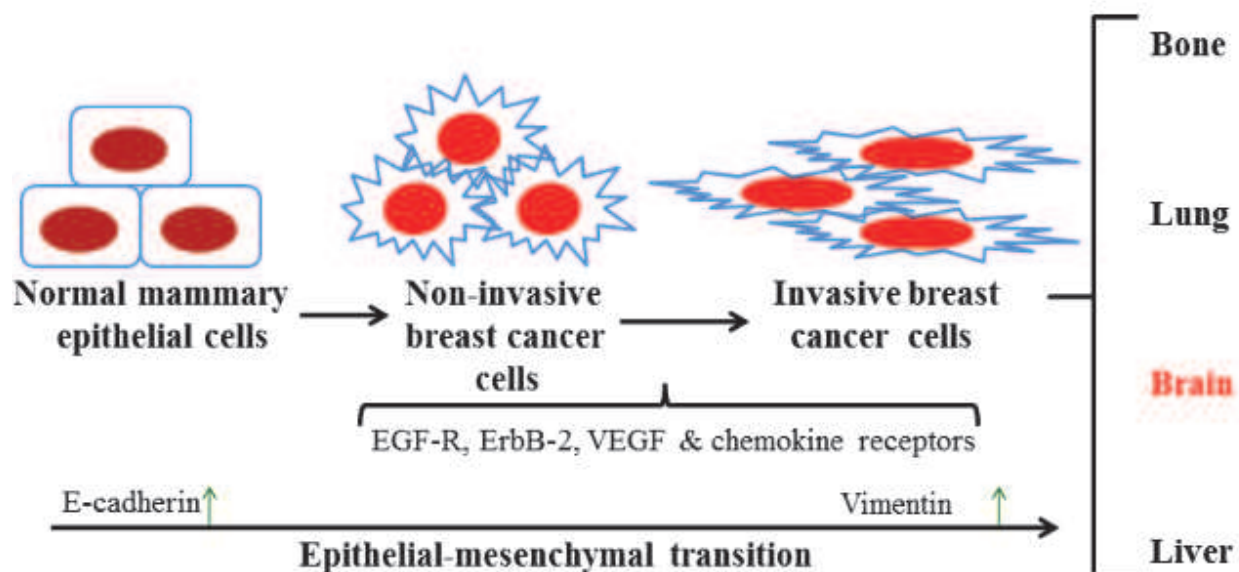


Fig. 1. Transformation of normal mammary epithelial to non-invasive and invasive cancer cells. Several oncogenes can transform normal epithelial cells to cancer ones; meanwhile, other genes such as, EGF-R, ErbB-2, VEGFs and chemokines, convert non-invasive cancer cells to invasive ones which can invade several vital organs including bone, lung, brain and liver. Invasion is a multi-step process which allows cell migration and invasion through dysfunctional cell-cell adhesive interactions, loss of cell-cell junctions and reorganization of the cytoskeleton; these procedures result in the loss of apical polarity and the acquisition of a more spindle-shaped morphology; this process is identified as the epithelial-mesenchymal transition (EMT). This event is accompanied by inhibition of epithelial markers such as E-cadherin and over-expression of mesenchymal markers such as vimentin.

3. EGF-R and ErbB-2 in brain metastasis

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptor tyrosine kinases. This family includes four receptors: EGF-R/ErbB-1/HER-1, ErbB-2/HER-2/Neu, ErbB-3/HER-3, and ErbB-4/HER-4 (Carney et al., 2007; Lee-Hoeflich et al., 2008) that are structurally related. All HER members except HER-3 contain intracellular tyrosine kinase domain and all except HER-2, bind to extracellular ligands (Carpenter et al., 1990). Certain discrete genes, with several alternative splice variants, encode either the “Epidermal Growth Factor (EGF) receptor ligands” or the Neuregulins that bind to different ErbB receptors as a co-receptor. Different ligands bind to more than one receptor with high affinity; consequently ErbB-2 ligands readily activate ErbB-2 in combination with the appropriate high affinity co-receptor. The biological activity and affinity is often higher with the presence of ErbB2 complex than without it. The mammalian ligands that bind to the ErbB family include EGF, Transforming growth factor- α (TGF- α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AR), betacellulin (BTC), epiregulin (EPR), epigen, tomoregulin and neuregulins (NRG-1, NRG-2, NRG-3 and NRG-4) (Chang et al., 1997; Bublil and Yarden, 2007). The architecture of ErbB kinases, like most receptor tyrosine kinases (RTKs), is characterized by an extracellular ligand-binding domain, a transmembrane domain, a juxtamembrane (JM) segment, a kinase domain, and a COOH

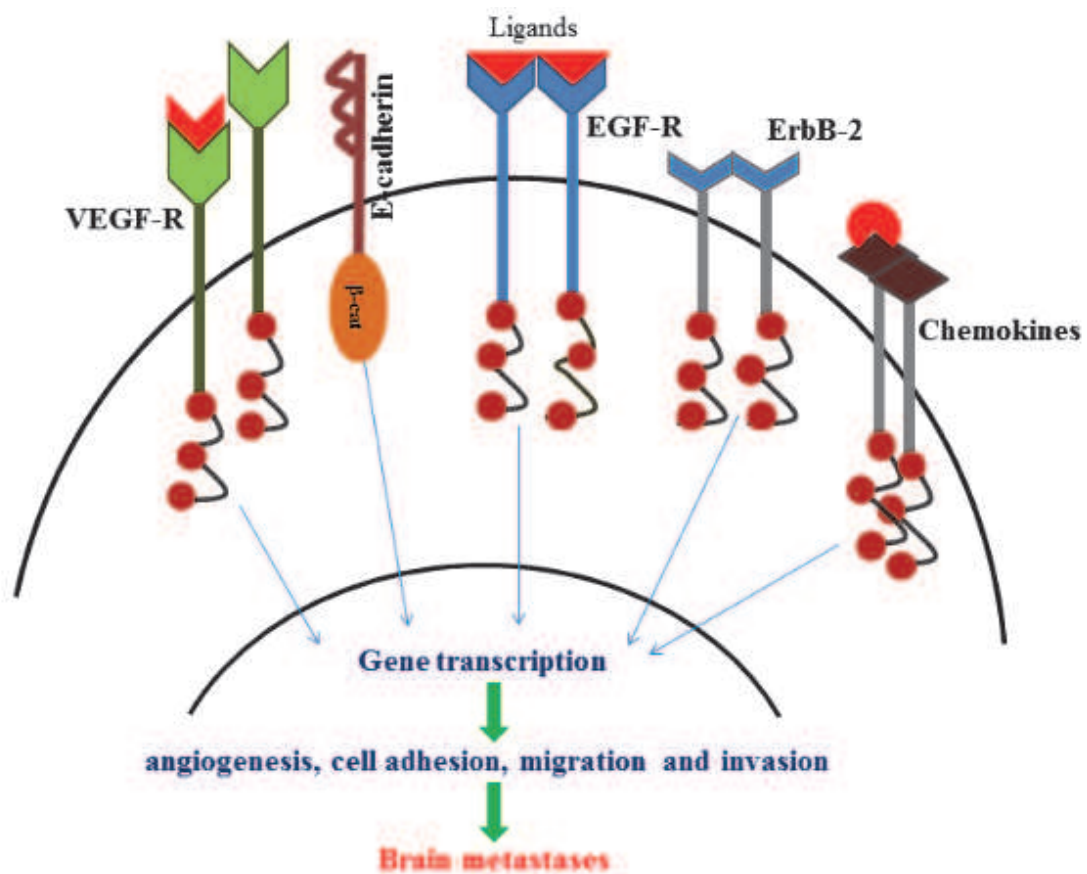


Fig. 2. VEGF-R, EGF-R, ErbB-2 and chemokines receptor signaling pathways in cancer cells. Ligands can activate downstream-signaling pathways of these receptors which also can interact with other protein complexes such as E-cadherin/catenins. Therefore, these pathways alter the activity of multiple nuclear transcription factors which in turn can activate several genes implicated in diverse cellular procedures such as angiogenesis, cell adhesion, migration and invasion; after which cancer cells can migrate to several organs including brain.

terminal tail (C-terminal tail). The EGF-R is involved in many cellular processes including cell proliferation, motility, adhesion and angiogenesis via the activation of primarily two pathways: Phosphatidylinositol-3 Kinase (PI3K)/Akt pathway, and the External signal-Regulated Kinase (ERK) pathway (Yasmeen et al., 2006; Bublil and Yarden, 2007) (Figure 2). EGF-R is widely expressed in a variety of human cancers including non-small-cell lung cancer NSCLC, colorectal, pancreatic, breast, ovarian, prostate and gastric cancers (Raymond et al., 2000). It is thought that EGF-R plays an important role in the tumour development and progression (Grandis et al., 2004). In addition to their well established contributions to cell proliferation and survival, EGF-R and ErbB-2 are also linked with other characteristics of aggressive tumours such as local invasion and intravasation (Figure 2), independently of their effects on growth (Xue et al., 2006; Zhan et al., 2006). Gene expression profiling and immunohistochemical studies have indicated that 50–70% of basal-type breast tumours, which are ErbB-2 “triple-negative” carcinomas, exhibit EGF-R expression (Burness et al., 2010). This type of breast cancers is associated with large size, high tumour grade, increased frequency of distant metastases to several vital organs including brain (Da Silva et al., 2007).

ErbB-2/HER-2/Neu oncogene, located on the long arm of chromosome 17 (17q12-q21), is over-expressed or amplified in 18–35% of invasive breast cancers and in 60% of intraductal breast carcinomas but are not over-expressed relative to the normal breast epithelium (Pawlowski et al., 2000). Over-expression of ErbB-2 in breast carcinoma patients is associated with a shorter survival period and more frequent disease recurrence compared with patients without ErbB-2 over-expression (Slamon et al., 1987). Moreover, over-expression of ErbB-2 in breast cancer cell lines increases the portion of cells that present stem-like properties (Korkaya et al., 2008) and display intrinsic resistance to antiestrogen therapy (Jordan et al., 2007; Fan et al., 2009). ErbB-2 amplification/over-expression is a prognostic and predictive factor for the development of CNS metastases (Evans et al., 2004; Gabos et al., 2006). Autopsy data show that the incidence rate for CNS metastases in ErbB-2-positive breast cancer patients is higher (ie, 30% to 50%) than that in ErbB-2-negative breast cancer patients (approximately 30%) (Aragon-Ching et al., 2007). On the other hand, a retrospective study on 9524 women with early stage breast cancer identified ErbB-2 as a clear risk factor for the development of CNS relapse (Pestalozzi et al., 2006). However, the precise biological explanation for the tendency of ErbB-2-positive breast cancer cells to metastasize to CNS has not been completely elucidated; although it has been suggested that it may occur as a result of both the aggressiveness of this breast cancer subtype and of a particular affinity for CNS. Interestingly, the survival time after the diagnosis of brain metastasis is longer for patients with ErbB-2-positive disease than ErbB-2-negative. It is estimated that one-third of women receiving Herceptin for metastatic ErbB-2-positive breast cancer develop CNS metastases during the course of their illness (Bendell et al., 2003; Lai et al., 2004). Herceptin levels in cerebrospinal fluid are 300-fold lower than those in plasma (Pestalozzi et al., 2000; Rusnak et al., 2001), indicating that Herceptin cannot cross the BBB due to its large molecular weight. The inability of Herceptin to cross the BBB may also contribute to the increased incidence of brain metastases in patients with ErbB-2-over-expressing breast cancer. This is most likely because of the inherent aggressiveness of ErbB-2-positive disease, as well as the prolongation in survival and control of extracranial disease attributable to Herceptin therapy (Clayton et al., 2004). Interestingly, ErbB-3 expression was increased in breast cancer cells residing in the brain. Neuregulin-1, the ligand for this receptor, is abundantly expressed in the brain (Law et al., 2004; Da Silva et al., 2010). These findings suggest that neuregulin/ErbB-3 activation is an important mechanism for breast cancer cell colonization of the brain and imply that the inhibition of ErbB family receptors especially EGF-R and/or ErbB-2 may play a significant role in the treatment of patients with brain metastases from breast cancer.

4. VEGFs in brain metastasis

Vascular endothelial growth factor (VEGF) belongs to VEGF family that consists of five members: VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) (Li et al., 2001; Nagy et al., 2003; Yamazaki et al., 2003). There are three receptor protein-tyrosine kinases for the VEGF family ligands (VEGFR-1, VEGFR-2, and VEGFR-3), which are primarily expressed by the endothelium and are required for normal vascular development (Millauer et al., 1993; Peters et al., 1993; Terman et al., 1994). Each of these receptors consists of seven immunoglobulin-like loops in the extracellular domain, a single transmembrane domain, and an intracellular protein-tyrosine kinase segment that contains a kinase insert, and a carboxy-terminal tail (Fantl et al., 1993) (Figure 2). Several ligands of

VEGF family bind to two non-enzymatic receptors (neuropilin-1 and -2), and heparan sulfate proteoglycans that are found on the plasma membrane and in the extracellular matrix (Dougher et al., 1997; Gluzman-Poltorak et al., 2000). Binding of VEGF to its receptors induces proliferation and migration of cancer cells (Figure 1 and 2).

Although VEGF is considered potent mitogen for vascular endothelial cells, it is also considerably involved in the mitogenic activity of other cells. VEGF mRNA and protein are found in several tissues and organs (Berse et al., 1992; Ng et al., 2001; Maharaj et al., 2006). Also, VEGF gene expression and protein are found in many of human malignancies such as breast, non-small cell lung, colorectal, neuroblastoma, and prostate carcinomas (Fukuzawa et al., 2002; Hoeben et al., 2004; Xu et al., 2004). On the contrary, VEGF receptors are generally limited to endothelial cells in the cardiovascular and lymphatic systems (Kukkk et al., 1996; Lymboussaki et al., 1999).

In the nervous tissue, VEGF is crucial for vascular growth during brain development (Breier et al., 1992; Ogunshola et al., 2000; Vates et al., 2005). However, in the intact adult CNS, the expression of VEGF becomes restricted to the choroid plexus, area postrema cerebellar granule cells (Monacci et al., 1993), and VEGF receptor expression becomes extremely low (Kremer et al., 1997; Soker et al., 1998). VEGF expression was demonstrated to be up-regulated in neurons and astroglia during pathological processes in the CNS that are associated with angiogenesis and increased BBB permeability, including tumours and ischemia (Pietsch et al., 1997; Issa et al., 1999; Lee et al., 1999; Plate et al., 1999; Jin et al., 2000; Graumann et al., 2003). VEGF direct application to fetal cortical and ventral mesencephalic explants has been shown to induce significant angiogenesis and astroglial proliferation (Silverman et al., 1999; Mani et al., 2005; Krum et al., 2008). Furthermore, continuous interstitial infusion of recombinant human VEGF₁₆₅ protein administered to the cerebrum produced significant increases in the activity and, unexpectedly, in the astroglial proliferation within the adult CNS (Krum et al., 2002). VEGF, thus, was considered a direct astroglial mitogen (Krum et al., 2002).

It was postulated, forty years ago, by Folkman that tumours require to be vascularized to grow (Folkman, 1971). Tumour cells enter the vascular system after switching on the angiogenic process, and forming new vessels, leading to the initiation of metastasis. VEGF, among other various angiogenic factors, plays an essential role in tumour angiogenesis. VEGF is expressed and secreted by most solid tumours, but little occurs in endothelial cells (Ribatti et al., 1998; Shemirani and Crowe, 2000). In contrast, VEGF receptors (VEGFR-1 and VEGFR-2 mRNAs and proteins) are largely expressed in vessels lining and penetrating the tumours; where they are exclusively expressed in endothelial cells (Brown et al., 1995; Mentzel et al., 2001). These observations are consistent with the notion that VEGF acts in a paracrine manner, in which VEGF that is secreted from tumour cells influences nearby endothelial cells.

The finding that VEGF is highly expressed in metastatic cerebral tumours originating from angiosarcoma, renal cell carcinomas, melanomas, and adenocarcinomas provide further evidence that supports the significant role for VEGF in human metastases (Strugar et al., 1994). VEGF expression was associated with considerable staining of microvascular and the formation of vasogenic brain edema, revealing both the angiogenic and permeability properties of VEGF (Strugar et al., 1994). On the other hand, VEGF- mRNA is significantly correlated with vascularisation in both gliomas and meningiomas, indicating a pivotal role for VEGF in the vascularization of primary brain tumours (Samoto et al., 1995). It is currently well established that the formation of metastases correlates with the number of microvessels (the amount of vascularisation) that can be detected in a primary tumour.

A number of mechanisms account for tumour vascularisation, including sprouting angiogenesis, intussusceptions, recruitment of circulating endothelial precursors, cooption, mosaic vessels, and vascular mimicry. VEGF family members are considered the major players that control these mechanisms. Sprouting angiogenesis has been suggested as the mechanism that is used by the brain for vascularization. In sprouting angiogenesis, VEGF-A produces vasodilatation of preexisting capillaries and increases permeability (Auguste et al., 2005). VEGF-A also induces endothelial cell proliferation (Auguste et al., 2005) and an increase in metalloproteases and plasminogen activators, which lead to the degradation of the extracellular matrix permitting endothelial cell migration (Pepper et al., 1991; Vu et al., 1998; Bergers et al., 2000). Vessel guidance mechanisms that direct host vessels into the tumour have been identified in the brain. VEGF and its receptors have been postulated as important guidance signal. It seems that cells located at the invading front of the blood vessels, huddle VEGFR-2 and follow a VEGF gradient (Gerhardt et al., 2003). Tumour cells injected into the brain were found to develop vascularization immediately by angiogenic sprouting with loss of the BBB. Tumour cells are speculated to be organized in cuffs of pseudopalisading cells around VEGFR-2 positive vessels, and to use these vessels to invade other brain areas. Vessels supply tumour cells with oxygen and nutrients.

A different mechanism of brain tumour vascularization that is distinct from the sprouting mechanism has been described. Accordingly, tumours in the brain can use a cooption mechanism for vascularization (Holash et al., 1999; Fischer et al., 2005). Vessels are surrounded by tumour cells, and cooped endothelial cells are induced to express angiopoietin-2. Binding of angiopoietin-2 to its receptors located at the endothelial cell surface leads to the dissociation of the mural cells from endothelial cells, and an increase in apoptosis. Angiopoietin-2 activity causes a significant decrease in tumour vessel number and an increase in vessel diameter. Accordingly, the scarcity of vessels leads to hypoxia which upregulates VEGF-A expression in tumour cells. As a consequence, strong angiogenesis develops mainly at the tumour periphery (Holash et al., 1999; Zagzag et al., 2000; Fischer et al., 2005). Rat mammary carcinomas was shown to be vascularized by cooption when cells are injected inside the brain. Metastases of Lewis lung carcinoma and melanoma cells into brain have been demonstrated to be partially vascularized by cooption (Holash et al., 1999; Kusters et al., 2002). Decreasing VEGF production, by antisense transfection, to 20–50% of original cell level was shown to be associated with inhibition of both angiogenesis and brain metastasis formation (Yano et al., 2000). In conclusion, VEGF is a key factor in the vascularization and metastasis of primary tumours into brain.

5. Chemokines and chemokine receptors

Chemotactic cytokines, or *chemo-kines*, are a large subfamily of cytokines that coordinate leukocyte recruitment and activation, two crucial elements in the pathogenesis of several immuno-mediated human diseases. Chemokines have been recognized in the last few years as important mediators in the pathogenesis of many human diseases and have assumed growing relevance in clinical pathology as markers of disease onset, progression, and remission (Hinton et al., 2010). Since the description of the first chemokine in 1977, over 40 related molecules have been discovered in humans and chemokines have been recognized as a family of functionally related small secreted molecules named "chemo-kine" because of leukocyte chemoattractant and cytokine-like activities (Luster, 1998; Locati and Murphy,

1999). Human chemokine family is currently known to include more than 40 chemokines and 20 chemokine receptors (Bonecchi et al., 2009). These receptors are defined by their ability to induce directional migration of cells toward a gradient of a chemotactic cytokine (a process known as chemotaxis) (Figure 2). Chemokine receptors are a family of seven transmembrane G protein-coupled cell surface receptors (GPCR) that are classified into four groups (CXC, CC, C, and CX3C) based on the position of the first two cysteines (Murphy et al., 2000; Zlotnik and Yoshie, 2000). While chemokine receptors have been found in many different cell types, these receptors were initially identified on leukocytes and were found to play an important role in the homing of such cells to sites of inflammation (Loetscher et al., 2000).

During the past several years, other types of non-hematopoietic cells have been found to express receptors for various chemokines found in their distinct tissue microenvironments. The interactions between such receptors and their respective chemokines are thought to help coordinate the trafficking and organization of cells within various tissue compartments (Baggiolini, 1998; Moser and Loetscher, 2001). CXCR4 is one of the best studied chemokine receptors, primarily due to its role as a co-receptor for HIV entry (Feng et al., 1996) and its ability to mediate the metastasis of a variety of cancers, including prostate cancer (Zlotnik, 2006a and b; Burger and Kipps, 2006; Sun et al., 2003). CXCR4 is a 352-amino acid rhodopsin-like GPCR that selectively binds the CXC chemokine stromal cell-derived factor 1 (SDF-1), also known as CXCL12 (Fredriksson et al., 2003; Burger and Kipps, 2006). On the other hand, lack of either SDF-1 or CXCR4 resulted in a phenotype almost identical to that of late gestational lethality with defects in B cell lymphopoiesis, bone marrow colonization, and cardiac septal formation (Nagasawa et al., 1996; Zou et al., 1998). These studies indicate that CXCR4 is essential for development, hematopoiesis, organogenesis, as well as vascularization (Tachibana et al., 1998; McGrath et al., 1999) and that it functions as a classical chemokine receptor in adults (Murphy, 1994; Baggiolini, 1998). A growing body of evidence now shows that CXCR4 has a role in both cancer metastasis and in cancer stem cells. The physiological mechanism of tissue-specific recruitment (i.e. a homing system for normal tissue replacement) also seems to be functional for cancer stem cells. The CXCR4-SDF-1 axis seems to have a large influence on the biology of tumours. High levels of SDF-1 in organs and tissue structures such as the lymph nodes, lungs, liver, brain and bones are believed to direct the metastasis of CXCR4-expressing tumour cells. In support of this hypothesis, several researchers have shown that multiple cancers expressing CXCR4 (e.g. breast, ovarian, and prostate cancers, as well as rhabdomyosarcomas and neuroblastomas) metastasize to the bones and the brain through the bloodstream in an SDF-1 (CXCL12)-dependent manner (Dontu et al., 2003; Porcile et al., 2004; Sun et al., 2003; Geminder et al., 2001; Hinton et al., 2010). The CXCR4-SDF-1-mediated trafficking/homing of tumour cells during metastasis seems to share some molecular mechanisms with normal stem cell processes. Additionally, the mobilization, trafficking and homing of both cancer and normal stem cells seem to be multistep processes, as described in several studies (Hattori et al., 2001; Lapidot et al., 2002; Hinton et al., 2010). Previous study by Muller et al. (2001) reported in breast cancer that CXCR4 and CXCL12 are central players in regulating metastasis by showing that normal breast tissues express little CXCR4, whereas breast neoplasms express high levels of CXCR4; CXCR4 signaling in response to CXCL12 mediates actin polymerization and pseudopodia formation, and subsequently induces chemotactic and invasive responses (Muller et al., 2001). These data formed the basis of the hypothesis that malignant cells may employ chemokine receptors to migrate toward chemokine ligands

expressed at common metastatic sites, such as the lungs, bone marrow, brain and lymph nodes. Indeed, CXCR4 appears to be one of a limited number of genes that are enriched in a subpopulation of metastatic breast cancer cells, as over-expression of CXCR4 alone significantly increased the number of bone and brain metastases *in vivo* (Kang et al., 2003). Supporting evidence for the hypothesis was demonstrated by Liang et al. (2005) as blocking CXCR4 expression by siRNAs decreased breast cancer cell invasion *in vitro* and inhibited metastasis in animal models. Interestingly, the CXCR4 carboxy-terminal domain appears to play a major role in regulating receptor desensitization and down-regulation, whereas deletion of the C-terminal domain of CXCR4 leads to the down-regulation of cell-to-cell contact, enhanced motility, and proliferation in breast carcinoma cells (Ueda et al., 2006). Elucidation of the underlying mechanisms of breast cancer invasion and metastasis focusing on CXCR4 has resulted in several important observations. Ligand-binding studies indicate that the number and affinity of CXCR4 receptors are similar in nonmetastatic cells versus highly metastatic cells. In metastatic cells, CXCL12 binding to the $G\alpha\beta\gamma$ /GDP protein complex leads to a GTP-for-GDP exchange, allowing $G_{\alpha i}$ to dissociate from the $G\beta\gamma$ subunit, leading to activation of ERK1/2, I κ B α , JNK, Akt, p38 MAPK, and GSK-3 $\alpha\beta$. In nonmetastatic cells, CXCR4 is able to independently form a complex with $G_{\alpha i}$ or $G\beta$ subunits, but no $G\alpha\beta\gamma$ heterotrimer could be associated with CXCR4 and, ultimately, $G\beta\gamma$ -dependent downstream signaling did not occur (Holland et al., 2006). Although the molecular basis for the difference in G-protein signaling in metastatic versus nonmetastatic cells remains to be elucidated, these studies have implications for clinical studies that are examining CXCR4 protein expression but not receptor function. As observed in breast cancer cell lines, detection of CXCR4 protein does not necessarily indicate CXCR4-mediated signaling (Fulton, 2009).

There is increasing evidence that CXCR4 interacts with several growth factor receptor tyrosine kinases. Upon activating IGF-1R, IGF-1 was shown to transactivate CXCR4 signal transduction in metastatic MDA-MB-231 cells but not in nonmetastatic MCF-7 cells, even though both cell lines are positive for IGF-1R and CXCR4 (Akekawatchai et al., 2005). Myofibroblasts associated with breast cancer, but not those in normal breast tissue, produce CXCL12 and enhance growth of tumours through mechanisms that include proliferation and survival of malignant cells and angiogenesis (Allinen et al., 2004; Orimo et al., 2005). Specific alleles of CXCL12 are associated with an increased risk of breast cancer (Razmkhah et al., 2005), and CXCL12 has been shown to transactivate ErbB-2 (Cabioglu et al., 2005). CXCR4 expression was also identified as a predictive factor of worse outcome in some metastatic tumours and in malignant gliomas (Scala et al., 2005; Ottaiano et al., 2006; Bian et al., 2007). CXCL12/CXCR4 axis is supposed to be crucial in brain metastases formation from breast cancer (Hinton et al., 2008). Recently, another CXCL12 receptor has been identified: the orphan G protein-coupled receptor (GPCR) RDC1, now called CXCR7 (Balabanian et al., 2005; Burns et al., 2006). This receptor does not mediate typical GPCR signaling through G_i or Ca^{2+} mobilization. Recent findings in zebrafish primordial germ cells showed a scavenger activity of CXCR7 generating a CXCL12 gradient that would lead to the formation of a guidance cue for CXCR4-positive cells (Thelen and Thelen, 2008). On the other hand, formation of CXCR4/CXCR7 heterodimers enhancing CXCL12 signaling in embryonic cells was observed, suggesting a potential interaction between the two receptors (Sierro et al., 2007). Nevertheless, CXCL12/CXCR4 relevance in brain metastasis establishment/progression needs more investigation especially on the molecular level.

6. Conclusions/Perspectives

Cancer cell migration and invasion are critical processes in the metastatic cascade. They can be induced and executed by various signalling pathways and regulatory networks. Many of these pathways seem to overlap with developmental processes and are being abused by invasive carcinomas cells and their microenvironment. Although we have made substantial progress in understanding the molecular mechanisms underlying cancer cell migration and invasion in experimental systems, we still lack sufficient insights into the actual processes at work in metastatic cancer patients especially brain metastatic disease. This divergence between clinicopathologic and experimental observations is mainly based on the lack of appropriate surrogate markers and the lack of complex *in vivo* models that appropriately recapitulate human stochastic carcinogenesis. However, it is expected that the ongoing cellular and molecular research on cell migration will provide the urgently needed tools for the development of improved diagnosis, prognosis and eventually for the design of innovative therapies.

There are few therapeutic approaches that are currently under development or in clinical trials specifically targeting metastatic breast cancer of the brain, such as interfering with specific pathways of some regulator genes of invasive cancer cells. However, by interfering with important signaling pathways that are known to modulate cell proliferation, survival, and differentiation, they may also affect cell migration and invasion. Examples are inhibitors against the activities of different receptor tyrosine kinases, such as EGF-R, ErbB-2, VEGF-Rs, fibroblast growth factor receptors, chemokine receptors, and c-Met, as well as various anti-angiogenesis regimen or even in combinations. Altogether, such multifaceted inhibitory approaches may provide efficient therapeutic measures that repress not only primary tumour outgrowth but also metastasis formation by interfering with cancer cell migration and invasion to the brain and other organs. However, the cellular and molecular variations to cancer cell migration discussed above raise the caveat that this endeavour will not be easy. We believe that using microarray technology and new *in vitro* and *in vivo* cancer metastatic models, including brain, should help us to understand the mechanism of cancer metastasis and consequently facilitate the design of more successful, personalized cancer therapies.

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8. References

- Akekawatchai C, Holland JD, Kochetkova M, Wallace JC, McColl SR. Transactivation of CXCR4 by the insulin-like growth factor-1 receptor (IGF-1R) in human MDA-MB-231 breast cancer epithelial cells. *J Biol Chem*. 2005 Dec 2;280(48):39701-8.
- Al Moustafa A-E, Achkhar A, Yasmeeen A. EGF-receptor signaling and epithelial-mesenchymal transition in human carcinomas. *Frontiers in Bioscience journal*, in press.

- Al Moustafa AE, Kassab A, Darnel A, Yasmeen A. High-risk HPV/ErbB-2 interaction on E-cadherin/catenin regulation in human carcinogenesis. *Curr Pharm Des*. 2008;14(22):2159-72.
- Allinen M, Beroukhi R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. *Cancer Cell*. 2004 Jul;6(1):17-32.
- Altundag K, Bondy ML, Mirza NQ, Kau SW, Broglio K, Hortobagyi GN, Rivera E. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. *Cancer*. 2007 Dec 15;110(12):2640-7.
- Aragon-Ching JB, Zujewski JA. (2007). CNS metastasis: an old problem in a new guise. *Clin Cancer Res*, vol.13, no.6, (mar 2007), pp. 1644-1647.
- Arnold SM, Young AB, Munn RK, Patchell RA, Nanayakkara N, Markesbery WR. Expression of p53, bcl-2, E-cadherin, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1 in paired primary tumors and brain metastasis. *Clin Cancer Res*. 1999 Dec;5(12):4028-33.
- Auguste P, Lemiere S, Larrieu-Lahargue F, Bikfalvi A. Molecular mechanisms of tumor vascularization. *Crit Rev Oncol Hematol* 2005;54:53-61.
- Baggiolini M. Chemokines and leukocyte traffic. *Nature* 1998; 392: 565-8.
- Balabanian K, Lagane B, Infantino S, Chow KY, Harriague J, Moepps B, Arenzana-Seisdedos F, Thelen M, Bachelier F. The chemokine SDF-1/CXCL12 binds to and signals through the orphan receptor RDC1 in T lymphocytes. *J Biol Chem*. 2005 Oct 21;280(42):35760-6.
- Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis*. 2004 Jun;16(1):1-13.
- Bartholdi D., Rubin B.P., Schwab M.E., 1997. VEGF mRNA induction correlates with changes in the vascular architecture upon spinal cord damage in the rat. *Eur. J. Neurosci*. 9, 2549-2560.
- Bendell JC, Domchek SM, Burstein HJ, et al. 2003. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*, vol. 97, no. 12, pp. 2972-2977.
- Bergers G, Brekken R, McMahon G, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol* 2000;2:737-44.
- Berse B, Brown LF, Van de Water L, Dvorak HF, Senger DR. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. *Mol Biol Cell* 1992;3:211-20.
- Bian XW, Yang SX, Chen JH, Ping YF, Zhou XD, Wang QL, Jiang XF, Gong W, Xiao HL, Du LL, Chen ZQ, Zhao W, Shi JQ, Wang JM. Preferential expression of chemokine receptor CXCR4 by highly malignant human gliomas and its association with poor patient survival. *Neurosurgery*. 2007 Sep;61(3):570-8; discussion 578-9.
- Bonecchi R, Galliera E, Borroni EM, Corsi MM, Locati M, Mantovani A. Chemokines and chemokine receptors: an overview. *Front Biosci*. 2009 Jan 1;14:540-51.
- Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA, Massagué J. Genes that mediate breast cancer metastasis to the brain. *Nature*. 2009 Jun 18;459(7249):1005-9.

- Breier G, Albrecht U, Sterrer S, Risau W. Expression of vascular endothelial growth factor during embryonic angiogenesis and endothelial cell differentiation. *Development* 1992;114:521-32.
- Bremnes RM, Veve R, Hirsch FR, Franklin WA. The E-cadherin cell-cell adhesion complex and lung cancer invasion, metastasis, and prognosis. *Lung Cancer*. 2002 May;36(2):115-24.
- Brown, L. F., Berse, B., Jackman, R. W. Tognazzi, K. Guidi, A. J. Dvorak, H. F. Senger, D. R. Connolly, J. L. Schnitt, S. J. 1995. "Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer." *Hum Pathol* 26(1): 86-91.
- Bublil EM, Yarden Y. The EGF receptor family: spearheading a merger of signaling and therapeutics. *Current opinion in cell biology* 2007; 19:124-34.
- Burger JA, Kipps TJ. CXCR4: A key receptor in the crosstalk between tumor cells and their microenvironment. *Blood* 2006; 107: 1761-7.
- Burns JM, Summers BC, Wang Y, Melikian A, Berahovich R, Miao Z, Penfold ME, Sunshine MJ, Littman DR, Kuo CJ, Wei K, McMaster BE, Wright K, Howard MC, Schall TJ. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J Exp Med*. 2006 Sep 4;203(9):2201-13.
- Burness ML, Grushko TA, Olopade OI. 2010. Epidermal growth factor receptor in triple-negative and basal-like breast cancer: promising clinical target or only a marker?. *Cancer J*, vol. 16, pp.23-32.
- Cabioglu N, Summy J, Miller C, Parikh NU, Sahin AA, Tuzlali S, Pumiglia K, Gallick GE, Price JE. CXCL-12/stromal cell-derived factor-1 α transactivates HER2-neu in breast cancer cells by a novel pathway involving Src kinase activation. *Cancer Res*. 2005 Aug 1;65(15):6493-7.
- Carney W, Leitzel K, Ali S, Neumann R, Lipton A. 2007. HER-2 therapy. HER-2/neu diagnostics in breast cancer. *Breast Cancer Res.* vol. 9:207.
- Carotenuto P, Roma C, Rachiglio AM, Botti G, D'Alessio A, Normanno N. Triple negative breast cancer: from molecular portrait to therapeutic intervention. *Crit Rev Eukaryot Gene Expr*. 2010;20(1):17-34.
- Carpenter G, Cohen S. Epidermal growth factor. 1990. *J Biol Chem*; vol. 265, pp.7709-7712.
- Chang H, Riese DJ, 2nd, Gilbert W, Stern DF, McMahan UJ. Ligands for ErbB-family receptors encoded by a neuregulin-like gene. *Nature* 1997; 387:509-12.
- Cheng X, Hung MC. Breast cancer brain metastases. *Cancer Metastasis Rev*. 2007 Dec;26(3-4):635-43.
- Clayton AJ, Danson S, Jolly S, et al. 2004. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer*, vol. 91, no. 4, pp. 639-643.
- Da Silva L, Clarke C, Lakhani SR. 2007. Demystifying basal-like breast carcinomas. *J Clin Pathol*, vol. 60, no.12, pp 1328-1332.
- Da Silva L, Simpson PT, Smart CE, Cocciardi S, Waddell N, et al. 2010. HER3 and downstream pathways are involved in colonization of brain metastases from breast cancer. *Breast Cancer Research*, vol. 12, no. 4, pp. 1-13.
- Deryugina EI, Quigley JP. Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Rev*. 2006 Mar;25(1):9-34.

- Dontu G, Al-Hajj M, Abdallah WM, Clarke MF, Wicha MS. Stem cells in normal breast development and breast cancer. *Cell Prolif* 2003; 36 (Suppl 1): 59–72.
- Dougher, A. M., Wasserstrom, H., Torley, L. Shridaran, L. Westdock, P. Hileman, R. E. Fromm, J. R. Anderberg, R. Lyman, S. Linhardt, R. J. Kaplan, J. Terman, B. I. 1997. "Identification of a heparin binding peptide on the extracellular domain of the KDR VEGF receptor." *Growth Factors* 14(4): 257-68.
- Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: 2004.identification of a high-risk group. *Clin Oncol (R Coll Radiol (Great Britain))*; vol. 16, no. 5, pp. 345–349.
- Fan P, Yue W, Wang JP, Aiyar S, Li Y, Kim TH, et al. 2009. Mechanisms of resistance to structurally diverse antiestrogens differ under premenopausal and postmenopausal conditions: evidence from in vitro breast cancer cell models. *Endocrinology*, vol. 150, no.5, pp. 2036–2045.
- Fantl WJ, Johnson DE, Williams LT. Signalling by receptor tyrosine kinases. *Annu Rev Biochem* 1993;62:453–81.
- Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: Functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996; 272: 872–7.
- Figarella-Branger D, Pellissier JF, Bouillot P, Bianco N, Mayan M, Grisoli F, Rougon G.Expression of neural cell-adhesion molecule isoforms and epithelial cadherin adhesion molecules in 47 human meningiomas: correlation with clinical and morphological data. *Mod Pathol*. 1994 Sep;7(7):752-61.
- Fischer, I., J. P. Gagner, Law, M. Newcomb, E. W. Zagzag, D. 2005. "Angiogenesis in gliomas: biology and molecular pathophysiology." *Brain Pathol* 15(4): 297-310.
- Folkman J. (1971) Tumor angiogenesis: therapeutic implications. *N Engl J Med*; 285:1182-1186.
- Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol Pharmacol* 2003; 63: 1256–72.
- Fukuzawa, M., Sugiura, H., Koshinaga, T., Ikeda, T., Hagiwara, N., Sawada, T. (2002). "Expression of vascular endothelial growth factor and its receptor Flk-1 in human neuroblastoma using in situ hybridization." *J Pediatr Surg* 37(12): 1747-50.
- Fulton AM. The chemokine receptors CXCR4 and CXCR3 in cancer. *Curr Oncol Rep*. 2009 Mar;11(2):125-31.
- Furusato B, Mohamed A, Uhlén M, Rhim JS. CXCR4 and cancer. *Pathol Int*. 2010 Jul;60(7):497-505
- Gabos Z, Sinha R, Hanson J, et al. 2006. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. *J Clin Oncol* , vol. 24, no.36, pp. 5658–5663.
- Geminder H, Sagi-Assif O, Goldberg L, Meshel T, Rechavi G, Witz IP, Ben-Baruch A. A possible role for CXCR4 and its ligand, the CXC chemokine stromal cell-derived factor-1, in the development of bone marrow metastases in neuroblastoma. *J Immunol*. 2001 Oct 15;167(8):4747-57.
- Gerhardt H, Golding M, Fruttiger M, et al. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J Cell Biol* 2003;161:1163–77.

- Gluzman-Poltorak, Z., Cohen, T., Herzog, Y. Neufeld, G. 2000. "Neuropilin-2 is a receptor for the vascular endothelial growth factor (VEGF) forms VEGF-145 and VEGF-165 [corrected]." *J Biol Chem* 275(24): 18040-5.
- Grandis JR, Sok JC .(2004). Signaling through the epidermal growth factor receptor during the development of malignancy. *Pharmacol Ther*, vol 102, pp. 37- 46.
- Graumann, U., R. Reynolds, Steck, A. J., Schaeren-Wiemers, N. 2003. "Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult." *Brain Pathol* 13(4): 554-73.
- Harlozinska A. Progress in molecular mechanisms of tumor metastasis and angiogenesis. *Anticancer Res.* 2005; 25: 3327-33.
- Hattori K, Heissig B, Tashiro K, Honjo T, Tateno M, Shieh JH, Hackett NR, Quitoriano MS, Crystal RG, Rafii S, Moore MA. Plasma elevation of stromal cell-derived factor-1 induces mobilization of mature and immature hematopoietic progenitor and stem cells. *Blood.* 2001 Jun 1;97(11):3354-60.
- Hinton CV, Avraham S, Avraham HK. Contributions of integrin-linked kinase to breast cancer metastasis and tumorigenesis. *J Cell Mol Med.* 2008 Sep-Oct;12(5A):1517-26.
- Hinton CV, Avraham S, Avraham HK. Role of the CXCR4/CXCL12 signaling axis in breast cancer metastasis to the brain. *Clin Exp Metastasis.* 2010 Feb;27(2):97-105.
- Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis. *Pharmacol Rev* 2004;56:549-80.
- Holash J, Maisonpierre PC, Compton D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science* 1999;284:1994-8.
- Holland JD, Kochetkova M, Akekawatchai C, Dottore M, Lopez A, McColl SR. Differential functional activation of chemokine receptor CXCR4 is mediated by G proteins in breast cancer cells. *Cancer Res.* 2006 Apr 15;66(8):4117-24.
- Howng SL, Wu CH, Cheng TS, Sy WD, Lin PC, Wang C, Hong YR. Differential expression of Wnt genes, beta-catenin and E-cadherin in human brain tumors. *Cancer Lett.* 2002 Sep 8;183(1):95-101.
- Issa, R., Krupinski, J., Bujny, T., Kumar, S., Kaluza, J., Kumar, P., 1999. Vascular endothelial growth factor and its receptor, KDR, in human brain tissue after ischemic stroke. *Lab. Invest.* 79, 417-425.
- Jäälinojä J, Herva R, Korpela M, Höyhty M, Turpeenniemi-Hujanen T. Matrix metalloproteinase 2 (MMP-2) immunoreactive protein is associated with poor grade and survival in brain neoplasms. *J Neurooncol.* 2000;46(1):81-90.
- Jin, K.L., Mao, X.O., Nagayama, T., Goldsmith, P.C., Greenberg, D.A., 2000. Induction of vascular endothelial growth factor and hypoxia-inducible factor-1 alpha by global ischemia in rat brain. *Neuroscience* 99, 577-585.
- Jordan VC, O'Malley BW. (2007). Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. *J Clin Oncol*, vol. 25, no.36, pp. 5815-5824.
- Kang Y, Siegel PM, Shu W, Drobnjak M, Kakonen SM, Cordon-Cardo C, Guise TA, Massagué J. A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell.* 2003 Jun;3(6):537-49.
- Kaplan RN, Rafii S, Lyden D. Preparing the "soil": the premetastatic niche. *Cancer Res.* 2006; 66: 11089-93.

- Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Gelmon K. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010 Jul 10;28(20):3271-7.
- Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell*. 2010 Apr 2;141(1):52-67.
- Klein A, Olendrowitz C, Schmutzler R, Hampl J, Schlag PM, Maass N, Arnold N, Wessel R, Ramser J, Meindl A, Scherneck S, Seitz S. Identification of brain- and bone-specific breast cancer metastasis genes. *Cancer Lett*. 2009 Apr 18;276(2):212-20.
- Korkaya H, Paulson A, Iovino F, Wicha MS. 2008. HER2 regulates the mammary stem/progenitor cell population driving tumorigenesis and invasion. *Oncogene*, vol. 27, pp. 6120–6130.
- Kremer, C., Breier, G., Risau, W., Plate, K.H., 1997. Up-regulation of flk-1/vascular endothelial growth factor receptor 2 by its ligand in a cerebral slice culture system. *Cancer Res*. 57, 3852–3859.
- Krum, J. M., Mani, N., Rosenstein, J. M. 2008. "Roles of the endogenous VEGF receptors flt-1 and flk-1 in astroglial and vascular remodeling after brain injury." *Exp Neurol* 212(1): 108-17.
- Krum, J.M., Mani, N., Rosenstein, J.M., 2002. Angiogenic and astroglial responses to vascular endothelial growth factor administration in adult rat brain. *Neuroscience* 110, 589–604.
- Krum, J.M., Rosenstein, J.M., 1999. Transient coexpression of nestin, GFAP, and vascular endothelial growth factor in mature reactive astroglia following neural grafting or brain wounds. *Exp. Neurol*. 160, 348–360.
- Kukk E, Lymboussaki A, Taira S, et al. VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development. *Development* 1996;122:3829–37.
- Kunkel P, Ulbricht U, Bohlen P, et al. Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2. *Cancer Res* 2001;61:6624–8.
- Kusters B, Leenders WP, Wesseling P, et al. Vascular endothelial growth factor-A(165) induces progression of melanoma brain metastases without induction of sprouting angiogenesis. *Cancer Res* 2002;62:341–5.
- Lai R, Dang CT, Malkin MG, Abrey LE. 2004. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. *Cancer*; vol. 101, pp. 810–6.
- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin*. 1999 Jan-Feb;49(1):8-31, 1.
- Lapidot T, Petit I. Current understanding of stem cell mobilization: The roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. *Exp Hematol* 2002; 30: 973–81.
- Law AJ, Shannon Weickert C, Hyde TM, Kleinman JE, Harrison PJ. 2004. Neuregulin-1 (NRG-1) mRNA and protein in the adult human brain. *Neuroscience*, vol. 127, pp. 125-136.
- Lee SS, Ahn JH, Kim MK, Sym SJ, Gong G, Ahn SD, Kim SB, Kim WK. Brain metastases in breast cancer: prognostic factors and management. *Breast Cancer Res Treat*. 2008 Oct;111(3):523-30.

- Lee, M.Y., Ju, W.K., Cha, J.H., Son, B.C., Chun, M.H., Kang, J.K., Park, C.K., 1999. Expression of vascular endothelial growth factor mRNA following transient forebrain ischemia in rats. *Neurosci. Lett.* 265, 107-110.
- Lee-Hoeflich ST, Crocker L, Yao E, Pham T, Munroe X, Hoeflich KP, et al. 2008. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*, vol. 68, pp. 5878-5887.
- Lewis-Tuffin LJ, Rodriguez F, Giannini C, Scheithauer B, Necela BM, Sarkaria JN, Anastasiadis PZ. Misregulated E-cadherin expression associated with an aggressive brain tumor phenotype. *PLoS One*. 2010 Oct 27;5(10):e13665.
- Li, X., U. Eriksson, Novel VEGF family members: VEGF-B, VEGF-C and VEGF-D, *Int. J. Biochem. Cell Biol.* 2001, 33, 421-426.
- Liang Z, Yoon Y, Votaw J, Goodman MM, Williams L, Shim H. Silencing of CXCR4 blocks breast cancer metastasis. *Cancer Res*. 2005 Feb 1;65(3):967-71.
- Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004;22:3608-3617.
- Locati M, Murphy PM. Chemokines and chemokine receptors: biology and clinical relevance in inflammation and AIDS. *Annu Rev Med*. 1999;50:425-40.
- Loetscher P, Moser B, Baggiolini M. Chemokines and their receptors in lymphocyte traffic and HIV infection. *Adv Immunol* 2000; 74: 127-80.
- Luster AD. Chemokines--chemotactic cytokines that mediate inflammation. *N Engl J Med*. 1998 Feb 12;338(7):436-45
- Lymboussaki, A., Olofsson, B., Eriksson, U., Alitalo, K., 1999. "Vascular endothelial growth factor (VEGF) and VEGF-C show overlapping binding sites in embryonic endothelia and distinct sites in differentiated adult endothelia." *Circ Res* 85(11): 992-9.
- Maharaj AS, Saint-Geniez M, Maldonado AE, D'Amore PA. Vascular endothelial growth factor localization in the adult. *Am J Pathol* 2006;168:639-48.
- Mani, N., Khaibullina, A., Krum, J. M., Rosenstein, J. M. 2005. "Astrocyte growth effects of vascular endothelial growth factor (VEGF) application to perinatal neocortical explants: receptor mediation and signal transduction pathways." *Exp Neurol* 192(2): 394-406.
- Mayer M. A patient perspective on brain metastases in breast cancer. *Clin Cancer Res* 2007;13:1623-1624.
- McGrath KE, Koniski AD, Maltby KM, McGann JK, Palis J. Embryonic expression and function of the chemokine SDF-1 and its receptor, CXCR4. *Dev Biol* 1999; 213: 442-56.
- Mendes O, Kim HT, Stoica G. Expression of MMP2, MMP9 and MMP3 in breast cancer brain metastasis in a rat model. *Clin Exp Metastasis*. 2005;22(3):237-46.
- Mentzel, T., L. F. Brown, Dvorak, H. F. Kuhnen, C. Stiller, K. J. Katenkamp, D. Fletcher, C. D. 2001. "The association between tumour progression and vascularity in myxofibrosarcoma and myxoid/round cell liposarcoma." *Virchows Arch* 438(1): 13-22.
- Millauer, B., Wizigmann-Voos, S., Schnurch, H., Martinez, R., Moller, N.P., Risau, W., Ullrich, A., 1993. High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. *Cell* 72, 835-846.

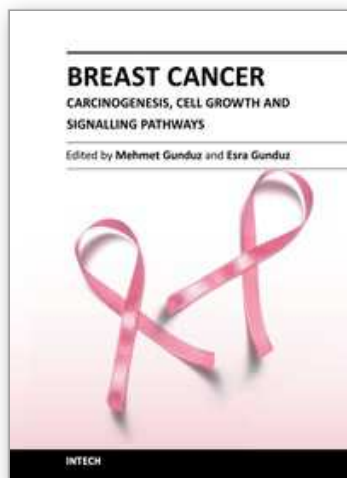
- Monacci, W.T., Merrill, M.J., Oldfield, E.H., 1993. Expression of vascular permeability factor/vascular endothelial growth factor in normal rat tissues. *Am. J. Physiol.* 264, 995–1002.
- Moser B, Loetscher P. Lymphocyte traffic control by chemokines. *Nat Immunol* 2001; 2: 123–8.
- Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN, Barrera JL, Mohar A, Verástegui E, Zlotnik A. Involvement of chemokine receptors in breast cancer metastasis. *Nature*. 2001 Mar 1;410(6824):50-6.
- Murphy G. The ADAMs: signalling scissors in the tumour microenvironment. *Nat Rev Cancer*. 2008 Dec;8(12):929-41.
- Murphy PM, Baggiolini M, Charo IF, Hébert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ, Power CA. International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev.* 2000 Mar;52(1):145-76.
- Murphy PM. The molecular biology of leukocyte chemoattractant receptors. *Annu Rev Immunol* 1994; 12: 593–633.
- Nag, S., Takahashi, J.L., Kilty, D.W., 1997. Role of vascular endothelial growth factor in blood-brain barrier breakdown and angiogenesis in brain trauma. *J. Neuropathol. Exp. Neurol.* 56, 912–921.
- Nagasawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, Yoshida N, Kikutani H, Kishimoto T. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature*. 1996 Aug 15;382(6592):635-8.
- Nagy, J.A., A.M. Dvorak, H.F. Dvorak, VEGF-A(164/165) and PlGF: roles in angiogenesis and arteriogenesis, *Trends Cardiovasc. Med.* 2003, 13, 169– 175.
- Nathoo N, Chahlavi A, Barnett GH, Toms SA. Pathobiology of brain metastases. *J Clin Pathol.* 2005 Mar;58(3):237-42.
- Ng YS, Rohan R, Sunday ME, Demello DE, D'Amore PA. Differential expression of VEGF isoforms in mouse during development and in the adult. *Dev Dyn* 2001;220:112–21.
- Ogawa K, Yoshii Y, Nishimaki T, Tamaki N, Miyaguni T, Tsuchida Y, Kamada Y, Toita T, Kakinohana Y, Tamaki W, Iraha S, Adachi G, Hyodo A, Murayama S. Treatment and prognosis of brain metastases from breast cancer. *J Neurooncol.* 2008 Jan;86(2):231-8.
- Ogunshola, O.O., Stewart, W.B., Mihalcik, V., Solli, T., Madri, J.A., Ment, L.R., 2000. Neuronal VEGF expression correlates with angiogenesis in postnatal developing rat brain. *Brain Res. Dev. Brain Res.* 119, 139– 153.
- Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*. 2005 May 6;121(3):335-48.
- Ottaiano A, Franco R, Aiello Talamanca A, Liguori G, Tatangelo F, Delrio P, Nasti G, Barletta E, Facchini G, Daniele B, Di Blasi A, Napolitano M, Ieranò C, Calemme R, Leonardi E, Albino V, De Angelis V, Falanga M, Boccia V, Capuozzo M, Parisi V, Botti G, Castello G, Vincenzo Iaffaioli R, Scala S. Overexpression of both CXC chemokine receptor 4 and vascular endothelial growth factor proteins predicts early distant relapse in stage II-III colorectal cancer patients. *Clin Cancer Res.* 2006 May 1;12(9):2795-803.

- Palmieri D, Smith QR, Lockman PR, Bronder J, Gril B, Chambers AF, Weil RJ, Steeg PS. Brain metastases of breast cancer. *Breast Dis.* 2006-2007; 26: 139-47.
- Papavassiliou, E., Gogate, N., Proescholdt, M., Heiss, J.D., Walbridge, S., Edwards, N.A., Oldfield, E.H., Merrill, M.J., 1997. Vascular endothelial growth factor (vascular permeability factor) expression in injured rat brain. *J. Neurosci. Res.* 49, 451-460.
- Patchell RA. The management of brain metastases. *Cancer Treat Rev.* 2003 Dec;29(6):533-40.
- Pawlowski V, Revillion F, Hebbar M, Hornez L, Peyrat JP. 2000. Prognostic value of the type I growth factor receptors in a large series of human primary breast cancers quantified with a real-time reverse transcription-polymerase chain reaction assay. *Clin Cancer Res*, 6, pp. 4217-4225.
- Pepper MS, Ferrara N, Orci L, Montesano R. Vascular endothelial growth factor (VEGF) induces plasminogen activators and plasminogen activator inhibitor-1 in microvascular endothelial cells. *Biochem Biophys Res Commun* 1991;181:902-6.
- Pestalozzi BC, Brignoli S. 2000. Trastuzumab in CSF. *J Clin Oncol*, vol. 18, no.11, pp. 2349-2351.
- Pestalozzi BC, Zahrieh D, Price KN, et al. 2006. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). *Ann Oncol*, vol. 17, no. 6, pp. 935-944.
- Peters, K.G., De Vries, C., Williams, L.T., 1993. Vascular endothelial growth factor receptor expression during embryogenesis and tissue repair suggests a role in endothelial differentiation and blood vessel growth. *Proc. Natl. Acad. Sci. USA* 90, 8915-8919.
- Pietsch, T., Valter, M.M., Wolf, H.K., von Deimling, A., Huang, H.J., Cavenee, W.K., Wiestler, O.D., 1997. Expression and distribution of vascular endothelial growth factor protein in human brain tumors. *Acta Neuropathol.* 93, 109-117.
- Plate, K.H., Beck, H., Danner, S., Allegrini, P.R., Wiessner, C., 1999. Cell type specific upregulation of vascular endothelial growth factor in an MCA-occlusion model of cerebral infarct. *J. Neuropathol. Exp. Neurol.* 58, 654-666.
- Porcile C, Bajetto A, Barbero S, Pirani P, Schettini G. CXCR4 activation induces epidermal growth factor receptor transactivation in an ovarian cancer cell line. *Ann N Y Acad Sci* 2004; 1030: 162-9.
- Prudkin L, Liu DD, Ozburn NC, Sun M, Behrens C, Tang X, Brown KC, Bekele BN, Moran C, Wistuba II. Epithelial-to-mesenchymal transition in the development and progression of adenocarcinoma and squamous cell carcinoma of the lung. *Mod Pathol.* 2009 May;22(5):668-78.
- Razmkhah M, Talei AR, Doroudchi M, Khalili-Azad T, Ghaderi A. Stromal cell-derived factor-1 (SDF-1) alleles and susceptibility to breast carcinoma. *Cancer Lett.* 2005 Jul 28;225(2):261-6.
- Raymond E, Faivre S, Armand JP: Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. *Drugs* 2000, 60 Suppl, no.1, pp. 15-23.
- Ribatti, D., Alessandri, G., Vacca, A. Iurlaro, M., Ponzoni, M., (1998). "Human neuroblastoma cells produce extracellular matrix-degrading enzymes, induce endothelial cell proliferation and are angiogenic in vivo." *Int J Cancer* 77(3): 449-54.
- Rusnak DW, Lackey K, Affleck K, et al. 2001. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. *Mol Cancer Ther.* 2001, vol. 1, no. 2, (Dec 2001), pp. 85-94.

- Saad AG, Yeap BY, Thunnissen FB, Pinkus GS, Pinkus JL, Loda M, Sugarbaker DJ, Johnson BE, Chirieac LR. Immunohistochemical markers associated with brain metastases in patients with nonsmall cell lung carcinoma. *Cancer*. 2008 Oct 15;113(8):2129-38.
- Samoto K, Ikezaki K, One M, Shone T, Kohno K, Kuwano M, Fukui M: Expression of vascular endothelial growth factor and its possible relation with ueovascularization in human brain tumours. *Cancer Res* 1995, 55:1189-1193.
- Sanna G, Franceschelli L, Rotmensz N, Botteri E, Adamoli L, Marengi C, Munzone E, Cossu Rocca M, Verri E, Minchella I, Medici M, Catania C, Magni E, Goldhirsch A, Nolè F. Brain metastases in patients with advanced breast cancer. *Anticancer Res*. 2007; 27: 2865-9.
- Scala S, Ottaiano A, Ascierto PA, Cavalli M, Simeone E, Giuliano P, Napolitano M, Franco R, Botti G, Castello G. Expression of CXCR4 predicts poor prognosis in patients with malignant melanoma. *Clin Cancer Res*. 2005 Mar 1;11(5):1835-41.
- Schwechheimer K, Zhou L, Birchmeier W. E-Cadherin in human brain tumours: loss of immunoreactivity in malignant meningiomas. *Virchows Arch*. 1998 Feb;432(2):163-7.
- Shabani HK, Kitange G, Tsunoda K, Anda T, Tokunaga Y, Shibata S, Kaminogo M, Hayashi T, Ayabe H, Iseki M. Immunohistochemical expression of E-cadherin in metastatic brain tumors. *Brain Tumor Pathol*. 2003;20(1):7-12.
- Shemirani, B. and D. L. Crowe. 2000. "Head and neck squamous cell carcinoma lines produce biologically active angiogenic factors." *Oral Oncol* 36(1): 61-6.
- Sierro F, Biben C, Martínez-Muñoz L, Mellado M, Ransohoff RM, Li M, Woehl B, Leung H, Groom J, Batten M, Harvey RP, Martínez-A C, Mackay CR, Mackay F. Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7. *Proc Natl Acad Sci U S A*. 2007 Sep 11;104(37):14759-64.
- Silverman WF, Krum JM, Mani N, Rosenstein JM. Vascular, glial and neuronal effects of vascular endothelial growth factor in mesencephalic explant cultures. *Neuroscience*. 1999;90(4):1529-41.
- Slamon DJ, Clark GM, Wong SG, et al. 1987. Human breast cancer: correlation of relapse and survival with amplification of the HER2/neu oncogene. *Science*, vol. 235, pp.177-182.
- Soker, S., Takashima, S., Miao, H.Q., Neufeld, G., Klagsbrun, M., 1998. Neuropilin-1 is expressed by endothelial and tumor cells as an isoformspecific receptor for vascular endothelial growth factor. *Cell* 92, 735- 745.
- Stark AM, Anuszkiewicz B, Mentlein R, Yoneda T, Mehdorn HM, Held-Feindt J. Differential expression of matrix metalloproteinases in brain- and bone-seeking clones of metastatic MDA-MB-231 breast cancer cells. *J Neurooncol*. 2007 Jan;81(1):39-48.
- Strugar JS, Rothbart D, Harrington W, Criscuolo GR: Vascular permeability factor in brain metastases: correlation with vasogenic brain edema and tumour angiogenesis. *J Neurosurg* 1994, 81:560-566.
- Sun YX, Wang J, Shelburne CE, Lopatin DE, Chinnaiyan AM, Rubin MA, Pienta KJ, Taichman RS. Expression of CXCR4 and CXCL12 (SDF-1) in human prostate cancers (PCa) in vivo. *J Cell Biochem*. 2003 Jun 1;89(3):462-73.
- Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, Kitamura Y, Matsushima K, Yoshida N, Nishikawa S, Kishimoto T, Nagasawa T. The

- chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. *Nature*. 1998 Jun 11;393(6685):591-4.
- Terman B, Khandke L, Dougher-Vermazan M, Maglione D, Lassam NJ, Gospodarowicz D, Persico MG, Böhlen P, Eisinger M. VEGF receptor subtypes KDR and FLT1 show different sensitivities to heparin and placenta growth factor. *Growth Factors*. 1994;11(3):187-95.
- Tester AM, Waltham M, Oh SJ, Bae SN, Bills MM, Walker EC, Kern FG, Stetler-Stevenson WG, Lippman ME, Thompson EW. Pro-matrix metalloproteinase-2 transfection increases orthotopic primary growth and experimental metastasis of MDA-MB-231 human breast cancer cells in nude mice. *Cancer Res*. 2004 Jan 15;64(2):652-8.
- Thelen M, Thelen S. CXCR7, CXCR4 and CXCL12: an eccentric trio? *J Neuroimmunol*. 2008 Jul 31;198(1-2):9-13.
- Tohma Y, Yamashima T, Yamashita J. Immunohistochemical localization of cell adhesion molecule epithelial cadherin in human arachnoid villi and meningiomas. *Cancer Res*. 1992 Apr 1;52(7):1981-7.
- Tsao, M.N., Li, Y.Q., Lu, G., Xu, Y., Wong, C.S., 1999. Upregulation of vascular endothelial growth factor is associated with radiation-induced blood-spinal cord barrier breakdown. *J. Neuropathol. Exp. Neurol.* 58, 1051-1060.
- Ueda Y, Neel NF, Schutyser E, Raman D, Richmond A. Deletion of the COOH-terminal domain of CXC chemokine receptor 4 leads to the down-regulation of cell-to-cell contact, enhanced motility and proliferation in breast carcinoma cells. *Cancer Res*. 2006 Jun 1;66(11):5665-75.
- Vajkoczy P, Farhadi M, Gaumann A, et al. Microtumor growth initiates angiogenic sprouting with simultaneous expression of VEGF, VEGF receptor-2, and angiopoietin-2. *J Clin Invest* 2002;109:777-85.
- VanMeter TE, Rooprai HK, Kibble MM, Fillmore HL, Broaddus WC, Pilkington GJ. The role of matrix metalloproteinase genes in glioma invasion: co-dependent and interactive proteolysis. *J Neurooncol*. 2001 Jun;53(2):213-35.
- Vaquero, J., Zurita, M., de Oya, S., Coca, S., 1999. Vascular endothelial growth/permeability factor in spinal cord injury. *J. Neurosurg.* 90, 220-223.
- Vates, G. E., Hashimoto, T., Young, W. L., Lawton, M. T. 2005. "Angiogenesis in the brain during development: the effects of vascular endothelial growth factor and angiopoietin-2 in an animal model." *J Neurosurg* 103(1): 136-45.
- Vu TH, Shipley JM, Bergers G, et al. MMP-9/gelatinase B is a key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes. *Cell* 1998;93:411-22.
- Wang J, Jarrett J, Huang CC, Satcher RL Jr, Levenson AS. Identification of estrogen-responsive genes involved in breast cancer metastases to the bone. *Clin Exp Metastasis*. 2007; 24: 411-22.
- Xu, T., Chen, D., Chen, J. 2004. "Expression of vascular endothelial growth factor C and its correlation with lymph node metastasis in colorectal carcinoma." *J Huazhong Univ Sci Technolog Med Sci* 24(6): 596-8.
- Xue C, Liang F, Mahmood R, Vuolo M, Wyckoff J, et al. 2006. ErbB3-dependent motility and intravasation in breast cancer metastasis. *Cancer Res*, vol. 66, no.3, pp.1418-1426.

- Yamazaki, Y. , K. Takani, H. Atoda, T. Morita, Snake venom vascular endothelial growth factors (VEGFs) exhibit potent activity through their specific recognition of KDR (VEGF receptor 2), *J. Biol. Chem.* 2003 278, 51985– 51988.
- Yang W, Lam P, Kitching R, Kahn HJ, Yee A, Aubin JE, Seth A. Breast cancer metastasis in a human bone NOD/SCID mouse model. *Cancer Biol Ther.* 2007; 6: 1289–94.
- Yang W, Lam P, Kitching R, Kahn HJ, Yee A, Aubin JE, Seth A. Breast cancer metastasis in a human bone NOD/SCID mouse model. *Cancer Biol Ther.* 2007; 6: 1289–94.
- Yano, S., H. Shinohara, Herbst, R. S. Kuniyasu, H. Bucana, C. D. Ellis, L. M. Davis, D. W. McConkey, D. J. Fidler, I. J. 2000. "Expression of vascular endothelial growth factor is necessary but not sufficient for production and growth of brain metastasis." *Cancer Res* 60(17): 4959-67.
- Yasmeen A, Bismar TA, Al Moustafa AE ErbB receptors and epithelial-cadherin-catenin complex in human carcinomas. *Future Oncol.* 2006 Dec;2(6):765-81.
- Yasmeen A, Bismar TA, Dekhil H, Ricciardi R, Kassab A, Gambacorti-Passerini C, Al Moustafa AE. ErbB-2 receptor cooperates with E6/E7 oncoproteins of HPV type 16 in breast tumorigenesis. *Cell Cycle.* 2007 Dec 1;6(23):2939-43.
- Zagzag D, Amirnovin R, Greco MA, et al. Vascular apoptosis and involution in gliomas precede neovascularization: a novel concept for glioma growth and angiogenesis. *Lab Invest* 2000;80: 837–49.
- Zeljko M, Pecina-Slaus N, Martic TN, Kusec V, Beros V, Tomas D. Molecular alterations of E-cadherin and beta-catenin in brain metastases. *Front Biosci (Elite Ed).* 2011 Jan 1;3:616-24.
- Zhan L, Xiang B, Muthuswamy SK. 2006. Controlled activation of ErbB1/ErbB2 heterodimers promote invasion of three-dimensional organized epithelia in an ErbB1-dependent manner: implications for progression of ErbB2-overexpressing tumors. *Cancer Res*, 66, no. 3, pp. 5201–5208.
- Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity.* 2000 Feb;12(2):121-7.
- Zlotnik A. Chemokines and cancer. *Int J Cancer* 2006b; 119: 2026–9.
- Zlotnik A. Involvement of chemokine receptors in organ-specific metastasis. *Contrib Microbiol* 2006a; 13: 191–9.
- Zou YR, Kottmann AH, Kuroda M, Taniuchi I, Littman DR. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature* 1998; 393: 595–9.



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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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