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Epithelial-Mesenchymal Interactions in Oral Cancer Metastasis

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1. Introduction

Squamous cell carcinoma of the oral cavity is one of the most prevalent tumors of the head and neck region. Despite an ever-expanding fund of knowledge regarding the etiology and pathophysiology of malignant neoplasms, oral squamous cell carcinoma (OSCC) continues to be a disfiguring and deadly disease. For patients with squamous cell carcinoma of the oral cavity or oropharynx, the 5-year survival is a dismal 56%, which has remained relatively unchanged in recent years (Davis et al., 2010). This poor prognosis reflects the fact that most patients present with advanced-stage disease, often making a complete cure a seemingly unattainable goal. In fact, just 46% of oral cavity and 16% of oropharyngeal cancers are diagnosed when there is only local disease (Davis et al., 2010). Despite recent improvements in therapeutic approaches, treatment failure takes the form of local and regional recurrences, but as disease control in these areas improves OSCC treatment failures more commonly occur as distant metastasis. Metastatic behavior is critical to survival, since patients with oral carcinomas that have distant disease have a five-year survival rate that is three times less than that of patients with spread to lymph nodes (Singh and Shah, 2003).

OSCC displays a wide range of metastatic behavior that cannot be predicted by tumor size, standard histology, or even individual gene or protein expression/activity (Singh and Shah, 2003). Despite the clinically obvious heterogeneity of OSCC, there are currently no means of predicting individual tumor behavior (Myers, 2010). Even small primary tumors of the oral cavity have a propensity to metastasize to cervical nodes, mandating that the majority of patients, even those with no clinical or radiographic evidence of nodal metastases, undergo some form of neck treatment either for staging or therapeutic purposes. Accurate prediction of metastasis in OSCC would have an immediate clinical impact through avoidance of unnecessary treatment of patients at low risk with appropriate direction of resources toward aggressive treatment of patients at high risk of having metastatic disease. Additionally,

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elucidation of key pathways and molecular mechanisms in tumor metastasis may direct therapeutic investigation and intervention.

Loss of epithelial morphology and acquisition of mesenchymal characteristics, termed the epithelial-to-mesenchymal transition (EMT), are typical for carcinoma cells during tumor progression and correlate with the local invasiveness and metastatic potential of the tumor (Birchmeier et al., 1996; Hollier et al., 2009). Cancer metastasis follows a sequential series of events, and many of the critical steps are distinctly similar to EMT-like transformations that occur during normal embryonic development. Recently, it was proposed that carcinoma cells, especially in metastatic sites, could acquire the mesenchymal-to-epithelial reverting transition (MErT) in order to adapt the microenvironments (Baum et al., 2008). This chapter explores the current status of investigations into the EMT/MErT transformations during the OSCC progression and the potential of these studies to positively impact the clinical management of OSCC in the future. The promise of using biomarker-based treatment decisions has yet to be fully realized given our limited understanding of the biology of metastatic spread in OSCC.

EMT describes a process in which epithelial cells undergo alterations in cellular architecture (lose of their characteristic epithelial polarity), adhesion (disassemble of cell-cell junctions), morphology (assuming a fibroblastoid mesenchymal morphology) and acquisition of migratory and invasive capabilities (Iwatsuki et al., 2010; Maeda et al., 2005; Thiery, 2002; Wells et al., 2008). EMT has been postulated as a versatile mechanism which facilitates cellular repositioning and redeployment during embryonic development, tissue reconstruction after injury, carcinogenesis, and tumor metastasis (Boyer et al., 2000; Roussos et al., 2010). In this context, EMT, a process first appreciated by developmental biologists, is attracting increasing attention from oncologists. Tumors are often viewed as corrupt forms of normal developmental processes (Thiery et al., 2009). Indeed, genes that are important in embryonic development are frequently found to be culprits in cancer. Conversely, genes discovered for their oncogenic role are often found to be key players in embryogenesis (Yang et al., 2008). This trend applies to the steps that initiate tumor formation. It also applies to the cross-talk with the inflammation (Lopez-Novoa and Nieto, 2009; Yadav et al., 2011) as well as to the steps that mediate tumor progression, including local invasion, intravasation into circulation and, most devastatingly, metastatic development through the establishment of secondary growths at sites distant from the primary tumor (Iwatsuki et al., 2010; Kalluri and Weinberg, 2009). There is good evidence that EMT gives rise to the dissemination of single carcinoma cells from the sites of the primary tumors (Wellner et al., 2009; Wu and Yang, 2011). More generally, it has been postulated that EMT might be involved in the dedifferentiation program that leads to malignant carcinoma. Some authors highlight the concept of altered differentiation program leading to the loss of type-specific epithelial differentiation markers and/or expression of typical mesenchymal-type proteins (Thiery, 2002). The typical example is a dedifferentiated epithelial cancer showing loss of cytokeratins and acquisition of mesenchymal markers such as Snail1, vimentin and/or fibronectin. Among many others, commonly used molecular markers for EMT include increased expression of N-cadherin and vimentin, nuclear localization of β-catenin, and increased production of the transcription factors such as Snail1 (Snail), Snail2 (Slug), Twist, EF1/ZEB1, SIP1/ZEB2, and/or E47 that inhibit E-cadherin production. Phenotypic markers for an EMT include an increased capacity for migration and three-dimensional invasion, as

well as resistance to anoikis/apoptosis. Recent research conducted in embryonic model system and in normal and transformed cell lines has identified several signal-transduction pathways for EMT, and has examined the roles of a number of growth factors in inducing EMT (Said and Williams, 2011). Recent studies have focused on better understanding the role of cancer stem cells in EMT as it relates to tumor progression in general (Alison et al., 2010; Fuxe et al., 2010; Martin and Cano, 2010; Raimondi et al., 2011; Takahashi et al., 2010) and to oral, head and neck cancer in particular (Chen et al., 2011; Davis et al., 2010; Lo et al., 2011). In this review, only few of the most important EMT players are discussed with respect to other critical mediators and within most common pathways that promote the phenotypic transformation. It is important to note that individual players do not work in isolation – there is extensive crosstalk between pathways, and the effect of a given inducer on EMT seems to be contextual.

Deregulation of several other pathways has been implicated in EMT (Boyer et al., 2000). To name only few, transforming growth factor-β (TGF-β), epidermal growth factor (EGF) family members, fibroblast growth factors (FGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF) have all been shown to induce EMT in an autocrine or paracrine manner (Baum et al., 2008). TGF-β was the first EMT inducer described in normal mammary epithelial cells by signaling through its receptor serine-threonine kinase complex (Fuxe et al., 2010). It remains the main and the best-characterized inducer of EMT phenotype in a variety of biological and patho-physiological conditions. TGF-β has an important tumor suppressor function at the early stage of tumorigenesis by inducing apoptosis and cell cycle arrest. However, it acts as a positive modulator of tumor progression in the late phase of tumorigenesis. This tumor promotional function of TGF-β, which is consistent with its EMT-induction activity, plays an important role in tumor progression including invasion and metastasis (Fuxe et al., 2010). Recent evidence indicates that the underlying mechanism of the prognostic value of Smad (2 and 6) for overall survival in OSCC patients is the aberrant TGF-β signaling (Mangone et al., 2010). Disruption in TGF-β induced Smad signaling occur during induced hamster buccal-pouch squamous cell carcinogenesis (Chen et al., 2011). Furthermore, the inhibition of TGF-β pathway in normal human oral keratinocytes leads to suppression of Bmi1-mediated cell senescence (Kim et al., 2010). TGF-β also seems to play an important role in the bone invasion by OSCC cells (Goda et al., 2010) as well as in the metastatic dissemination of salivary adenoid cystic carcinoma (Dong et al., 2011). Being a major inducer of EMT, TGF-β is able to regulate the activation of other signaling pathways besides establishing a hierarchical gene network. TGF-β-mediated signaling during EMT involves both gene expression-dependent and -independent pathways (Said and Williams, 2011). TGF-β cooperates with Wnt, Hedgehog, Notch and Ras signaling pathways to induce complete EMT. EMT signaling pathways have many common endpoints and E-cadherin is a central target (Thiery and Sleeman, 2006).

Loss of E-cadherin: E-cadherin is emerging as one of the caretakers of the epithelial phenotype with critical roles in adherens junctions and desmosomes (Garrod et al., 1996; Papagerakis et al., 2009). Our groups have devoted a large number of studies on the cadherin/catenin mediated adhesion in oral carcinogenesis (Lo Muzio et al., 2005; Lo Muzio et al., 2004; Lo Muzio et al., 2002; Lo Muzio et al., 1999; Pannone et al., 1998; Papagerakis et al., 2011; Papagerakis et al., 2004; Papagerakis et al., 2009) Among the mechanisms largely associated with the metastatic conversion of epithelial cells and the EMT, the loss of E-cadherin-

mediated cell adhesion is prominent; overall there is a trend towards a loss of E-cadherin during carcinoma progression including the OSCC (Huber et al., 2011). E-cadherin production is maintain in most differentiated tumors including carcinomas of the head and neck, but there seems to be an inverse correlation between E-cadherin levels and patient survival (Hirohashi, 1998; Kaur et al., 2009; Nguyen et al., 2011). In most cases, down-regulation of E-cadherin during OSCC carcinoma progression occurs by epigenetic mechanisms, including transcriptional repression and promoter hypermethylation (Kudo et al., 2004). Occasionally, the E-cadherin gene is mutated leading to the absence or to the expression of a non-functional protein (Berx et al., 1995; Yoshimura et al., 1996), however no mutations have been reported in OSCC. In vitro, there is a direct correlation between the lack of E-cadherin production and loss of epithelial phenotype (Behrens et al., 1989). Acquisition of the mesenchymal phenotype has been also associated with invasive behavior in vitro in three-dimensional collagen gels and hearts explants (Chen and Obrink, 1991) and the partial or complete reversal of the invasive mesenchymal phenotype was observed if E-cadherin is constitutively produced (Behrens et al., 1991; Kim et al., 2000; Vleminckx et al., 1991). Recently, it was proposed that carcinoma cells, especially in metastatic sites, could acquire the mesenchymal-to-epithelial reverting transition (MErT) in order to adapt the microenvironments and re-expression of E-cadherin be a critical indicator of MErT (Baum et al., 2008; Wells et al., 2008). Among E-cadherin repressors counts Snail, considered a "master gene" in the conversion from the epithelial to fibroblastic state, and a closely related member of the same family, Slug, both detected at sites of EMT in vertebrates (Nieto et al., 1994). Carcinoma cell lines that lack E-cadherin produce significant amounts of Snail, and the transfection of E-cadherin-positive lines with Snail results in the induction of EMT and the expression of mesenchymal markers (Batlle et al., 2000; Cano et al., 2000). There seems to be a causal link between the production of these transcriptional repressors and the down-regulation of E-cadherin during tumor progression. Snail expression was inversely correlated with E-cadherin expression in a number of cancers including OSCC (Batlle et al., 2000; Cano et al., 2000; Takkunen et al., 2006; Yokoyama et al., 2001). Transcriptional repressors of the E-cadherin gene are activated downstream in these pathways, leading to the loss of the epithelial phenotype. Given that in most advanced human tumors including OSCC, the loss of E-cadherin might be incomplete, with foci of E-cadherin-positive carcinoma cells mingling with negative areas, along with E-cadherin detection in metastatic tumors, it may suggest that rather than a single-gene control it could be more likely a general mechanism that is associated with the dedifferentiation program in which E-cadherin is lost. It is important to note that the immunohistological detection of E-cadherin within the positive tumoral foci is not necessarily indicative of a normal function of the protein; additional investigations are required to asses its functionality even in the presence of an apparent normal cellular distribution. In vivo evidence of EMT in tumors can be difficult to obtain due to the transient nature of the EMT process and may require combined immunohistochemical staining for several EMT markers. The loss of E-cadherin in normal epithelial cells and more importantly in carcinoma cells might deregulate cell growth, suggesting that in addition to contributing to the maintenance of the differentiation program, E-cadherin might also regulate cell proliferation, via activation of the Fos oncogene (Eger et al., 2000; Reichmann et al., 1992) or by altering the ß-catenin transcriptional activity through the Wnt signaling pathway (Gottardi et al., 2001; Stockinger et al., 2001).

Cadherin switching: Aberrant N-cadherin expression and E-cadherin/N-cadherin switching (EN-Switch) have been involved in EMT. They represent an independent prognostic marker in cancer progression; this concept has been well documented in gastric, prostate and oral carcinomas (Gravdal et al., 2007; Kim et al., 2009; Liu et al., 2010). Furthermore, some studies demonstrate that cadherin switching is necessary for increased motility but it is not required for the morphological changes that accompany EMT (Maeda et al., 2005) therefore, immunohistochemical detection should be performed in order to detect EN-Switch and the consequent EMT in oral cancer.

Wnt signaling: Our groups have a particular interest in WNT/ ß-catenin pathway (Lo Muzio et al., 2002; Pannone et al., 2010; Papagerakis et al., 2011). Dysregulation of the Wnt pathway via ß-catenin is a frequent event in EMT involved in the pathogenesis of several human cancers. In OSCC its roles still remain unclear. Although it is evident that constitutive activation of the Wnt / ß-catenin is frequently observed in oral cancer progression, only infrequent mutations have been found in genes encoding various components of this pathway that are commonly mutated in other cancers (adenomatous polyposis coli APC, (Kok et al., 2002); Axin, (Iwai et al., 2005; Rui et al., 2007); no ß-catenin mutations have been reported in OSCC, (Lo Muzio et al., 2005). This suggests activation of this pathway by multiple mechanisms. Furthermore, the interaction between epithelial tumor cells and the different components of the surrounding microenvironment can locally affect the intracellular level of Wnt/ß-catenin signaling components and differentially trigger tumor cell stemness, EMT, invasive behavior, and metastasis (Myers, 2010).

β-catenin: has a dual role in the EMT; it enhances cell–cell adhesion when bound to cadherin complexes in adherens junctions and also functions as a transcriptional co-activator upon entry into the nucleus. When the WNT pathway is in resting state, cytoplasmic ß-catenin is phosphorylated by glycogen synthase kinase (GSK)3-ß and actively degraded by a multiprotein destruction complex that also includes casein kinase 1, APC and Axin. Thus, the levels of free ß-catenin are kept bellow the threshold where aberrant transcriptional activity will occur. In response to Wnt ligand binding to its specific receptor, the destruction complex is inactivated by inhibiting the activity of GSK3-ß which results in dephosphorylation and stabilization of ß-catenin, enabling it to accumulate within the nucleus, where it interacts with T-cell factor 4 /lymphocyte enhancer factor (TCF4/LEF) transcription factors to activate the transcription of Wnt target genes (Behrens et al., 1996; van de Wetering et al., 1997). It has been demonstrated that a number of genes targeted by nuclear ß-catenin LEF/TCF pathway plays a significant role in EMT (Table 1). Repression of E-cadherin by Snail, Twist, or other repressors leads indirectly to expression of vimentin and other mesenchymal gene products, partly because of β-catenin/TCF–Lef1 activation. TGF-β is known to activate this canonical Wnt pathway; TGF-β and Wnt pathway can independently or cooperatively regulate LEF/TCF target genes (Huber et al., 2005). TGF-β also directly activates the TCF–Lef1 transcription complex through tyrosine phosphorylation of SMAD-2. It has been reported that Smad-2/4 repressed E-cadherin transcription through TCF–Lef1 (Masszi et al., 2004; Nawshad et al., 2005). Loss of membranous ß-catenin and E-cadherin associated with EMT have been shown to correlate with metastatic formation and poor prognosis in multiple solid tumors and is a common feature of OSCC (Kudo et al., 2004; Odajima et al., 2005; Tanaka et al., 2003; Wang and Ma, 2007; Williams et al., 1998). Several studies have demonstrated that cytoplasmic and nuclear

localization of β-catenin is correlated with tumor progression, invasion and metastatic potential of OSCC (Ishida et al., 2007; Lo Muzio et al., 1999; Odajima et al., 2005; Yu et al., 2005). Cytoplasmic/nuclear β-catenin expression has also been found to significantly correlate with EGFR expression in OSCC (Odajima et al., 2005). In addition to the change in subcellular localization, phosphorylation of β-catenin may also be associated with OSCC progression and EMT (Tamura et al., 2003). It has been shown that tyrosine phosphorylation of β-catenin by EGFR is associated with the perturbation of E-cadherin - mediated cell adhesion and EMT acquisition and leads to increased cell motility that are requisite for metastatic dissemination (Hirohashi, 1998; Thiery, 2003). Furthermore, some authors have uncovered a new EMT pathway via p68 to nuclear ß-catenin (Yang et al., 2006). Given that EGF and TGF-β also induce p68 tyrosine phosphorylation, the nuclear ß-catenin is not simply a consequence of E-cadherin down-regulation during EMT, because phosphorylated p68 promotes ß-catenin nuclear localization regardless of whether E-cadherin is depleted or expressed. P68/ß-catenin axis may represent a common output for several signaling pathways. These pathways offer additional routes to nuclear ß-catenin signaling that are parallel to the Wnt pathway, which does not involve p68. The ability of β-catenin to enhance cadherin-dependent adhesion depends on β-catenin binding to α-catenin and on α-catenin binding to the cadherin (Chu et al., 2004). Phosphorylation of β-catenin residue Y142 prevents α-catenin interaction and enhances the binding of β-catenin to BCL9-2, which is the vertebrate homologue of the Drosophila melanogaster legless gene (Brembeck et al., 2006; Brembeck et al., 2004). Interaction of β-catenin with BCL9-2 enhances nuclear accumulation of both proteins simultaneously decreasing cadherin-mediated adhesion and activating catenin target gene transcription. Ectopic BCL9-2 expression is sufficient to induce EMT in cultured cells, and siRNA-mediated BCL9-2 inactivation drives the reverse mesenchymal–epithelial transition. Birchmeier reported that Y142 can be phosphorylated by the Met tyrosine kinase, indicating the existence of an EMT activation pathway where Met induces β-catenin nuclear translocation by enhancing BCL9-2 interaction (Heuberger and Birchmeier, 2010). This pathway satisfactorily links these two well known EMT regulators.

Akt pathway: Recently, activation of the Akt axis is emerging as a central feature of EMT. The Akt family of kinases is a downstream effector of phosphatidylinositol 3-kinase (PI3K) and is frequently activated in human epithelial cancers, including OSCC (Nakayama et al., 2001; Testa and Bellacosa, 2001). Akt activation in OSCC was linked to aggressive clinical behavior and the loss of histological features of epithelial differentiation (Lim et al., 2005). Akt-induced EMT involves down-regulation of E-cadherin, which appears to result from up-regulation of the transcription repressor Snail. Accordingly, inhibition of Akt activity induced down-regulation of EMT-related transcription factor Snail. Akt activity is induced by ligand stimulation of growth factor receptors such as the insulin-like growth factor-I receptor (IGF-IR) and the EGFRs (Hong et al., 2009; Hynes and Lane, 2005). It has been demonstrated that OSCC cells engineered to express constitutively active Akt underwent EMT, characterized by down-regulation of epithelial markers (desmoplakin, E-cadherin, β-catenin) and up-regulation of the mesenchymal marker vimentin, and exhibited enhanced tumor invasion (Grille et al., 2003). In contrast, the inhibition of Akt activity was able to restore epithelial characteristics, deplete mesenchymal features and reduce the migratory ability. This indicates that the inhibition of Akt activity could induce the MErT in OSCC cells and that the gain of epithelial characteristic might be an earlier or more prominent event in the MErT of the OSCC than the loss of mesenchymal one (Hong et al., 2009).

Name	Function	References
TNF-alpha	proinflammatory cytokine	Cawthorn WP et al *Cell Death Differ.* 2007
Osteopontin	extracellular matrix protein	Phlilip S et al *J Biol Chem.* 2005
Cyclin-D1 CCND1	Oncogene involved in cell proliferation	Cao J et al *World J Gastroenterol* 2006
c-myc	proto-oncogene involved in cellular proliferation	Cao J et al *World J Gastroenterol* 2006
Splicing Factor-1		
(SF-1)	regulates beta-cat gene transactivation and premessenger RNA splicing activities	Shitashige M et al *Gastroentetology* 2007
Notch1	transmembrane receptor that determines cell fate after its translocation to the nucleus where it activates gene transcription	Balint K et al *J Clin Invest.* 2005
Brn2	cell lineage-restricted genes	Larue L, Delmas V *Front Biosci.* 2006
Mitf-M	melanocyte-specific gene, with critical role in cell survival, proliferation and differentiation	Larue L, Delmas V *Front Biosci.* 2006
Dct	melanocyte-specific gene involved in melanoma proliferation	Larue L, Delmas V *Front Biosci.* 2006
MCP-1/CCL2	CC-chemokine implicated in tumour progression events such as angiogenesis or tumour associated macrophage (TAM) infiltration	Mestdagt M et al *Int J Cancer*, 2006
MYCBP	(myc binding protein)	Jung HC, Kim K *Life Sci.* 2005
MMP-7	Matrix Metalloproteinase Metastasis	Monaghan H.et al. *Histopathology.* 2007
CX43 (Connexin 43),	gap junctional protein	Husoy T et al. *Carcinogenesis.* 2003
PPAR-delta	peroxisome proliferator-activated receptor	Gupta RA et al *Proc Natl Acad Sci U S A.* 2000
ITF2 initiation transcription factor 2	transcription factor	Zhai Y et al. *Am J Pathol.* 2002
Survivin	Inhibition of apoptosis	Kim PJ et al. *Lancet* 2003
VEGF	Vascular endothelial growth factor	Calviello G et al *Carcinogenesis.* 2006
MT1-MMP	Membrane Type1-Matrix Metalloproteinase	Calviello G et al *Carcinogenesis.* 2006

Table 1.

C-met and tyrosine kinase receptors: The c-Met pathway has been implicated in the EMT during oral carcinogenesis; activating mutations have been found in metastatic head and neck carcinomas, but not in the corresponding primary tumors (Di Renzo et al., 2000).The activation of several other tyrosine kinase receptors, including fibroblast growth factor (FGF), insulin-like growth factor (IGF) and the ERBB family has been found to induce EMT in vivo and in vitro (Valles et al., 1990). Although the Met receptor-mediated signaling results in cell scattering, it has not been made clear whether Met signaling also has a more permanent effect on the expression or localization of some of the effectors of EMT, such as E-cadherin and β-catenin. Recent work suggests that Met also regulates intracellular localization of β-catenin (Heuberger and Birchmeier, 2010).

Twist: The basic helix-loop-helix transcription factor Twist, a master regulator of embryonic morphogenesis essential for initiating mesoderm development during gastrulation, was recently added to the growing list of developmental genes with a key role in E-cadherin repression and EMT induction, as well as metastasis (Kang and Massague, 2004; Martin and Cano, 2010). However, there have been very few reports on the relationship of Twist with the EMT in oral cancer cells. Hong et al (2009) reported that inhibition of Akt activity induced down-regulation of EMT-related Twist in OSCC cells. It has been recently reported that Twist directly regulates the stemness factor Bmi1, and that both proteins are required for the induction of EMT and stemness in head and neck squamous cell carcinoma (Yang et al., 2010). Twist is also induced by hypoxia showing a link between tumor microenvironment and the expression of EMT promoting transcription factors (Yang and Wu, 2008). Twist over-expression correlates with aggressive phenotypes and poor outcome in HNSCC (Yang et al., 2008). Twist can be up-regulated by Wnt signaling (Howe et al., 2003) and can bind and repress the E-cadherin promoter (Vesuna et al., 2008) in epithelial cells. Twist confers metastatic properties to breast tumor cells and stem-like properties in epithelial cells (Mani et al.; Morel et al., 2008; Yang et al., 2004).

Accumulating evidence demonstrates that tumor cells undergoing EMT acquire the capacity to migrate, invade the stroma and metastasize. EMT also involves other inducers such as matrix metalloproteinases (MMPs) and urokinase plasminogen activator which like growth factors, may be secreted by either the tumor cells themselves or by the surrounding tumor stromal cells. These molecules degrade the components of basal lamina leading to invasion of the migrating cancer cells into reactive stroma and subsequently lymphatic vessels and systemic circulation (Said and Williams, 2011). EMT cells also acquire stem cells characteristics suggesting crosstalk between EMT and pathways involved in promoting cellular stemness and that EMT might provide cells with both migratory and stem cells properties. Brabletz and colleagues proposed first the idea that disseminating cancer stem cells (CSC) represent the origin of metastasis (Brabletz et al., 2005). The experimental evidence to support this idea was provided by Weinberg and colleagues, by showing that cells induced to undergo EMT (by Twist/Snail/TFG-β) acquired a $CD44^{high}/Cd24^{low}$ signature, similar to a small sub-population of breast cancer stem cells that previously had been isolated and identified to have a unique ability to form tumors in xenograft models (Al-Hajj et al., 2003; Mani et al., 2008). Furthermore, EMT cells exhibited many properties of stem cells (mammospheres formation, ability to differentiate into cells of different lineages and to reconstitute a heterogenous tumor, (Mani et al., 2008). Another study reported that cells induced to undergo EMT by Ras-MAPK activation also displayed stem-like properties and a $CD44^{high}/CD24^{low}$ signature (Morel et al., 2008). Colleagues at the University of

Michigan first demonstrated that a $CD44^+$ population of cells possesses the properties of CSC in head and neck cancer (Prince et al., 2007), followed by other reports on head and neck cancer stem cells using other markers in addition to CD44 (Clay et al., 2010; Krishnamurthy et al., 2010; Krishnamurthy and Nor, 2011). In our recent study, we reported increased motility of $CD44^{high}$ CSC from head and neck cancer which is characteristic of cells undergoing EMT, and this may explain why, in our study, head and neck CSCs formed lung lesions in vivo, while non-CSCs did not (Davis et al., 2010). In fact, Takahashi et al. showed that, in EMT induced by tumor necrosis factor, the interaction between CD44 and hyaluronan indeed mediated cell-cell dissociation, actin remodeling, and, as a result, enhanced motility (Takahashi et al., 2010). These findings, in conjunction with our own, suggest that cell motility and the ability to undergo EMT are some of the most important characteristics of a metastatic cell, and it appears that CSCs may have those capabilities. Cancer stem cells seems to localize at the invasive fronts of the head and neck squamous cell carcinomas in the proximity of the blood vessels (Krishnamurthy and Nor, 2011) Future studies focused on better understanding the role of CSCs in EMT as it relates to oral, head and neck carcinomas are needed. In addition, further purification of the stemlike cell population in HNSCC is necessary to clarify what metastatic characteristics are indeed unique to these cells. Our laboratories are currently investigating these underlying mechanisms. Such knowledge would allow clinicians to exploit this particular set of attributes to target cancer cells that keep a tumor growing and allow it to spread. Furthermore, a better understanding of the EMT/MErT transformations during the OSCC progression will positively impact the clinical management of OSCC in the future.

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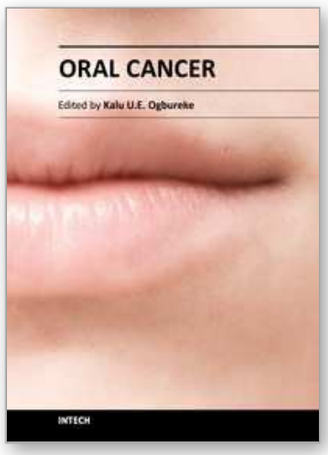

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Oral cancer is a significant public health challenge globally. Although the oral cavity is easily accessible, early diagnosis remains slow compared to the enhanced detection of cancers of the breast, colon, prostate, and melanoma. As a result, the mortality rate from oral cancer for the past four decades has remained high at over 50% in spite of advances in treatment modalities. This contrasts with considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period. This book attempts to provide a reference-friendly update on the etiologic/risk factors, current clinical diagnostic tools, management philosophies, molecular biomarkers, and progression indicators of oral cancer.

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