

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

3,500

Open access books available

108,000

International authors and editors

1.7 M

Downloads

Our authors are among the

151

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Kazushi Imai, Genta Maeda and Tadashige Chiba
*Department of Biochemistry, School of Life Dentistry at Tokyo,
The Nippon Dental University
Japan*

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).

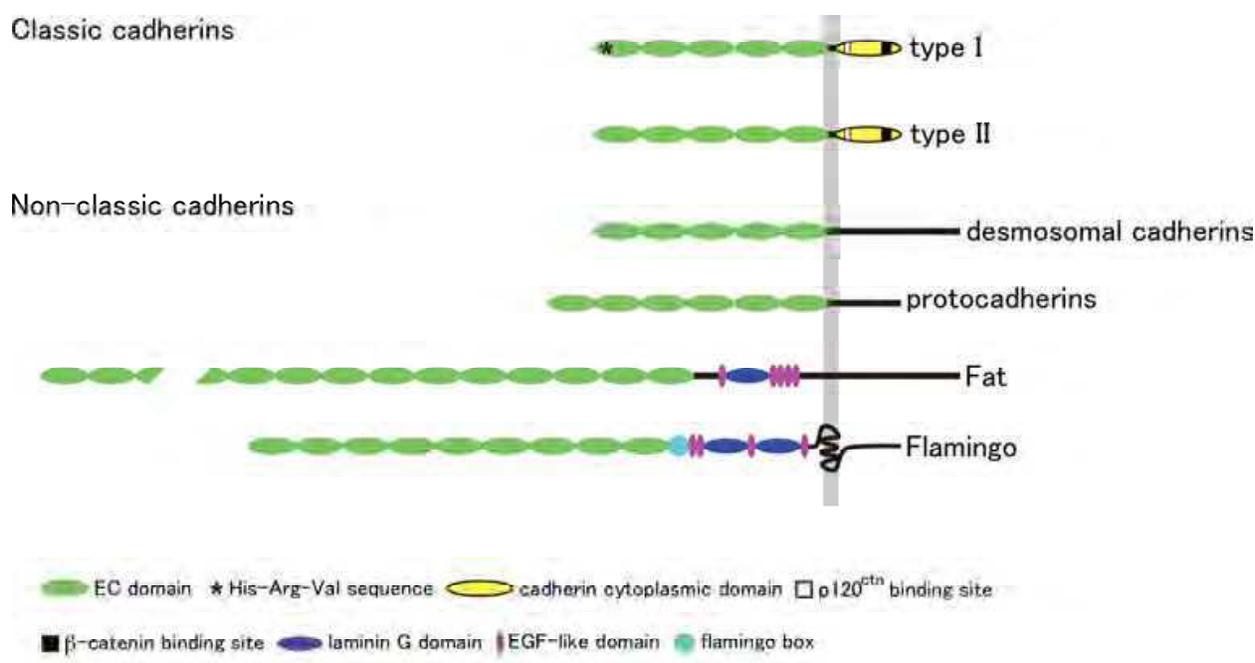


Fig. 1. Domain structures of cadherin superfamily. Molecules conserving EC domains in the extracellular region consist of the cadherin superfamily. The classic cadherins have five EC domains and the cytoplasmic domain possessing the binding sites for p120^{ctn} and β-catenin. They are subdivided into type I and type II 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

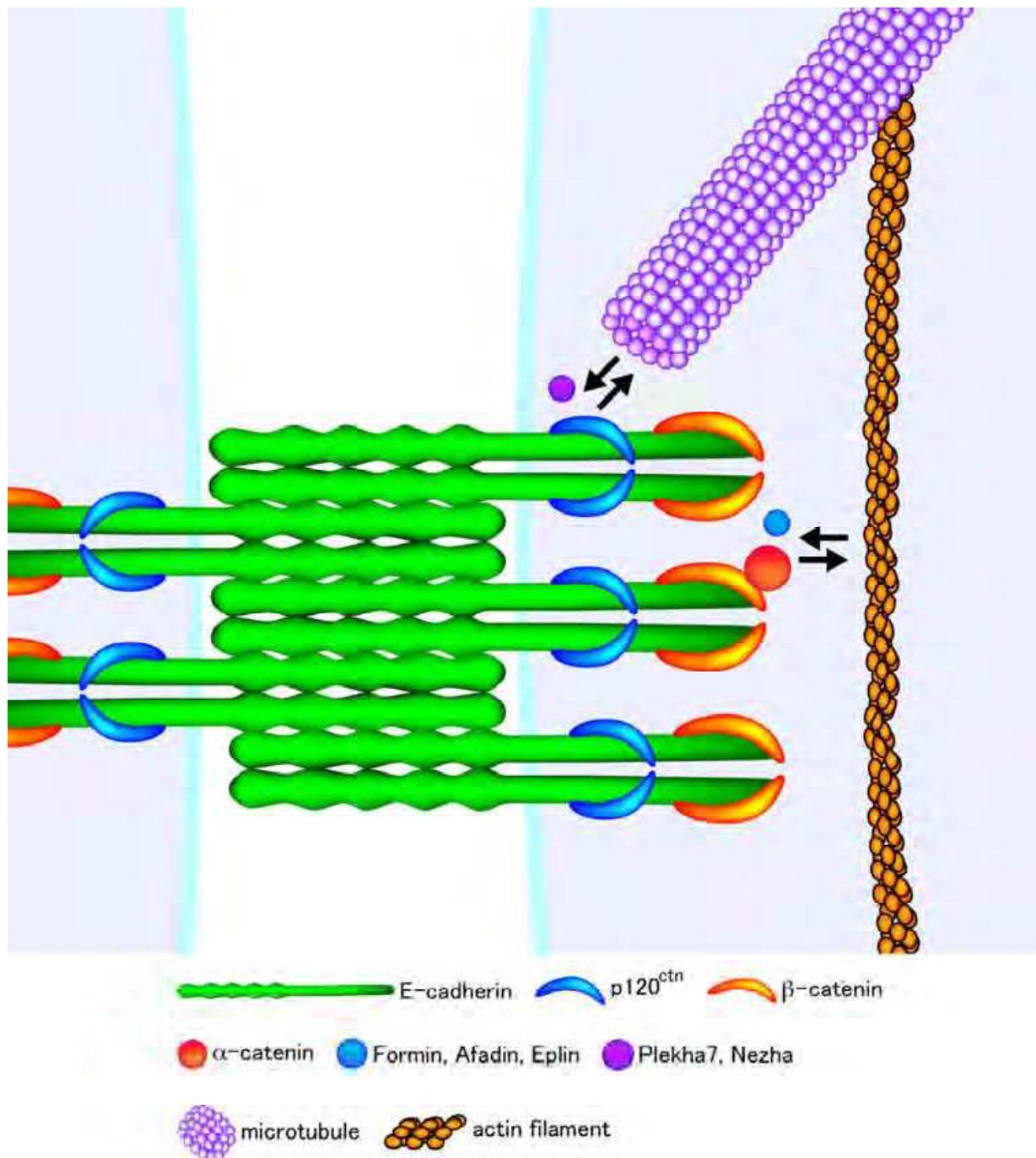


Fig. 2. Molecular structural organization of adherence junction containing E-cadherin. E-cadherins homotypically bind with adjacent cells by the EC domain interaction, and p120^{ctn} and β-catenin interact with the cytoplasmic domain of E-cadherin. p120^{ctn} directly associate with microtubules or indirectly 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).

(p120^{ctn}), 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. p120^{ctn} 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 p120^{ctn}, 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. p120^{ctn} also has a pivotal role in the microtubule assembly at adherence junctions. The p120^{ctn} 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 p120^{ctn} 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 p120^{ctn} 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 guanosine 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 & Grealley, 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 & Grealley, 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, TGF β 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

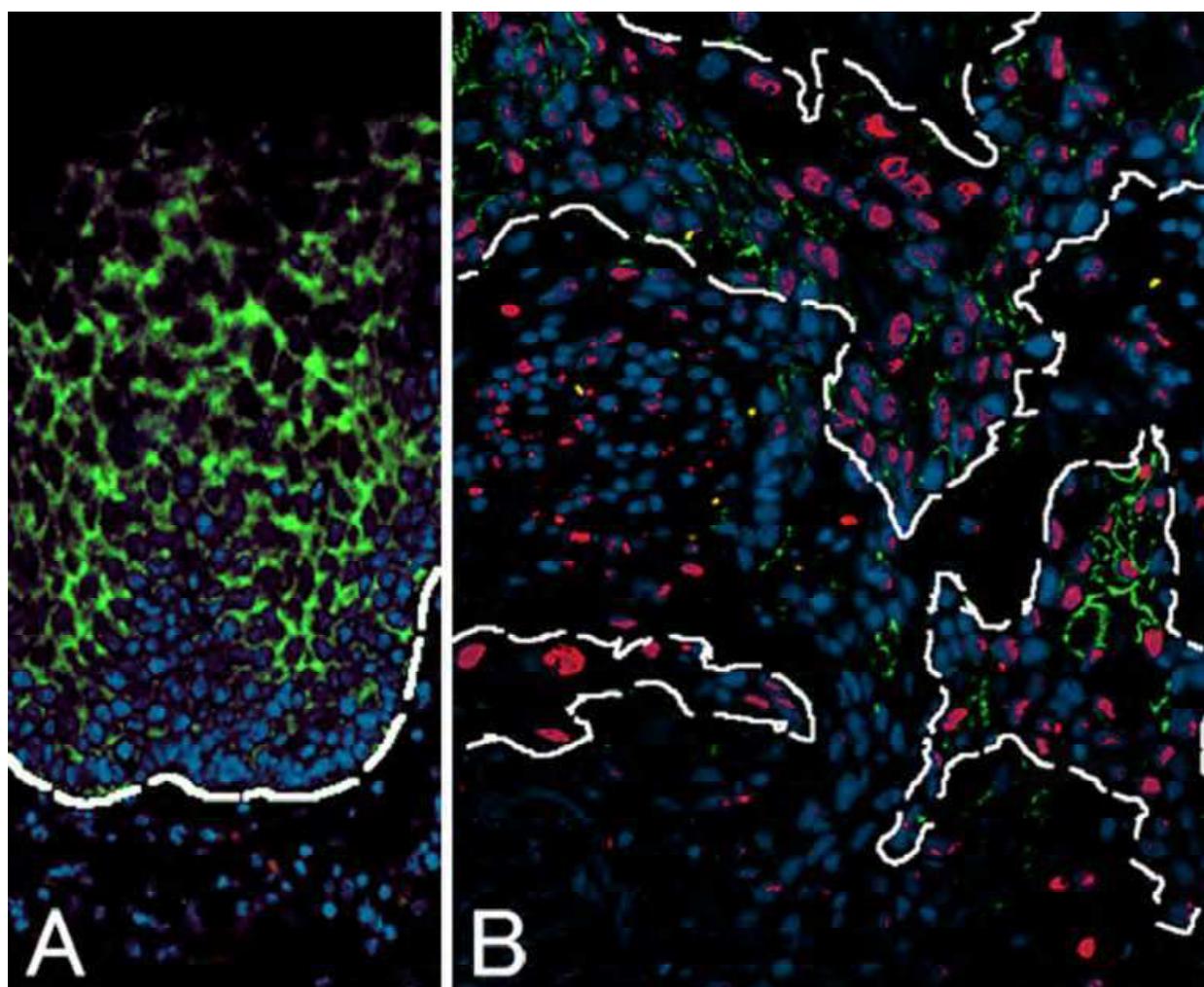


Fig. 3. Expression of E-cadherin and HMGA2 in oral epithelium and carcinomas. E-cadherin (green) expression is detected by immunofluorescent microscopy at the cell-cell boundaries of normal oral epithelium (A) while in carcinoma cells at the invasive dramatically lose the immunoreactivities (B). In contrast, 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 microRNAs (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 TGF β -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).

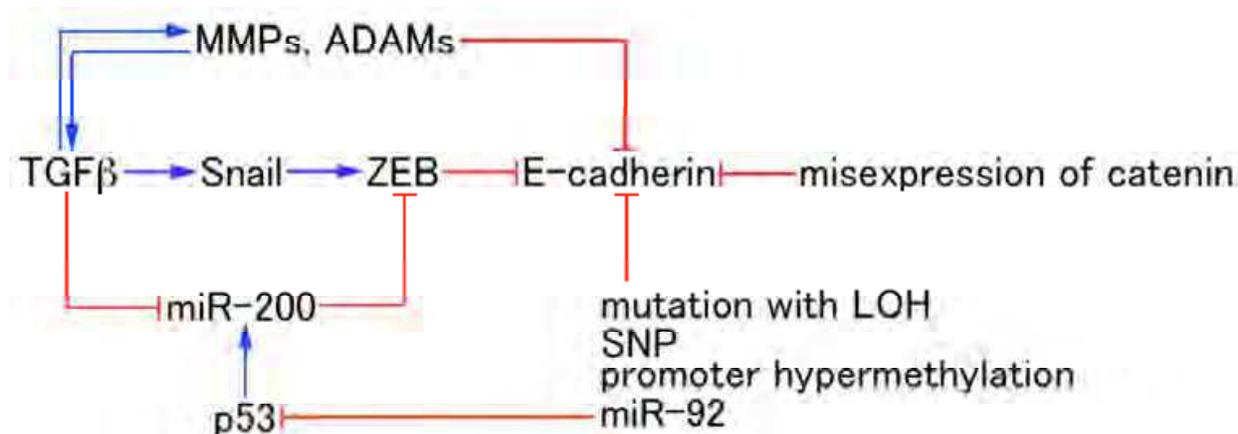


Fig. 4. A schematic representation for the E-cadherin expression and repression machineries. In carcinoma cells of epithelial origin, expression of E-cadherin is regulated by several pathways that directly or indirectly control the expression. Blue lines indicate stimulation and red lines indicate suppression.

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 hypermethylation 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 upregulated 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- κ B) 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- κ B, 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- κ B to the induction of EMT, maintenance of the mesenchymal phenotype, and metastasis (Huber et al., 2004). NF- κ B 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 stimulates 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.

9. References

- Abe, K. & Takeichi, M. (2008). EPLIN mediates linkage of the cadherin catenin complex to F-actin and stabilizes the circumferential actin belt. *Proceedings of the National Academy of Science of the U.S.A.*, Vol.105, No.(1) pp.13-19, ISSN 1091-6490
- Anastasiadis, P.Z. (2007). p120-ctn: A nexus for contextual signaling via Rho GTPases. *Biochimica et Biophysica Acta*, Vol.1173, No.(1) pp.34-46, ISSN 0006-3002
- Battle, E., Sancho, E., Francí, C., Domínguez, D., Monfar, M., Baulida, J. & Gariña de Herreros, A. (2000). The transcription factor Snail is a repressor of *E-cadherin* gene expression in epithelial tumor cells. *Nature Cell Biology*, Vol.2, No.(2) pp84-89, ISSN 1465-7392
- Black, P.C., Brown, G.A., Inamoto, T., Shrader, A., Arora, A., Siefker-Radtke, A.O., Adam, L., Theodorescu, D., Wu, X., Munsell, M.F., Bar-Eli, M.B., McConkey, D.J. & Dinney, C.P.N. (2008). Sensitivity to epidermal growth factor receptor inhibitor requires E-cadherin expression in urothelial carcinoma cells. *Clinical Cancer Research*, Vol.14, No.(5) pp.1478-1486, ISSN 1078-0432
- Brown, M.A. (1997). Tumor suppressor genes and human cancer. *Advances in Genetics*, Vol.36, No.(1) pp.45-135, ISSN 0065-2660
- Cano, A., Pérez-Moreno, M.A., Rodrigo, I., Locascio, A., Blanco, M.J., del Barrio, M.G., Portillo, F. & Nieto, A. (2000). The transcription factor Snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. *Nature Cell Biology*, Vol.2, No.(2) pp.76-83, ISSN 1465-7392
- Cavallaro, U. & Dejana, E. (2011). Adhesion molecules signalling: Not always a sticky business. *Nature Reviews Molecular Cell Biology*, Vol.12, No.(3) pp.189-197, ISSN 1471-0072
- Chen, H.C., Chen, G.H., Chen, Y.H., Liao, W.L., Liu, C.Y., Cheng, K.P., Chang, Y.S. & Chen, S.J. (2009). MicroRNA deregulation and pathway alterations in nasopharyngeal carcinoma. *British Journal of Cancer*, Vol.100, No.(6) pp.1002-1011, ISSN 0007-0920
- Chen, Z.L., Zhao, X.H., Wang, J.W., Li, B.Z., Wang, Z., Sun, J., Tan, F.W., Ding, D.P., Xu, X.H., Zhou, F., Tan, X.G., Hang, J., Shi, S.S., Feng, X.L. & He, J. (2011). MicroRNA-92a promotes lymph node metastasis of human esophageal squamous cell carcinoma via E-cadherin. *The Journal of Biological Chemistry*, Vol.286, No.(12) pp.10725-10734
- Cheng, C.W., Wu, P.E., Yu, J.C., Huang, C.S., Yue, C.T., Wu, C.W. & Shen, C.Y. (2001). Mechanisms of inactivation of E-cadherin in breast carcinoma: Modification of the two-hit hypothesis of tumor suppressor gene. *Oncogene*, Vol.20, No.(29) pp.3814-3823, ISSN 5532-5542

- Chiba, T., Maeda, G., Kawashiri, S., Kato, K. & Imai, K. (2009). Epigenetic loss of mucosa-associated lymphoid tissue 1 expression in patients with oral carcinomas. *Cancer Research*, Vol.69, No.(18) pp.7216-7223, ISSN 0008-5472
- Chua, H.L., Bhat-Nakshatri, P., Clare, S.E., Morimiya, A., Badve, S. & Nakshatri, H. (2007). NF-kappaB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: Potential involvement of ZEB-1 and ZEB-2. *Oncogene*, Vol.26, No.(5) pp.711-724, ISSN 5532-5542
- De Wever, O., Westbroek, W., Verloes, A., Bloemen, N., Bracke, M., Gespach, C., Bruyneel, E. & Mareel, M. (2004). Critical role of N-cadherin in myofibroblast invasion and migration in vitro stimulated by colon-cancer-cell derived TGF-beta or wounding. *Journal of Cell Science*, Vol.117, No.(20) pp.4619-4703, ISSN 0021-9533
- Diamond, M.E., Sun, L., Ottaviano, A.J., Joseph, M.J. & Munshi, HG. (2008). Differential growth factor regulation of N-cadherin expression and motility in normal and malignant oral epithelium. *Journal of Cell Science*, Vol.121, No.(13) pp.2197-2207, ISSN 0021-0533
- Drees, F., Pokutta, S., Yamada, S., Nelson, W.J. & Weis, W.I. (2005). α -catenin is a molecular switch that binds E-cadherin- β -catenin and regulates actin-filament assembly. *Cell*, Vol.123, No.(5) pp.903-915, ISSN 0092-8674
- Duan, Y. & Fan, M. (2011). Lentivirus-mediated gene silencing of beta-catenin inhibits growth of human tongue cancer cells. *Journal of Oral Pathology and Medicine*, early publication ahead of print. ISSN 1600-0714
- Fazzari, M.J. & Grealley, J.M. (2004). Epigenomics: Beyond CpG islands. *Nature Reviews Genetics*, Vol.5, No.(6) pp.446-455, ISSN 1471-0056
- Gayther, S.A., Goringe, K.L., Ramus, S.J., Huntsman, D., Roviello, F., Grehan, N., Machado, J.C., Pinto, E., Seruca, R., Halling, K., MacLeod, P., Powell, S.M., Jackson, C.E., Ponder, B.A. & Caldas, C. (1998). Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Research*, Vol.58, No.(18) pp.4086-4089, ISSN 0008-5472
- Georgopoulos, N.T., Kirkwood, L.A., Walker, D.C. & Southgate, J. (2010). Differential regulation of growth-promoting signalling pathways by E-cadherin. *PLoS One*, Vol.5, No.(10) pp.e13621. ISSN 1932-6203
- Gregory, P.A., Bracken, C.P., Smith, E., Wright, J.A., Roslan, S., Morris, M., Wyatt, L., Farshid, G., Lim, Y.Y., Lindeman, G.L., Shannon, M.F., Drew, P.A., Khew-Goodall, Y. & Goodall, G.J. (2011). An autocrine TGF- β /ZEB/miR-200 signaling network regulates establishment and maintenance of epithelial-mesenchymal transition. *Molecular Biology of Cells*, Vol.22, No.(10) pp.1686-1698, ISSN 1059-1524
- Guiford, P., Hopkins, J., Harraway, J., McLeod, M., McLeod, N., Harawira, P., Taite, H., Scoular, R., Miller, A. & Reeve, A.E. (1998). E-cadherin germline mutations in familial gastric cancer. *Nature*, Vol.392, No.(6674) pp.402-405, ISSN 0028-0836
- Gumbiner, B.M. (2005). Regulation of cadherin-mediated adhesion in morphogenesis. *Nature Reviews Molecular Cell Biology*, Vol.6, No.(8) pp.622-634, ISSN 1471-0072
- Hanahan, D. & Weinberg, R.A. (2011). Hallmarks of cancer: The next generation. *Cell*, Vol.144, No.(5) pp. 646-674, ISSN 0092-8674
- Harris, T.J.C. & Tepass, U. (2010). Adhesion junctions: From molecules to morphogenesis. *Nature Reviews Molecular Cell Biology*, Vol.11, No.(7) pp502-512, ISSN 1471-0072

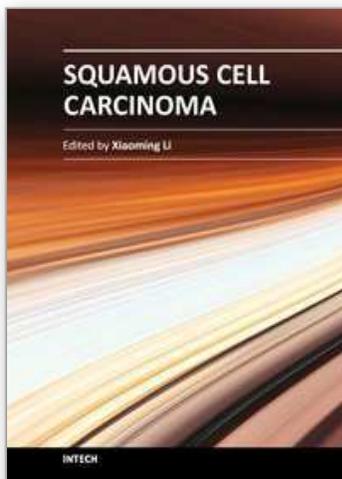
- Hermiston, M.L., Wong, M.H. & Gordon, J.I. (1996). Forced expression of E-cadherin in the mouse intestinal epithelium shows cell migration and provides evidence for nonautonomous regulation of cell fate in a self-renewing system. *Genes and Development*, Vol.10, No.(8) pp.985-996, ISSN 0890-9369
- Huber, M.A., Azoitei, N., Baumann, B., Grunert, S., Sommer, A., Pehamberger, H., Kraut, N., Beug, H. & Wirth, T. (2004). NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. *The Journal of Clinical Investigation*, Vol.114, No.(4) pp.569-581, ISSN 0021-9738
- Ichii, T. & Takeichi, M. (2007). p120-catenin regulates microtubules dynamics and cell migration in a cadherin-independent manner. *Genes to Cells*, Vol.12, No.(7) pp.827-839, ISSN 1356-9597
- Imai, K., Hiramatsu, A., Fukushima, D., Pierschbacher, M.D. & Okada, Y. (1997). Degradation of decorin by matrix metalloproteinases: Identification of the cleavage sites, kinetics and transforming growth factor- β 1 release. *The Biochemical Journal*, Vol.332, No.(3) pp.809-814, ISSN 0264-6021
- Imai, K. & Okada, Y. (2009). Purification of matrix metalloproteinases by column chromatography. *Nature Protocol*, Vol.3, No.(7) pp.1111-1124, ISSN 1750-2799
- Ishiyama, N., Lee, S.H., Liu, S., Li, G.Y., Smith, M.J., Reichardt, L.F. & Ikura, M. (2010). Dynamic and static interactions between p120 catenin and E-cadherin regulate the stability of cell-cell adhesion. *Cell*, Vol.141, No.(1) pp.117-128, ISSN 0092-8674
- Ivanov, A.I., McCall, I.C., Babbin, B., Samarin, S.N., Nusrat, A. & Parkos, C.A. (2006). Microtubules regulate disassembly of epithelial apical junctions. *BMC Cell Biol.*, Vol.7 No. (1) pp.12. ISSN 1471-2121
- Jones, P.A. & Baylin, S.B. (2002). The fundamental role of epigenetic events in cancer. *Nature Reviews Genetics*, Vol.3, No.(6) pp.415-428, ISSN 1471-0056
- Kim, B.G., An, H.J., Kang, S., Choi, Y.P., Gao, M.Q., Park, H. & Cho, N.H. (2011). Laminin-233-rich tumor microenvironment for tumor invasion in the interface zone of breast cancer. *American Journal of Pathology*, Vol.178, No.(1) pp.373-381, ISSN 0002-9440
- Kim, T., Veronese, A., Pichiorri, F., Lee, T.J., Jeon, Y.J., Volinia, S., Pineau, P., Marchio, A., Palatini, J., Suh, S.S., Alder, H., Liu, C.G., Dejean, A. & Croce, C.M. (2011). p53 regulates epithelial-mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. *Journal of Experimental Medicine*, Vol.208, No.(5) pp.875-883, ISSN 0022-1007
- Kobielak, A., Pasolli, H.A. & Fuchs, E. (2004). Mammalian formin-1 participates in adherens junctions and polymerization of linear actin cables. *Nature Cell Biology*, Vol.6, No.(1) pp.21-31, ISSN 1465-7392
- Kudo, Y., Kitajima, S., Ogawa, I., Hiraoka, M., Sargolzaei, S. Keikhaee, M.R., Sato, S., Miyauchi, M. & Takata, T. (2004). Invasion and metastasis of oral cancer cells require methylation of E-cadherin and/or degradation of membranous β -catenin. *Clinical Cancer Research*, Vol.10, No.(16) pp.5455-5463, ISSN 1078-0432
- Lee, S.H., Lee, N.H., Jin, S.M., Rho, Y.S. & Jo, S.J. (2011). Loss of heterozygosity of tumor suppressor genes (p16, Rb, E-cadherin, p53) in hypopharynx squamous cell carcinoma. *Otolaryngology Head and Neck Surgery*, early publication ahead of print, ISSN 0194-5998

- Lefort, C.T., Wojciechowski, K. & Hocking, D. (2011). N-cadherin cell-cell adhesion complexes are regulated by fibronectin matrix assembly. *The Journal of Biological Chemistry*, Vol.286, No.(4) pp.3149-3160, ISSN 0021-9258
- Li, L.C., Chui, R.M., Sasaki, M., Nakajima, K., Perincher, G., Au, H.C., Nojima, D., Carroll, P. & Dahiya, R. (2000). A single nucleotide polymorphism in the *E-cadherin* gene promoter alters transcriptional activities. *Cancer Research*, Vol.6, No.(4) pp.873-876, ISSN 1538-7445
- Li, S., Jiao, J., Lu, Z. & Zhang, M. (2009). An essential role for N-cadherin and β -catenin for progression in tongue squamous cell carcinoma and their effect on invasion and metastasis of Tca8113 tongue cancer cells. *Oncology Reports*, Vol.21, No.(5) pp.1223-1233, ISSN 1021-335X
- Liang, X., Zheng, M., Jiang, J., Zhu, G., Yang, J. & Tang, Y. (2011). Hypoxia-inducible factor-1 alpha, in association with TWIST2 and SNIP1, is a critical prognostic factor in patients with tongue squamous cell carcinoma. *Oral Oncology*, Vol.47, No.(2) pp.92-97, ISSN 1368-8375
- Libusova, L., Stemmler, M.P., Hierholzer, A., Schwarz, H. & Kemler, R (2010). N-cadherin can structurally substitute for E-cadherin during intestinal development but leads to polyp formation. *Development*, Vol.137, No.(14) pp.2297-2305, ISSN 0950-1991
- Liu, H., Komiyama, S., Shimizu, M., Fukunaga, Y. & Nagafuchi, A. (2007). Involvement of p120 carboxy-terminal domain in cadherin trafficking. *Cell Structure and Function*, Vol.32, No.(2) pp.127-137, ISSN 0386-7196
- Lo Muzio, L., Pannone, G., Staibano, S., Mignogna, M.D., Serpico, R., Fanali, S., De Rosa, G., Piattelli, A. & Mariglió, M.A. (2002). p120^{cat} delocalization in cell lines of oral cancer. *Oral Oncology*, Vol.38, No.(1) pp.64-72, ISSN 1368-8375
- Lu, S. L., Reh, D., Li, A.G., Woods, J., Corless, C.L., Kulesz-Martin, M. & Wang, X.J. (2004). Overexpression of transforming growth factor beta1 in head and neck epithelia results in inflammation, angiogenesis, and epithelial hyperproliferation. *Cancer Research*, Vol.64, No.(13) pp.4405-4410, ISSN 1078-0432
- Maeda, G., Chiba, T., Okazaki, M., Satoh, T., Taya, Y., Aoba, T., Kato, K., Kawashiri, S. & Imai, K. (2005). Expression of SIP1 in oral squamous cell carcinomas: Implications for E-cadherin expression and tumor progression. *International Journal of Oncology*, Vol.27, No.(6) pp.1535-1541, ISSN 1019-6439
- Maeda, G., Chiba, T., Aoba, T. & Imai, K. (2007a). Epigenetic inactivation of *E-cadherin* by promoter hypermethylation in oral carcinoma cells. *Odontology*, Vol.95, No.(1) pp.24-29, ISSN 1618-1247
- Maeda, G., Chiba, T., Kawashiri, S., Sato, T. & Imai, K. (2007b). Epigenetic inactivation of I κ B kinase- α in oral carcinomas and tumor progression. *Clinical Cancer Research*, Vol.13, No.(17) pp.5041-5047, ISSN 1078-0432
- Maher, M.T., Flozak, A.S., Stocker, A.M., Chenn, A. & Gottardi, C.J. (2009). Activity of the beta-catenin phosphodestruction complex at cell-cell contact is enhanced by cadherin-based adhesion. *The Journal of Cell Biology*, Vol.186, No.(2) pp.219-228, ISSN 0021-9525
- Mandai, K., Nakanishi, H., Satoh, A., Obaishi, H., Wada, M., Nishioka, H., Itoh, M., Mizoguchi, A., Aoki, T., Fujimoto, T., Matsuda, Y., Tsukita, S. & Takai, Y (1997). Afadin: A novel actin filament-binding protein with one PDZ domain localized at

- cadherin-based cell-to-cell adherence junction. *The Journal of Cell Biology*, Vol.139, No.(2) pp.517-528, ISSN 0021-9525
- Meira, L.B., Bugni, J.M., Green, S.L., Lee, C.W., Pang, B., Borenshtein, D., Rickman, B.H., Rogers, A.B., Moroski-Erkul, C.A., McFaline, J.L., Schauer, D.B., Dedon, P.C., Fox, J.G. & Samson, L.D. (2008). DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *Journal of Clinical Investigation*, Vol.118, No.(7) pp.2516-2525, ISSN 0021-9738
- Meng, W. & Takeichi, M (2009). Adherence junction: Molecular architecture and regulation. *Cold Spring Harbor Perspectives in Biology*, Vol.1, No.(6) a002899, ISSN 1943-0264
- Miyazawa, J., Mitoro, A., Kawashiri, S., Chada, K.K. & Imai, K. (2004). Expression of mesenchyme-specific gene HMGA2 in squamous cell carcinomas of the oral cavity. *Cancer Research*, Vol.64, No.(6) pp.2024-2029, ISSN 1078-0432
- Nakayama, S., Sasaki, A., Mese, H., Alcalde, R.E. Tsuji, T. & Matsumura, T. (2001). E-cadherin gene is silenced by CpG methylation in human oral squamous cell carcinomas. *International Journal of Cancer*, Vol.93, No.(5) pp.667-673, ISSN 0020-7136
- Neveu, P., Kye, M.J., Qi, S., Buchholz, D.E., Clegg, D.O., Sahin, M., Park, I.H., Kim, K.S., Daley, G.Q., Kornblum, H.I., Shraiman, B.I. & Kosik, K.S. (2010). MicroRNA profiling reveals two distinct p53-related human pluripotent stem cell states. *Cell Stem Cell*, Vol.7, No.(3) pp.671-681, ISSN 1934-5909
- Ohusugi, M., Laure, L., Schwarz, H. & Kemler, R. (1997). Cell-junctional and cytoskeletal organization in mouse blastocysts lacking E-cadherin. *Developmental Biology*, Vol.185, No.(2) pp.261-271, ISSN 0021-1606
- Peinado, H., Portillo, F. & Cano, A. (2004). Transcriptional regulation of cadherin during development and carcinogenesis. *The International Journal of Developmental Biology*, Vol.48, No.(5-6) pp.365-375, ISSN 0214-6282
- Peinado, H., Olmeda, D. & Cano, A. (2007). Snail, ZEB and bHLH factors in tumour progression: An alliance against the epithelial phenotype? *Nature Review Cancer*, Vol.7, No.(6) pp.415-428, ISSN 1474-175X
- Perez-Moreno, M., Dacia, M.A., Wong, E., Pasolli, H.A., Reynolds, A.B. & Fuchs, E. (2006). p120-catenin mediates inflammatory responses in the skin. *Cell*, Vol.124, No.(3) pp.631-644, ISSN 0092-8674
- Perl, A.K., Wilgenbus, P., Dahl, U., Semb, H. & Christofori, G. (1998). A causal role for E-cadherin in the transition from adenoma to carcinoma. *Nature*, Vol.392, No.(6672) pp.190-193, ISSN 0028-0836
- Pyo, S.W., Hashimoto, M., Kim, Y.S., Kim, C.H., Lee, S.H., Johnson, K.R., Wheelock, M.J. & Park, J.U. (2007). Expression of E-cadherin, P-cadherin and N-cadherin in oral squamous cell carcinoma: Correlation with the clinicopathologic features and patient outcome. *Journal of Cranio-Maxillofacial Surgery*, Vol.35, No.(1) pp.1-9, ISSN 1010-5182
- Reddy, P., Liu, L, Ren, C., Lindgren, P., Boman, K., Shen, Y., Ludin, E., Ottander, U., Rytinki, M. & Liu, K. (2005). Formation of E-cadherin-mediated cell-cell adhesion activates Akt and mitogen activated protein kinase via phosphatidylinositol 3 kinase and ligand-independent activation of epidermal growth factor receptor in ovarian cancer cells. *Molecular Endocrinology*, Vol.19, No.(10) pp.2564-2578, ISSN 0888-8809

- Saito, Y., Takazawa, H., Uzawa, K., Tanzawa, H. & Sato, K. (1998). Reduced expression of E-cadherin in oral squamous cell carcinoma: Relationship with DNA methylation of 5' CpG island. *International Journal of Oncology*, Vol.12, No.(2) pp.293-298, ISSN 1019-6439
- Saydam, O., Shen, Y., Würdinger, T., Senol, O., Boke, E., James, M.F., Tannous, B A., Stemmer-Rachamimov, A.O., Yi, M., Stephens, R.M., Fraefel, C., Gusella, J.F., Krichevsky, A.M. & Breakefield, X.O. (2009). Downregulated microRNA-200a in meningiomas promotes tumor growth by reducing E-cadherin and activating the Wnt/beta-catenin signaling pathway. *Molecular and Cellular Biology*, Vol.29, No.(21) pp. 5932-5940, ISSN 0270-7306
- Scapoli, L., Palmieri, A., Lo Muzio, L., Pazzetti, F., Rubini, C., Girardi, A., Farinella, F., Mazzotta, M. & Carnici, F. (2010). MicroRNA expression profiling of oral carcinoma identifies new markers of tumor progression. *International Journal of Immunotherapy and Pharmacology*, Vol.23, No.(4) pp.1229-1234, ISSN 0394-6320
- Shintani, Y., Fukumoto, Y., Chaika, N., Svoboda, R., Wheelock, M.J. & Johnson, K.R. (2008). Collagen I-mediated up-regulation of N-cadherin requires cooperative signals from integrins and discoidin domain receptor 1. *The Journal of Cell Biology*, Vol.180, No.(6) pp.1277-1289, ISSN 0021-9525
- Solanas, G., Porta-de-la-Riva, M., Agusti, C., Casagolda, D, Sánchez-Aguilera, F., Larriva, M.J., Pons, F., Peiró, S., Escriva, M., Muñoz, A., Duñach, M., de Herreros, A.G. & Baulida, J. (2008). E-cadherin controls β -catenin and NF- κ B transcriptional activity in mesenchymal gene expression. *Journal of Cell Science*, Vol.121, No.(13) pp.2224-2234, ISSN 0021-0533
- Stehbens, S.J., Paterson, A.D., Crampton, M.S., Shewan, A.M., Ferguson, C., Akmanova, A., Parton, R.G. & Yap, A.S. (2006). Dynamic microtubules regulated the local concentration of E-cadherin at cell-cell contacts. *Journal of Cell Science*, Vol.119 No.(9) pp.1801-1811, ISSN 0021-0533
- Suyama, K., Shapiro, I., Guttman, M. & Hazan, R.B. (2002). A signaling pathway leading to metastasis is controlled by N-cadherin and the FGF receptor. *Cancer Cell*, Vol.2, No.(4) pp.301-314. ISSN 1535-6108
- Thoreson, M.A. & Reynolds, A.B. (2002). Altered expression of the catenin p120 in human cancer: Implications for tumor progression. *Differentiation*, Vol.70, No.(9-10) pp.583-589, ISSN 0301-4681
- Thuault, S., Valcourt, U., Petersen, M., Manfioletti, G., Heldin, C.H. & Moustakas, A. (2006). Transforming growth factor-beta employs HMGA2 to elicit epithelial-mesenchymal transition. *The Journal of Cell Biology*, Vol.174, No.(2) pp.175-183, ISSN 0021-9525
- Tinkle, C.L., Lechler, T., Pasolli, H.A. & Fuchs, E. (2004). Conditional targeting of E-cadherin in skin: Insights into hyperproliferative and degenerative responses. *Proceeding of the National Academy of Science of the U.S.A.*, Vol.101, No.(2) pp.552-557, ISSN 1091-6490
- Tomita, K., van Bokhoven, A., van Leenders, G.J.L.H., Ruijter, E.T.G., Jansen, C.F.J., Bussemakers, M.J.B. & Schalken, J.A. (2000). Cadherin switch in human prostate cancer progression. *Cancer Research*, Vol.60, No.(13) pp.3650-3654, ISSN 1078-0432
- Uraguchi, M., Morikawa, M., Shirakawa, M., Sanada, K. & Imai, K. (2004). Activation of WNT family expression and signaling in squamous cell carcinomas of the oral cavity. *Journal of Dental Research*, Vol.83, No.(4) pp.327-332, ISSN 0022-0345

- Vered, M., Dayan, D., Yahalom, R., Dobriyan, A., Barshack, I., Bello, I.O., Kantola, S. & Salo, T. (2011). Cancer-associated fibroblasts and epithelial-mesenchymal transition in metastatic oral tongue squamous cell carcinoma. *International Journal of Cancer*, Vol.127, No.(6) pp.1356-1362, ISSN 0020-7136
- Viswanathan, M., Tsuchida, N. & Shanmugam, G. (2003). Promoter hypermethylation profile of tumor-associated genes p16, p15, MGMT and E-cadherin in oral squamous cell carcinoma. *International Journal of Cancer*, Vol.105, No.(1) pp.41-46, ISSN 0020-7136
- Waterman-Storer, C.M., Salmon, W.C. & Salmon, E.D. (2000). Feedback interactions between cell-cell adherence junctions and cytoskeletal dynamics in newt lung epithelial cells. *Molecular Biology of the Cell*, Vol.11 No.(7) pp.2471-2483, ISSN 1059-1524
- Wheelock, M.J., Shintani, Y., Maeda, M., Fukumoto, Y. and Johnson, K.R. (2008). Cadherin switching. *Journal of Cell Science*, Vol.121 No.(6) pp.727-735, ISSN 0021-0533
- Yamada, S., Pokutta, S., Drees, F., Weis, W.I. & Nelson, W.J. (2005). Deconstructing the cadherin-catenin-actin complex. *Cell*, Vol.123 No.(5) pp.889-901, ISSN 0092-8674
- Yeh, K.T., Shih, M.C., Lin, T.H., Chen, J.C., Chang, J.Y., Kao, C.F., Lin, K.L. & Chang, J.G. (2002). The correlation between CpG methylation on promoter and protein expression of E-cadherin in oral squamous cell carcinoma. *Anticancer Research*, Vol.22, No.(6C) pp.3971-3975, ISSN 0250-7005
- Yokoyama, K., Kamata, N., Hayashi, E., Hoteiya, T., Ueda, N., Fujimoto, R. & Nagayama, M. (2001). Reverse correlation of E-cadherin and snail expression in oral squamous cell carcinoma cells *in vitro*. *Oral Oncology*, Vol.37, No.(1) pp.65-71, ISSN 1368-8375
- Yoshida, C. & Takeichi, M. (1982). Teratocarcinoma cell adhesion: Identification of a cell-surface protein involved in calcium-dependent cell aggregation. *Cell*, Vol.28, No.(2) pp.217-224, ISSN 0092-8674
- Yu, C.C., Lo, W.L., Chen, Y.W., Huang, P.I., Hsu, H.S., Tseng, L.M., Hung, S.C., Kao, S.Y., Chang, C.J. & Chiou, S.H. (2011). Bmi-1 regulates Snail expression and promotes metastasis ability in head and neck squamous cancer-derived ALDH1 positive cells. *Journal of Oncology*, early publication ahead of print, ISSN 1687-8450
- Zheng, G., Lyons, J.G., Tan, T.K., Wang, Y., Hsu, T.T., Min, D., Succar, L., Rangan, G.K., Hu, M., Henderson, B.R., Alexander, S.I. & Harris, D.C.H. (2009). Disruption of E-cadherin by matrix metalloproteinase directly mediates epithelial-mesenchymal transition downstream of transforming growth factor- β 1 in renal tubular epithelial cells. *American Journal of Pathology*, Vol.175, No.(2) pp.580-591, ISSN 0002-9440
- Zhou, B.P., Deng, J., Xia, W., Xu, J., Li, Y.M., Gunduz, M. & Hung, M.C. (2004). Dual regulation of Snail by GSK-3 β -mediated phosphorylation in control of epithelial-mesenchymal transition. *Nature Cell Biology*, Vol.6, No.(10) pp.931-940, ISSN 1465-7392



Squamous Cell Carcinoma

Edited by Prof. Xiaoming Li

ISBN 978-953-51-0024-9

Hard cover, 302 pages

Publisher InTech

Published online 03, February, 2012

Published in print edition February, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Kazushi Imai, Genta Maeda and Tadashige Chiba (2012). Cadherin Expression and Progression of Squamous Cell Carcinomas of the Oral Cavity, Squamous Cell Carcinoma, Prof. Xiaoming Li (Ed.), ISBN: 978-953-51-0024-9, InTech, Available from: <http://www.intechopen.com/books/squamous-cell-carcinoma/cadherin-expression-and-progression-of-head-and-neck-squamous-cell-carcinomas>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821