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Cadherin Expression and Progression of Squamous Cell Carcinomas of the Oral Cavity

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1. Introduction

Cell-cell adhesion plays fundamental and dynamic roles in the development and maintenance of multi-cellular organisms. Epithelial sheet is a typical structure and composed of cells that work together and separate from a lumen or space from underlying tissue. It lines most internal surfaces, including gastrointestinal tract and kidney tubes, and external layer of the epithelium as the epidermis of skin. The oral cavity is covered with stratified squamous cell epithelium in which keratinizing epithelial cells strongly connect with each other and differentiate from basal cells at the bottom to keratinized surface cells. Epithelial cells are connected together by junctional complexes that have distinct order with respect to their ultra-structures; zonula occludens (tight junctions), gap junctions, zonula adherens (adherence junctions) and macula adherens (desmosomes). Adherence junctions in epithelial sheet are belt like junctions and composed of cadherins that bind with proteins at the cytoplasmic domain. In other cell types, adherence junctions display different morphology; spotty and discontinuous in fibroblastic cells and punctate in the synaptic junctions. Desmosome is a spot-like junction associated with desmosomal cadherins (desmogleins and desmocollins) and tightly associated with adjacent cell membranes compared to adherence junctions. Stratified squamous epithelial cells express large amount of cadherins and well organize adherence junctions and desmosomes. Disruption of desmosomes by autoantibodies against desmoglein causes pemphigus that are multiple and bullous diseases in the skin and oral mucosa. Cadherins are most characterized cell-cell adhesion molecules and implicated in the development and progression of carcinomas of the epithelial origin. In this chapter, we overview the regulation and role of cadherins in the pathology of oral squamous cell carcinomas (OSCCs).

2. The cadherin superfamily

Cadherins are calcium-dependent transmembrane proteins that are evolutionary conserved and have two or more extracellular domains (EC domains). Yoshida and Takeich (1992) cloned a transmembrane protein from the calcium-dependent junctions and termed cadherin. Since many related molecules were cloned, cadherins constitute a superfamily and the original cadherins are now called as “classic cadherins” (Fig. 1). Approximately twenty members of cadherins are included in the classic cadherin family depending on their

domain structures. In vertebrate, they have five repetitive EC domains that contains calcium-binding sequences and highly conserved cytoplasmic domain that directly interacts with catenins. The binding of calcium ions with the EC domains is prerequisite for the conformation and adhesive function of the extracellular region, and the extracellular region undergoes interactions with apposed cells. The classic cadherins are subdivided into type I and type II. Type I cadherin contains a His-Arg-Val sequence in the N-terminal EC domain, and other classic cadherins that do not contain the sequence are grouped into type II cadherin. The type I cadherin includes epithelial-cadherin (E-cadherin, CDH1), neural-cadherin (N-cadherin, CDH2), placental-cadherin (P-cadherin, CDH3) and others, and vascular endothelial-cadherin (VE-cadherin, CDH5), osteoblast-cadherin (OB-cadherin, CDH11) and others belong to the type II cadherins. Although it is still controversial, the classic cadherin basically binds with the same-type cadherin but not with other types. This nature of homophilic binding is implicated in the sorting of different cell types. Besides to the classic cadherins, a number of nonclassic cadherins that conserve EC domains but have divergent cytoplasmic sequences has been identified. Desmosomal cadherins are most closed to the classic cadherins and required for desmosome formation in the epithelium. Other nonclassic cadherins, including protocadherins, Fat and Flamingo, appear not to organize specialized junctions, nor to be the essential adherence junction components (Meng & Takeichi, 2009; Gumbiner, 2005).

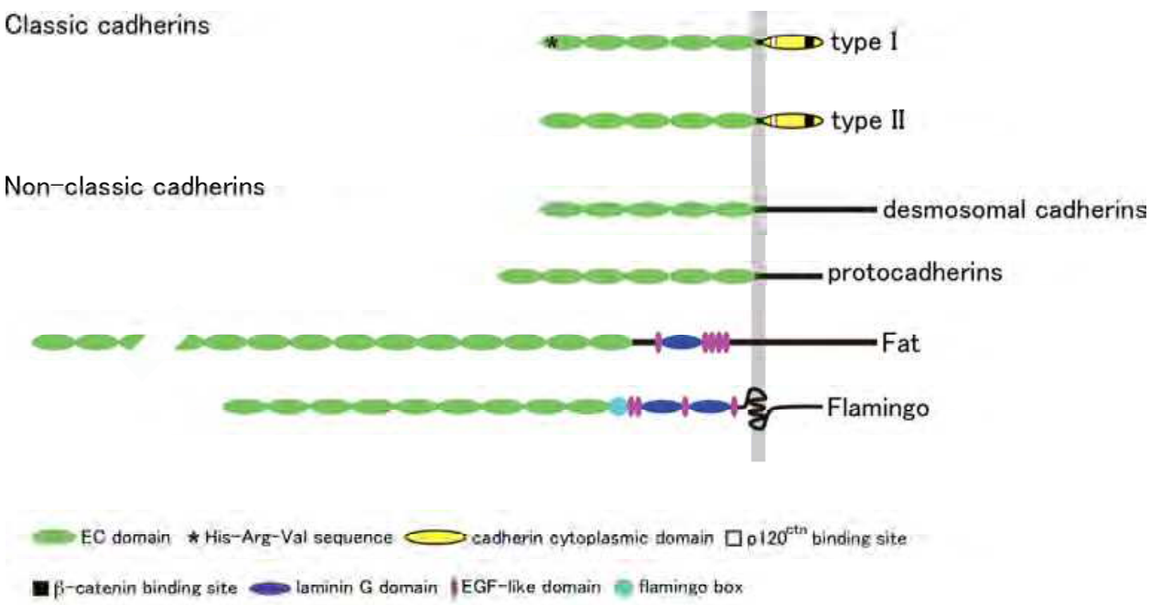

Fig. 1. Domain structures of cadherin superfamily. Molecules conserving EC domains in the extracellular region consist of the cadherin superfamily. The classic cadherins have five EC domains and the cytoplasmic domain possessing the binding sites for pl20^{ctn} and β-catenin. They are subdivided into type I and type ll groups according to the presence or absence of His-Arg-Val sequence in the N-terminal EC domain, respectively. Non-classic cadherins do not preserve the cytoplasmic domain and have unique cytoplasmic amino acid structures in each cadherin. Numbers of EC domains in each non-classic cadherin are different depending on members. For example, in desmosomal cadherins, desmoglein and desmocollin have four and five EC domains, respectively.

3. Cadherin functions at the adherence junction

The highly conserved cytoplasmic domains of the classic cadherins interact with catenins (Fig. 2). The juxtamembrane region of the cytoplasmic domain binds with p120-catenin

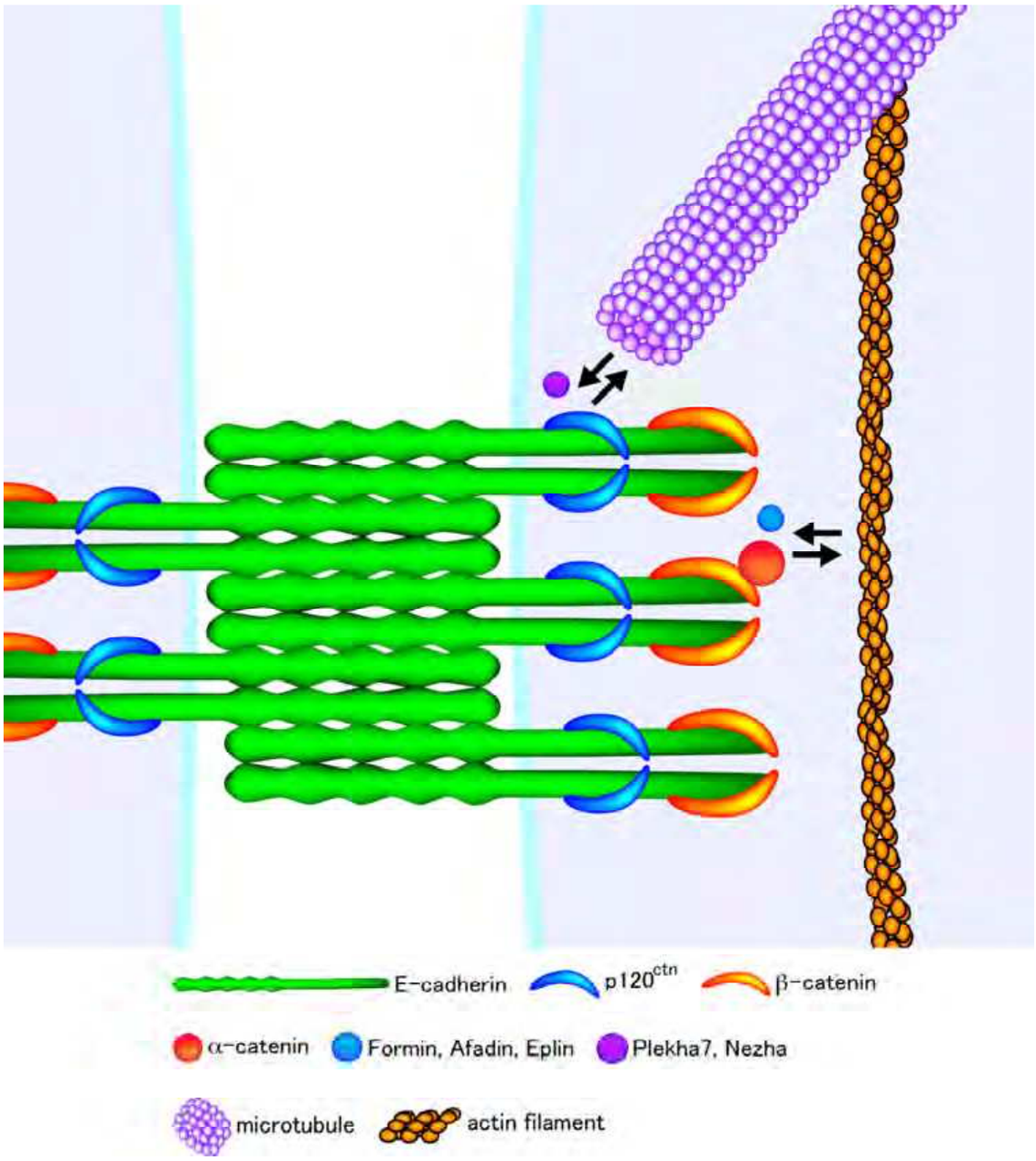

Fig. 2. Molecular structural organization of adherence junction containing E-cadherin. E-cadherins homotypically bind with adjacent cells by the EC domain interaction, and p12O^{ctn} and β-catenin interact with the cytoplasmic domain of E-cadherin. pl20^{ctn} directly associate with microtubules or indirectly mediated by Plekha 7 and Nezha. The β-catenin-α-catenin complex associates with actin filaments with or without linker proteins (Formin, Afadin and Eplin).

(p120ctn), and the carboxy-terminal half with β-catenin. The cytoplasmic domain indirectly binds with α-catenin through β-catenin, resulting in formation of the cadherin-β-catenin-α-catenin complex. The complex ligates with actin filaments that are essential for assembly and integrity of adherence junctions. Although early studies suggested that α-catenin acts as a linker protein which in turn interact with the complex and actin filament, recent studies showed that free α-catenin can bind the filament and promote the bundling of actin filaments, but not α-catenin in the complex (Drees et al., 2005; Yamada et al., 2005). Several proteins, including Formin (Kobielad et al., 2004), Afadin (Mandai, 1997) and Eplin (Abe & Takeichi, 2008), are suggested to work as a linker between α-catenin and actin filament. p120ctn protein also regulates actin reorganization and contractility by regulating RhoA activity (Anastasiadis et al., 2007). However, since the roles on the formation of adherence junction and the linkage with actin filament are appeared different depending on cell types (Meng & Takeichi, 2009), further studies are required to define the molecular mechanism for actin filament-binding to the adherence junction complex. Another cytoskeleton connected with the complex is microtubules. Microtubules extend to adherence junctions, and blocking the microtubules extension reduces accumulation of E-cadherin to the junctions (Stehbens et al., 2006; Harris & Tepass, 2010). Furthermore, depolymerization of microtubules disrupt the integrity of the junctions and inhibit disassembly of cell junctions (Waterman-Storer et al., 2000; Ivanov et al., 2006). Recent studies showed that microtubules interact with adherence junctions via p120ctn, Plekha7 and Nezha (Meng & Takeichi, 2009). The adherence junction is a static structure but cadherin proteins are recycled in epithelial cells. E-cadherin is endocytosed and transported to recycling endosomes followed by trafficking in late endosomes to the cell surface (Meng & Takeichi, 2009). The surface-located cadherins are stabilized by their homophilic interactions at adherence junctions. p120ctn also has a pivotal role in the microtubule assembly at adherence junctions. The p120ctn protein consist of the N-terminal region, armadillo repeat domain and C-terminal tail region. The N-terminal region and the armadillo repeat domain are responsible for binding with microtubules and the juxtamembrane domain of E-cadherin, respectively (Ichii & Takeichi, 2007; Ishiyama et al., 2010). The binding of p120ctn to E-cadherin masks a dileucine motif on the juxtamembrane domain, which is sensitive to endocytosis and ubiquitin-mediated degradation of E-cadherin (Ishiyama et al., 2010). It is suggested that p120ctn stabilizes the microtubule polymerization independent of a mechanistic trait of E-cadherin-mediated cell-cell adhesion (Ichii & Takeichi, 2007). Thus, the assembly and the function of adherence junctions are regulated by multi-dimensional factors, including E-cadherin *per se*, catenins, the related molecules and association with actin filaments and microtubules.

4. Roles of E-cadherin in the epithelium

E-cadherin-null mutation is lethal and the conditional knockout mice in skin epithelium show hyperproliferation of basal cells with defects in terminal differentiation (Ohsugi et al., 1997; Tinkle et al., 2004). An animal model of pancreatic carcinomas demonstrated a direct role of E-cadherin in adenoma-to-carcinoma conversion (Perl et al., 1998). These studies indicate that E-cadherin plays a critical role in developmental and pathological events *in vivo*. Forced expression of E-cadherin in the intestinal epithelium represses migration of epithelial cells along with the crypt-villus axis and stimulates the apoptotic rate of epithelial cells (Hermiston et al., 1996). Recent studies implicate that cadherins regulate interaction of growth factor receptors with ligands and modulate their signaling. Cadherins bind to growth factor receptors, including transforming growth factor-β receptor (TGFBR),

fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR), vascular endothelial cell growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), and the cytoplasmic domain can suppress growth-promoting cell signaling, such as Src, phosphatidylinositol-3-kinase (PI3K)/AKT and extracellular signal-regulated kinase (ERK) pathways (Reddy et al., 2005; Suyama et al., 2002; Georgopoulos et al., 2010; Cavallaro & Dejana, 2011). Sensitivity to the EGFR inhibitor, cetuximab, requires intact E-cadherin expression and silencing of E-cadherin reduces responsiveness to the inhibitor (Black et al., 2008). Cadherins regulate the growth factor signaling by recruiting the receptors at the cell surface, stimulating the receptor dimerization, and modulating their activities (Cavallaro & Dejana, 2011). β-catenin is a leading player in WNT signaling, which has a predominant role in developmental and pathophysiological conditions. Binding of WNTs to the receptors protected β-catenin from the degradation by the ubiquitin-protease pathway and increases the cytoplasmic free pool (Maher et al., 2009). The cytoplasmic free-β-catenin translocates into the nucleus and modulates gene transcription by interacting with lymphoid enhancer factor (LEF) and T cell factor (TCF). Since the cadherin-β-catenin interaction is constitutive, cadherins interfere with the transcriptional activity of β-catenin. Therefore, unveiling the regulatory mechanisms of E-cadherin expression is a pivotal theme to understand the initiation and progression of carcinomas and develop a novel strategy for the treatment of carcinoma patients.

5. Regulation of E-cadherin expression

Loss or reduction of E-cadherin expression results from somatic mutations, chromosomal deletions, proteolytic cleavage, promoter hypermethylation and transcriptional repression. Germ-line mutation of the E-cadherin gene causing inactivation of one allele has been reported in several families from New Zealand and Europe, and is associated with hereditary diffuse-type high-grade gastric carcinomas (Guiford et al., 1998; Gayther et al., 1998). Although single nucleotide polymorphisms have been described to associate with the reduction of transcription efficiency of E-cadherin gene (Li et al., 2000), the mechanism of reduction awaits for future studies to establish. However, genomic deletion and germ-line mutation with loss of heterozygosity, referred to as Knudson's two-hit theory, are rare events in sporadic carcinomas (Brown, 1997). Loss of E-cadherin expression stimulates carcinoma progression and carcinoma cells in the metastatic loci frequently re-express E-cadherin (Cheng et al., 2001), indicating the genetic mutation and polymorphism are not a major cause in sporadic carcinomas. In mammalian genome, methylation emerges at a cytosine located 5' to a guanosime in a CpG dinucleotide. CpG islands are found in promoter region of approximately half of the genes in human genome. In the development of cancers, epigenetic silencing of tumor-suppressive genes as a result of cytosine methylation in CpG islands has been documented as one of most important alterations. Increasing evidence highlight the fact that there are target genes for CpG island hypermethylation in many types of cancers, especially carcinomas of the epithelial origin (Fazzari & Greally, 2004; Jones & Baylin, 2002; Maeda et al., 2007a; Maeda et al., 2007b; Chiba et al., 2009). The hypermethylation at CpG islands determines the transcriptional status of a gene by blocking the access of certain transcription factors that are sensitive to cytosine methylation in their binding motifs, and by packaging chromatin into compacted nucleosomes with deacetylated histones and recruiting a methyl-cytosine-binding protein complex that represses transcription (Fazzari & Greally, 2004; Jones & Baylin, 2002). The transcription repressors, including Snail, Slug, Twist, zinc finger E-box binding homeobox

(ZEB)1, ZEB2, and E47, bind to the E-box (5′-CANNTG-3′) in the promoter and repress E-cadherin expression. After identification of Snail as a transcription repressor of E-cadherin in 2000 (Cano et al, 2000; Batlle et al, 2000), several other repressors were implicated in tumor progression and the epithelial-mesenchymal transition (EMT) induction. The EMT stimulates migration, earns the drug-resistance and the stem cell-like features of carcinoma cells and energizes carcinomas to an aggressive subset, and the loss of E-cadherin expression is the most prominent event (Hanahan & Weinberg, 2011). Expression of E-cadherin repressors is regulated by multiple pathways activated by growth factors. Among them, TGFβ signaling is frequently activated in aggressive carcinomas and induces the EMT of carcinoma cells at the invasive front. High mobility group protein A-2 (HMGA2), which is specifically expressed in undifferentiated mesenchymal cells, are strongly misexpressed in oral carcinoma cells at the invasive front in patients with poor prognosis (Fig. 3; Miyazawa

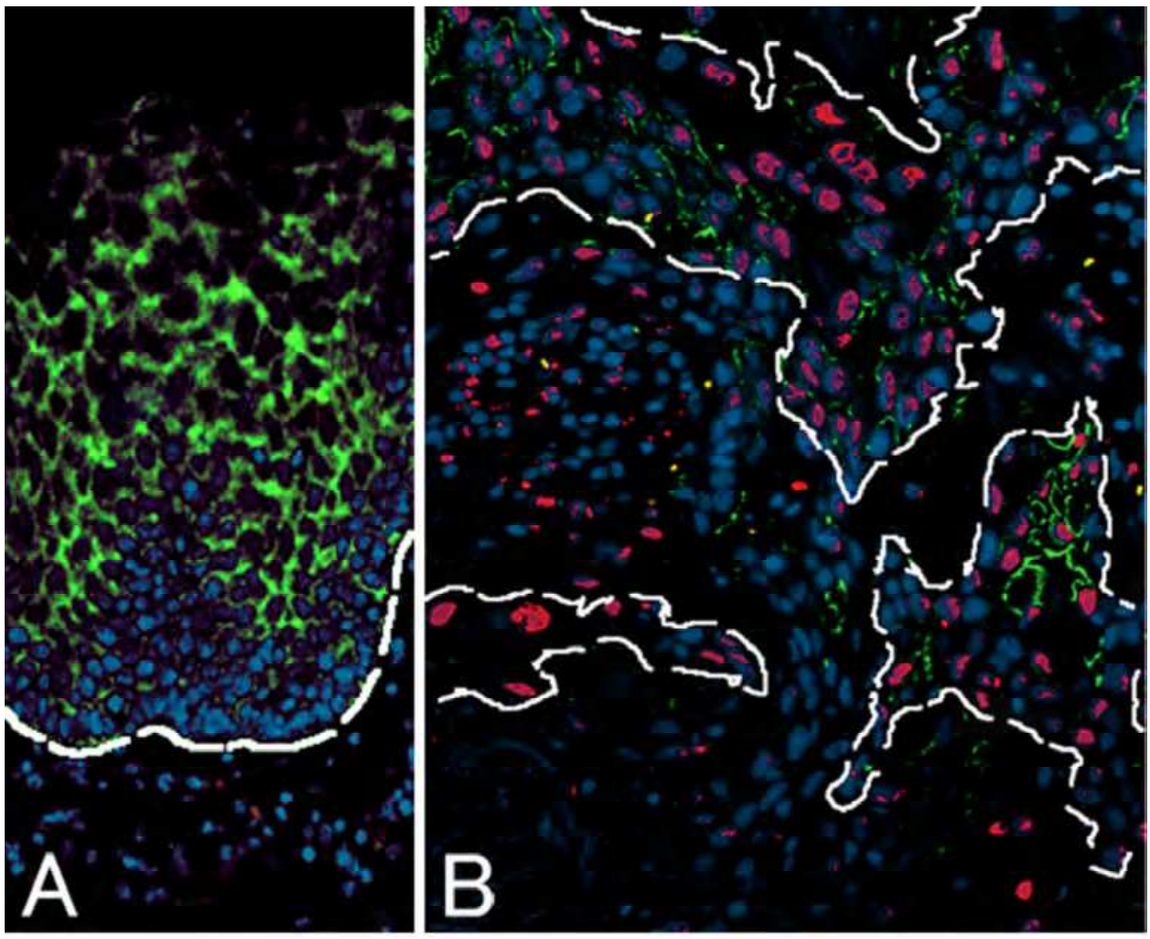

Fig. 3. Expression of E-cadherin and HMGA2 in oral epithelium and carcinomas. E-cadherin (green) expression is detected by iimmunofluorescent microscopy at the cell-cell boundaries of normal oral epithelium (A) while in carcinoma cells at the invasive dramatically lose the immunoreactivities (B). In contrast, the mesenchyme-specific HMGA2 expression (red) is localized in carcinoma cells that are negative for E-cadherin, and not detected in normal oral epithelial cells. The data in a panel B is reproduced from Miyazawa et al., [*Cancer Research*, Vol. 64, No.(6) pp.2024-2029, ISSN 1078-0432].

et al., 2004), and integrates the TGF-β-mediated EMT in carcinoma cell in combination with the induction of Snail, Slug and Twist (Thuault et al., 2006). In addition, inhibition of WNT signaling promotes degradation of Snail by the ubiquitin-proteasome pathway (Shou et al, 2004). Expression of E-cadherin is also post-transcriptionally regulated by the microenvironment of carcinoma cells. Furthermore, series of immunohistochemical studies suggest the differential roles of repressors; Snail in the induction of initial migratory phenotype of carcinoma cells followed by the maintenance of phenotype by Slug, Twist and ZEB1/2 (Peinado et al., 2007). The transcription repressors attenuate E-cadherin expression while they are negatively regulated by micoRNAs (miRNAs). Expression of miR-200, which binds to ZEB1 and ZEB2 mRNAs and abrogates their translation into proteins, is inhibited by TGF-β signaling but stimulated a tumor suppressor gene p53 (Kim et al., 2011; Gregory et al., 2011). The miR-92, which directly targets E-cadherin mRNA, downregulates p53 expression (Neveu et al., 2010; Chen et al., 2011). TGF-β also upregulates expression of matrix metalloproteinases (MMPs), which liberate TGF-β from surrounding tissues to cells after degradation of extracellular matrix proteins (Imai et al., 1997). Since MMPs shed the extracellular region of E-cadherin (Zheng et al., 2009; Imai & Okada, 2009), the TGFβ-MMP loop enhances disruption of E-cadherin-mediated adherence junctions of carcinoma cells. Therefore, the state of E-cadherin comprehensively regulated by the intrinsic and extrinsic factors of carcinoma cells (Fig. 4).

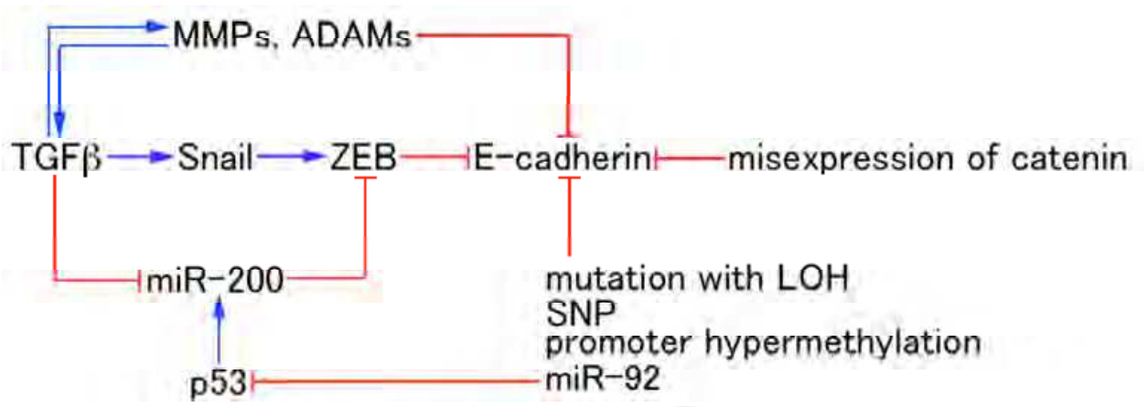

Fig. 4. A schematic representation for the E-cadherin expression and repression machineries. In carcinoma cells of epithelial origin, expression of E-cadherin is regulated by several pathways that directly or indirectly control the expression. Blue lines indicate stimulation and red lines indicate suppression.

6. Loss of E-cadherin expression in oral squamous cell carcinomas

As mentioned above, multi-factors may regulate the E-cadherin repression in oral carcinoma cells. Although germ-line mutation with the loss of heterozygosity is rare (Saito et al., 1998), epigenetic aberrations, including the promoter hypermethylation and expression of transcription repressors, are commonly observed in an aggressive subset of OSCCs. The hypermethylation is detected in 35-85% of OSCCs (Viswanathan et al., 2003; Yeh et al., 2002) and prompts carcinoma cells to develop invasive tumors (Nakayama et al., 2001). Kudo et al. (2004) reported that the hypermehtylation was observed in oral carcinoma cells at the invasive front but not in non-invasive areas. Although increasing number of investigations

revealed the presence of E-cadherin transcription repressors, their expression is largely dependent on cell and tissue types (Peinado et al., 2004). Snail is a most studied molecule that is responsible for repression of E-cadherin gene expression in many types of carcinomas including OSCCs (Yokoyama et al., 2001).

Snail expression is observed at the invasive front oral carcinoma cells of patients with poor prognosis (Yu et al., 2011). Although we could not find a reverse correlation between expression of Snail and E-cadherin in oral carcinoma cells, ZEB2 expression was upregualted in the E-cadherin-low cells and detected in carcinoma cells at the invasive front of OSCC patients with poor prognosis (Maeda et al., 2005). Upregulation of Twist in OSCCs is reported while its significance to E-cadherin expression is uncertain (Vered et al., 2010; Liang et al., 2011). In addition to the loss of E-cadherin expression, the involvement of catenins is also documented. The role of $p120^{ctn}$ in E-cadherin expression and carcinoma progression has been attracting a lot of attention. Loss of $p120^{ctn}$ expression in the oral epithelium in mice spontaneously develops invasive OSCCs, induces the EMT of carcinoma cells, and recruits chronic inflammatory reactions within carcinoma tissues (Stairs et al., 2011). Cell membrane-associated E-cadherin become endocytosis upon the loss of $p120^{ctn}$, leading to the reduction of cell-cell adhesion (Liu et al., 2007). The loss or mislocalization of $p120^{ctn}$ correlates with poor patient prognoses of carcinomas of the colon, bladder, stomach, breast, prostate, lung and pancreas (Thoreson & Reynolds, 2002). Cytoplasmic mislocation of $p120^{ctn}$ in oral carcinoma cell lines, while it is localized at the cell membrane of normal oral keratinocytes, was reported previously (Lo Muzio et al., 2002). However, the loss of expression in the epidermis does not have an obvious effect on cell-cell adhesion but reduces expression level of E-cadherin. The mice show epidermal inflammation due to activation of nuclear factor-kappa B (NF-κB) signaling (Perez-Moreno et al., 2006). Chronic inflammation increases production of inflammatory cytokines and reactive oxygen species and DNA damage, and results in development and progression of carcinomas (Meira et al., 2008). Oral carcinoma cells upregulate the E-cadherin-targeting miR-92 (Scapoli et al., 2010). Although expression of miR-200 in OSCCs is not known at present, nasopharyngeal carcinomas downregulate it which destabilizes ZEB1/2 mRNA (Chen et al., 2009). Regardless of the cause, loss of E-cadherin results in the liberation of β-catenin from adherence junctions and the increase of the cytoplasmic free-pool, which synergistically acts with the canonical WNT signaling. In fact, carcinoma cells at the invasive front, where loss of E-cadherin and expression of WNTs are observed, exhibit the cytoplasmic and/or nuclear staining of β-catenin (Uraguchi et al., 2004; Miyazawa et al., 2004). Silencing of β-catenin by RNA interference reduces proliferation of oral carcinoma cells (Duan & Fan, 2011). A recent study suggests that the loss of E-cadherin-mediated cell-cell adhesion and sequestering the β-catenin from E-cadherin have a differential role establishing metastatic properties of carcinoma cells (Onder et al., 2008). Although a precise mechanism is under debate, loss of E-cadherin expression and the gain of WNT expression may synergistically increase the cytoplasmic β-catenin and preserve it from degradation, allowing the nuclear translocation and transcriptional control of target genes toward the tumor progression. The WNT signaling represses transcription of E-cadherin gene but stimulates WNT protein expressions *per se*. The WNTs also upregulate E-cadherin suppressors, including Snail and Twist, and downregulate miR-200 (Saydam et al., 2009). E-cadherin suppresses activation of NF-κB, which strongly enhances aggressive behaviors of oral carcinoma cells and is upregulated in patients with poor outcome (Solanas et al., 2008). A mouse EMT model

demonstrated the essential contribution of NF-κB to the induction of EMT, maintenance of the mesenchymal phenotype, and metastasis (Huber et al., 2004). NF-κB suppresses E-cadherin expression through ZEB1 and ZEB2 induction (Chua et al., 2007). Therefore, reduction and loss of E-cadherin expression in OSCCs is under the control of multiple factors and pathways including the gene transcription, catenins and growth factor signaling.

7. Cadherin switch and oral carcinoma progression

E-cadherin and N-cadherin are the most prominent members of the classic cadherins, and a numbers of studies have been reported about their roles in carcinoma progression. During the progression of many human gastrointestinal tumors, gradual loss of E-cadherin expression at the invasive front accompanies a *de novo* N-cadherin expression (Wheelock et al., 2008). Replacing the member of cadherins, usually E-cadherin-to-N-cadherin in carcinoma cells, is referred as the cadherin switch. Followed by the cadherin switch, carcinoma cells acquire motile, invasive and metastatic abilities. Although functional implications are unknown at present, expression pattern of N-cadherin in a belt-like structure in low-grade prostate carcinomas becomes a dotted pattern at the interface of interaction with stromal fibroblasts in parallel with loss of E-cadherin expression (Tomita et al., 2000). Inhibition of N-cadherin expression or function blocks motility and invasion of carcinoma cells (De Wever et al., 2004). The cadherin switch is initiated by the internal and microenvironmental programs of carcinoma cells. Carcinoma cell adhesion on extracellular matrix proteins, including laminin (Kim et al., 2011), type I collagen (Shintani et al., 2008) and fibronectin (Lefort et al., 2011), induces N-cadherin expression. Another key regulator of N-cadherin is TGF-β, which can act to carcinoma cells after the extracellular matrix degradation and promotes invasion of oral carcinomas (Imai et al., 1997; Lu et al., 2004).

In OSCCs, TGF-β and N-cadherin is predominantly expressed at the invasive front and stimulates the motility of cells (Franz et al., 2007). The TGF-β signaling promotes oral carcinoma cells to express N-cadherin without affecting E-cadherin expression and regulate the motility (Diamond et al., 2008). Li et al. (2009) reported that N-cadherin was positively stained in 92.4% of tongue carcinomas while E-cadherin in 11.3%. A previous study reported that N-cadherin was upregulated in OSCCs with reduced expression of E-cadherin, and that N-cadherin expressing OSCCs had a tendency to be less histologically differentiated, more invasive and metastatic to lymph nodes (Pyo et al., 2007). However, from a stand of view that the carcinoma cell EMT is a representative event at the invasive front, there is no clear experimental study to investigate the role of the EMT in OSCC progression so far.

8. Conclusion

Investigators have reported numerous molecules related to the stimulation and the suppression of OSCC progression. Among the molecules, E-cadherin is one of most well-studied and powerful suppressor of carcinoma progression. It is frequently downregulated in aggressive OSCCs at the invasive front. Its expression is negatively regulated by many factors, including genetic and epigenetic factors, transcriptional repressors, miRNAs, growth factor signaling, shedding and catenin expression. In addition to loss of E-cadherin expression, carcinoma cells become to express N-cadherin referred as the cadherin switch.

The cadherin switch takes an important part in the EMT, which strongly stimulate aggressive behaviors of carcinoma cells. Since E-cadherin expression is negatively regulated by multi-dimension, re-activation of E-cadherin in carcinoma cells may not be a straightforward strategy to treat OSCC patients. However, unveiling the regulatory mechanism and roles of E-cadherin downregulation and cadherin switch will greatly improve our knowledge on the pathology of OSCCs and contribute to establish the future direction for the patient treatment.

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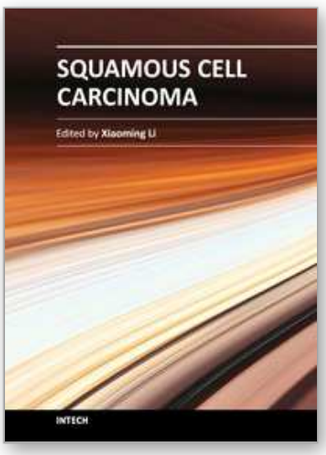

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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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