

# Exploring the Role of Cadherins in Epithelial–Mesenchymal Transition and Mesenchymal–Epithelial Transition-Associated Tumorigenesis

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## Abstract

### Keywords

- ▶ cadherins
- ▶ epithelial-to-mesenchymal transition
- ▶ mesenchymal-to-epithelial transition
- ▶ metastasis
- ▶ tumorigenesis

The malignant tumors develop when tumor cells overcome the cell–cell adhesion and invade the surrounding tissue. The epithelium consists of E-cadherin as the main adhesion molecule, which is mainly implicated in the carcinogenesis as it is frequently lost in the human epithelial tumors. Epithelial–mesenchymal transition (EMT) and its reverse mesenchymal–epithelial transition (MET) have been suggested to play crucial roles in metastatic dissemination of carcinomas. E-cadherin loss may promote invasion, and re-expression may facilitate cell survival within metastatic deposits. The mechanisms underlying such plasticity are unclear. Here, we summarize the role of cadherins in EMT- and MET-associated tumorigenesis by accumulating the experimental evidences that directly supports it.

## Introduction

Epithelial tissues are the basis of the most complex organs.<sup>1</sup> The thin layers of epithelia which line both the external surface and the internal cavities of the body are made up of highly specialized cells. Epithelial cells possess extensive junctional networks, which provide adhesion and facilitate intercellular communication, thus restricting motility, preserving tissue integrity, and permitting individual cells to function as a cohesive unit.<sup>2</sup>

Cadherins belong to a superfamily of adhesion molecules that mediate Ca<sup>2+</sup> dependent cell–cell adhesion in all solid tissues of the organism. It consists of the following:

- Classical cadherins that are the major component of cell–cell adhesive junctions (E-Cadherin);
- Desmosomal cadherins (desmocollins and desmogleins);
- Protocadherins;
- Some other cadherin-related molecules (e.g., the fat protein of *Drosophila*).

Cadherins-mediated cell–cell junctions occur due to interactions between extracellular domains of adjacent identical

cadherins. The stability of these adhesive junctions is ensured by binding of the intracellular cadherin domain with the actin cytoskeleton (▶ **Fig. 1**). Such highly specific homophilic cell–cell adhesion plays a key role in tissue and organ development during embryogenesis and in maintenance of normal tissue structure in the adult organism.<sup>3</sup> It has been reported that the E-cadherin/β-catenin system of adhesion molecules plays a potential role in this processes.<sup>4</sup> Acquisition of invasive properties in epithelial malignancies is due to disruption of intercellular adhesions. Alterations of E-cadherin/β-catenin have been implicated in the oncogenesis of carcinomas that have been correlated with adverse clinico-pathological parameters.<sup>5,6,7</sup>

An epithelial–mesenchymal transition is an important process in which an epithelial cell undergoes multiple biochemical changes when interacts with the basement membrane to assume a mesenchymal cell phenotype, with special properties as enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of extracellular matrix (ECM) components.<sup>8</sup> Epithelial–mesenchymal transition (EMT) has received much attention by the

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research community since Greenburg and Hay first described a mesenchymal-like transformation of epithelial cells when suspended in collagen gels.<sup>9</sup> The best studied processes of EMT is the loss of intercellular cohesion between epithelial cells by limiting the expression of E-cadherin (epithelial cadherin), whereas the cells which undergo the EMT process aberrantly express higher levels of N-cadherin (mesenchymal cadherin). This whole mechanism is called “cadherin switching.”<sup>10</sup>

► **Fig. 2** depicts the summary of cellular events during EMT.<sup>11</sup> According to the circumstances of its occurrence, EMT can be classified into three types. This concept was discussed at Poland in 2007 and a subsequent meeting in

March 2008 at Cold Spring Harbor Laboratories. EMTs are classified as follows:

- EMT type I: EMT during implantation, embryogenesis, and organ development.
- EMT type II: EMT associated with tissue regeneration and organ fibrosis.
- EMT type III: EMT associated with malignancies.<sup>12</sup>

The phenotypic plasticity afforded by an EMT is revealed by the occurrence of the reverse process—a mesenchymal-epithelial transition (MET), which involves the conversion of mesenchymal cells to epithelial derivatives. Relatively,

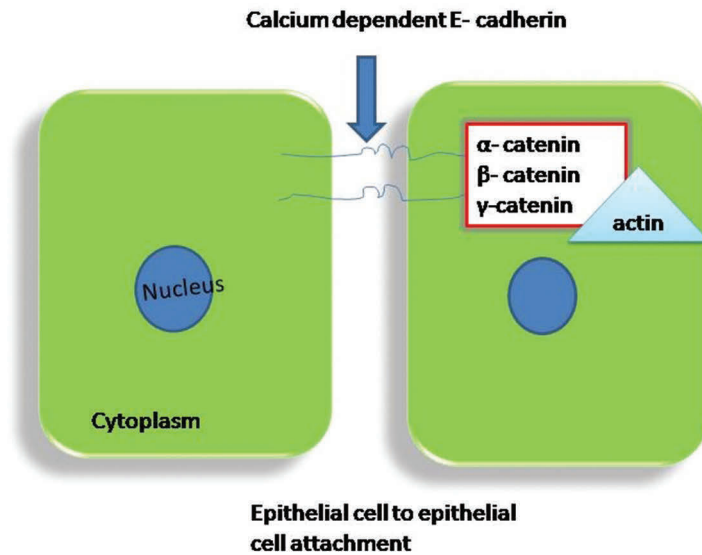


Fig. 1 Cadherin–catenin cell adhesion complex.

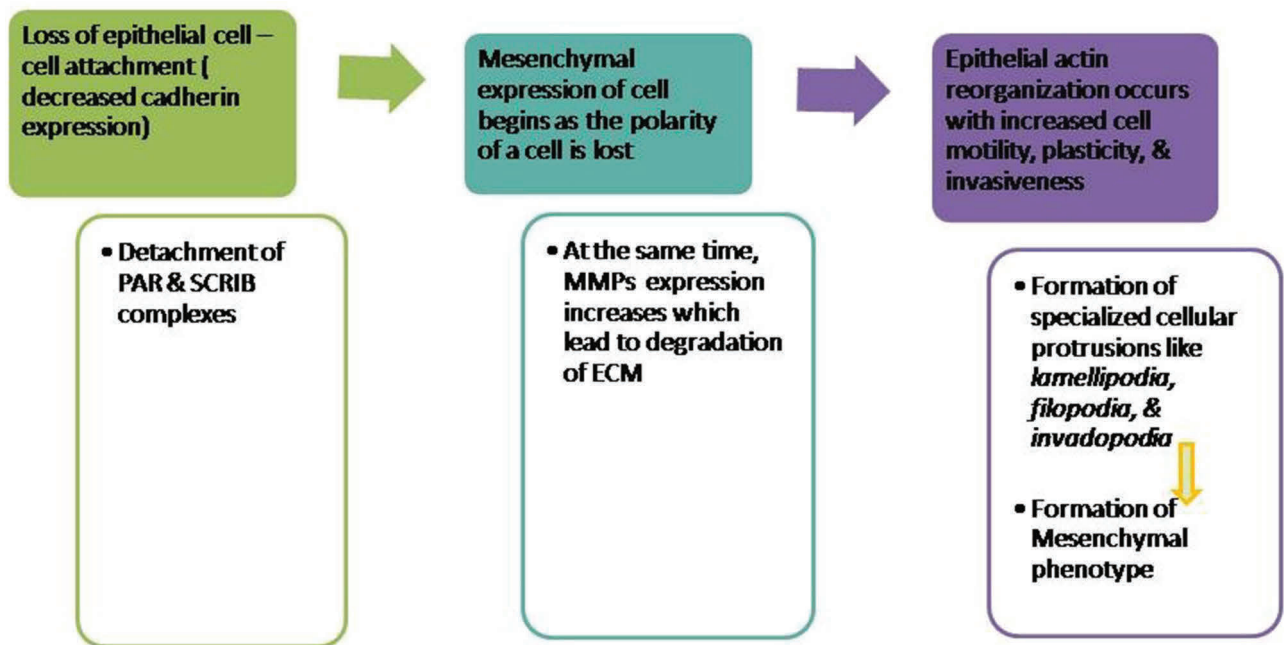


Fig. 2 Cellular events during epithelial-mesenchymal transition. ECM, extracellular matrix.

little is known about this process; the best-studied example is the MET-associated kidney formation.<sup>13</sup> The initial transformation from benign to invasive carcinoma requires EMT process, whereas later steps of metastasis involves MET (the reverse of EMT). EMT process is characterized by the downregulation or silencing of E-cadherin, whereas the re-expression of E-cadherin is proposed to be the important hallmark of MET.<sup>14</sup> In this review, we are highlighting the behavior of classical cadherins in EMT and MET associated with tumorigenesis.

### EMT in Primary Tumors

Tumor cells which undergo EMT in the primary tumor show molecular and cellular changes that result in loss of adhesion

between epithelial cells, which leads to local migration and invasion, entry into blood vessels (i.e., intravasation), survival either as single cells or cells coated with platelets, and dissemination by exiting the vessels (extravasation) into the parenchyma of distant specific organs (→ Fig. 3). Once colonization occurs in the metastatic organs, EMT cancer cells may re-differentiate into an epithelial phenotype by MET through interactions with the tumor microenvironment to progress into macrometastasis.<sup>15</sup> Many studies suggest that an EMT process occurring within cancer stem cells (CSCs) and circulating tumor cells (CTCs) characterizes a subpopulation of patients prone to relapse. In addition, CTCs with an EMT signature may co-exist or transform into relapse-initiating CSCs. Furthermore, an EMT process within cancer cells enables the remodeling of the ECM, which awakens the relapse-initiating CSCs.<sup>16</sup>

Fig. 3 Depiction of epithelial–mesenchymal plasticity in metastasis.

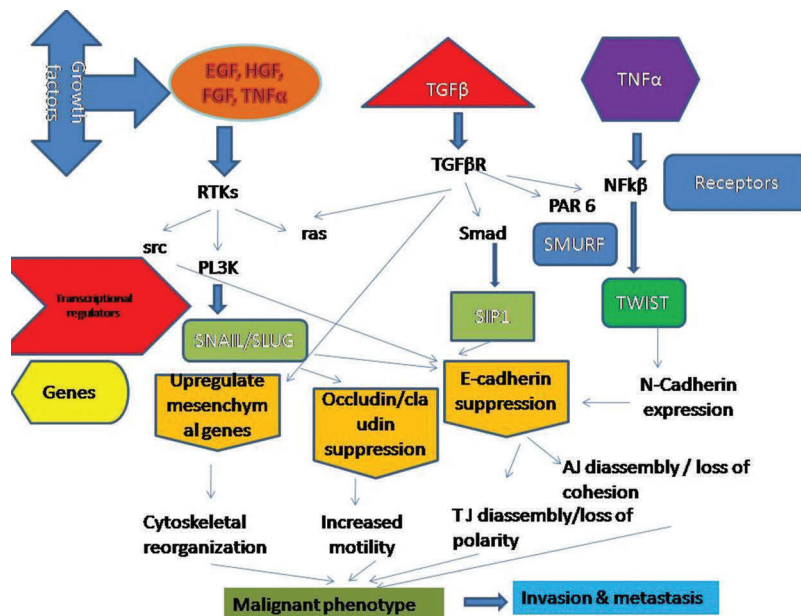


Fig. 4 Pivotal role of E-cadherin, β-catenin in EMT program. EMT, epithelial-to-mesenchymal transition.

## Role of Cadherins in EMT Associated with Tumorigenesis

The epithelial integrity is maintained due to the protein complexes present on the epithelial cell surface, which provides cell–cell junctions (►Fig. 4). E-cadherin glycoprotein is a Ca<sup>2+</sup>-dependent intercellular adhesion molecule in epithelial cells, which forms adherens junctions with its cytoplasmic tail linked to the actin cytoskeleton by  $\alpha$ - and  $\beta$ -catenin. The loss of E-cadherin is an important hallmark in EMT process and a key feature of metastatic cells. Epigenetic silencing at the E-cadherin promoter region is induced by Snail, Zeb and Twist (E-cadherin repressors) through hypermethylation and histone deacetylation.<sup>8</sup> Therefore, the integrity of epithelial layer is lost due to loss of E-cadherin and further allows individual cells to move freely, which is observed in cancer metastasis.

Along with adherens junctions disruption, tight junctions disruption also occur during an EMT process, which shows the decreased expression of claudin and occludin junctional proteins and the relocation of the zonula occludens 1 protein (ZO-1; also called tight junction protein [TJP1]). Adherens junctions destabilization involves the cleavage of E-cadherin at the cell membrane and its subsequent degradation.<sup>17</sup> As a result of this E-cadherin cleavage,  $\beta$ -catenin no longer interacts with E-cadherin and then is either degraded or protected from degradation to activate the downstream transcription.<sup>18</sup> The initiation of an EMT process also disrupts desmosomes and gap junctions. As an EMT progresses, the expression of junctional proteins is transcriptionally repressed, which secures the permanent loss of epithelial junctions.<sup>19</sup>

The loss of epithelial cell polarity is another key step in the EMT process. Epithelial cell polarity loss is induced by Snail 1 through repressing Crumbs3 transcription and by abolishing Par and Crumbs3 localization at the cell junctions.<sup>20</sup> TGF- $\beta$  utilizes the canonical pathway and non-canonical pathways to promote the loss of cell polarity. The canonical pathway induces Snail and Zeb gene expression. The noncanonical pathway downregulates Par3 expression, degrades RhoA (Par6-mediated), and alters the actin cytoskeleton.<sup>21,22</sup> Par and Crumbs complexes, which are associated with Lin-7, localize apically in association with tight junctions and define the apical compartment, whereas Scribble complexes define the basolateral compartment.<sup>23,24</sup>

There is also disruption of the apical–basal polarity due to loss of epithelial junctions during an EMT process. The interaction of SCRIB with the lateral cell membrane is prevented in cancer cells, which resulted from decreased expression of E-cadherin.<sup>25</sup> Furthermore, it also leads to reduced cell adhesion and increased cell motility.<sup>26</sup> Rho family small GTPases as well as apical–basal polarity proteins are involved in the change from apical–basal polarity to front–rear polarity.<sup>27</sup> The decreased expression of CRB3 and LGL2 (polarity complex proteins) during an EMT process<sup>28,29</sup> further destabilizes the apical–basal polarity.

The loss of E-cadherin gene expression is an important event in an EMT and also in the destabilization of adherens junctions. Consequently, many studies have focused on the mechanism by which E-cadherin is regulated during

cancer progression. Recently, Zheng et al<sup>30</sup> (►Table 2) studied the induction of EMT by ELF3 in hepatocellular carcinoma. They found that ELF3 repressed E-cadherin and promoted EMT in hepatocellular carcinoma cell (HCC) by suppressing miR-141–3p, thereby activating ZEB1. Thus, ELF3 may be a potential prognostic biomarker and/or therapeutic target for HCC. Another study by Sun et al<sup>31</sup> (►Table 2) hypothesized that SIRT1 promotes melanoma metastasis by inducing the EMT. Their findings suggested that SIRT1 could induce the EMT by promoting the autophagy-linked lysosomal degradation of E-cadherin, the master suppressor of the EMT. Therefore, their study demonstrated a novel mechanism for SIRT1 in promoting EMT in melanoma cells and provided a potential therapeutic target for metastatic melanoma.

The factors which promote the EMT process are classified according to their ability to repress E-cadherin directly or indirectly (►Table 1). In addition, the disruption of apical tight junctions results from the repression of claudin and occludin gene expression. Whereas, the repression of desmoplakin and plakophilin gene expression promotes the disruption of desmosomes.<sup>32</sup> This repression of gene expressions inhibits the de novo formation of cell–cell junctions and results in the disruption of the epithelial cell layer.<sup>33</sup> The above-mentioned repression of gene expression for cell junction proteins is accompanied by the activation of gene expression for proteins expressed in mesenchymal cells.

The  $\alpha$ -catenin and  $\beta$ -catenin helps the N-cadherin to binds its cytoskeleton. In addition, N-cadherin has interaction with p120, various signaling molecules, and receptor tyrosine kinases (RTKs) such as platelet-derived growth factor (PDGF) and fibroblast growth factor receptors (FGFRs).<sup>34–36</sup> N-cadherin also interacts with the neural cell adhesion molecule (NCAM) during the EMT process.<sup>34,37</sup> NCAM modulates the activity of various RTKs and FYN (an SRC family tyrosine kinase), which facilitates the assembly of focal adhesions, cell migration, and cell invasion.<sup>38</sup>

Gene expression-related to cytoskeletal proteins and cell polarity complex proteins also change during the EMT process. For example, changes occur in the composition of intermediate filaments during the EMT process as evidenced by the repression of the cytokeratin gene and the expression of the vimentin gene.<sup>32</sup> Keratin and vimentin intermediate

**Table 1** EMT molecules that repress E-Cadherin

	Molecules
Direct E-Cadherin repressors	Snail 1 (Snail), Snail 2 (Slug), and Snail 3 (Smuc)
	Zeb 1, Zeb 2, Tcf 8
	E47
	Klf 8
Indirect E-Cadherin repressors	Twist 1, Twist 2
	GSC & SIX 1
	E2.2
	Fox c2

Abbreviation: EMT, epithelial–mesenchymal transition.

**Table 2** Studies related to cadherins role in EMT and MET associated tumorigenesis

	Year	Author	Study
1	2018	Zheng et al <sup>30</sup>	Revealed increased ELF expression which promoted HCC proliferation, migration, and invasion. Also found ELF promoted EMT through decreased E-cadherin expression
2	2018	Sun et al <sup>31</sup>	Reported that SIRT1 induced EMT and promoted cell migration and invasion by decreasing E-cadherin expression
3	2016	Takaishi et al <sup>58</sup>	Showed the effects of RFs on SCC cells. RICs regained epithelial properties through MET and showed reduced cancer malignancy in vitro and in vivo
4	2016	Cheng et al <sup>63</sup>	Illustrated the clinical significance and molecular mechanisms of tumor suppressive GDF10 in OSCC. GDF 10 acted as a hinge to collaborate with TGFBR3 in transition of EMT-MET program
5	2014	Ayed-Guerfali et al <sup>6</sup>	Suggested deregulation of Wnt pathway via abnormal expression of $\beta$ -catenin & E-cadherin which occurred frequently in gastric carcinoma
6	2013	Bhagat et al <sup>7</sup>	Found reduced expression of E-cadherin association with promoter methylation of E-cadherin gene, in addition provided evidence of aberrant nuclear localization of E-Cadherin in EOC
7	2013	Nguyen et al <sup>61</sup>	Suggested that PDI73074 (inhibitor of FGFR1) inhibits the MAPK pathway which regulates the activity of AP-1 and induce MET.
8	2011	Shen et al <sup>5</sup>	Concluded that TWIST may act upstream of E-cadherin which can directly regulate the expression levels of $\beta$ -catenin.
9	2010	Schwock et al <sup>59</sup>	Found that SNAI1 was expressed at low levels, in a substantial proportion of OSCC
10	2009	Hong et al <sup>60</sup>	Suggested that Akt inhibition could induce the MErT through decreased NF-kappa $\beta$ signaling and downregulation of SNAI1 and TWIST in OSCC cells

Abbreviations: Akt, AK strain transforming; ELF3, E74-like ETS transcription factor 3; EMT, epithelial–mesenchymal transition; EOC, epithelial ovarian carcinoma; FGFR1, fibroblast growth factor receptor; GDF10, growth differentiation factor10; HCC, hepatic cell carcinoma; MAPK, mitogen activated protein kinase; MErT, mesenchymal to epithelial reverting transition; MET, mesenchymal–epithelial transition; NF, nuclear factor; RFs, reprogramming factors; RICs, reprogramming factors induced cancers; SCC, squamous cell carcinoma; SIRT, sirtuin; TGFBR3, transforming growth factor  $\beta$  receptor.

filaments both regulate trafficking of organelles and membrane-associated proteins, but keratin and vimentin traffic different membrane-associated proteins to the cell membrane.<sup>39</sup> Another example explains the changes in the direction of cell motility during the EMT process as evidenced by the repression of the Crumbs3 gene, PATJ gene, and LGL2 gene. Crumbs3 and PATJ are apical Crumbs complex proteins and LGL2 is a basolateral Scribble complex protein.<sup>34,40</sup>

When the differentiation of epithelial cells occurs into mesenchymal cells, there is a loss of interaction of epithelial cells with the basement membrane, and they start interacting with the underlying ECM. This indicates that at one end there is downregulation of some epithelial integrins, but at the other end, other integrins show upregulation, which plays a key role in the EMT process.<sup>34</sup> The changes in the integrin profile during an EMT correlate with the increased expression of proteases (e.g., MMP2 and MMP9 matrix metalloproteinases) that enhance protein degradation and promote cell invasion. MMPs also target transmembrane proteins (e.g., E-cadherin), which results in shedding of the extracellular domain of E-cadherin and the disruption of adherens junctions.<sup>41</sup>

The implication of nuclear factor nB (NF-nB) has been found in EMT, which promotes expression of the basic helix–loop–helix transcription factor Twist-like Snail, Slug, and SIP-1, Twist also binds to E-box sequences and downregulates

E-cadherin. However, the mechanism by which Twist promotes EMT is poorly understood, as Twist is believed to function as a transcriptional activator when bound to E-box sequences. The mesenchymal characteristics are promoted by Twist which activates N-cadherin. Further there is downregulation of E-cadherin, and Twist induces mesenchymal morphology in mammary tumor cell lines. In addition, activation of NF-nB may promote expression of mesenchymal proteins independently of Twist, as NF-nB binds regulatory sequences within the promoter of vimentin.<sup>2</sup>

Finally, studies have shown that expression of an inappropriate cadherin in epithelial cells is yet another way that tumor cells can alter their adhesive function.<sup>42–46</sup> Mesenchymal cadherins can have a direct and dominant influence on the phenotype of epithelial cells, despite their continued expression of E-cadherin.<sup>47</sup> Non-epithelial cadherins, including N-cadherin, R-cadherin, and cadherin-11, are expressed by some tumors in situ, and their expression has been correlated with high tumor grade and with an aggressive, metastatic phenotype.<sup>43,45,48–52</sup>

### Role of Cadherins in MET

MET is defined as a reversible biological process that involves the transition from motile, multipolar, or spindle-shaped

mesenchymal cells to polarized epithelial cells. MET, just like EMT, also takes place during normal development in processes such as somitogenesis, kidney development, cardiogenesis, hepatogenesis, and celomic cavity formation. MET occurs in cancer metastasis, induced pluripotent stem cell reprogramming, and mucosal healing.<sup>53</sup>

A recent hypothesis states that the disseminated metastatic cells revert back to epithelial phenotype, typically demonstrating re-expression of E-cadherin to allow efficient colonization at secondary sites. This process is termed MET or mesenchymal-to-epithelial reverting transition.<sup>54</sup> The MET process enhances survival edge to some tumor cells at a lower metabolic load because of E-cadherin adhesions and also is the reason behind why metastases recapitulate the primary tumor pathology.<sup>55</sup> Brabletz et al<sup>56</sup> observed that metastases from tumors originally expressing nuclear  $\beta$ -catenin were found to re-express E-cadherin, and their  $\beta$ -catenin became cytoplasmic, which is indicative of an MET.

## Mechanism

Two possibilities are defined. One possibility states that tumor cells which have already undergone EMT process intravasate blood capillaries at the primary tumor site and extravasate into the distant organ, but to revert back to the epithelial phenotype, the tumor cells have to grow at the secondary site and become a clinically relevant and detectable mass. This premise is based upon strong evidence in embryonic systems, but confirmation in human cancer patients as to when the MET event occurs, if at all, is unclear. Some suggest that there is cooperation between epithelial and mesenchymal cells such that mesenchymal cells “pave the way” for the escape of epithelial cells, while epithelial cells have a proliferative advantage at the secondary location and therefore make up the majority of the second mass.<sup>57</sup> Re-expression of E-cadherin in the metastatic site, therefore, represents the second possibility (►Fig. 3). While this is consistent with the histopathological correlations, E-cadherin re-expression would represent tumor cell plasticity and that of reverting the carcinoma-associated EMT that has not been demonstrated to date. The nature of E-cadherin downregulation mechanisms suggests how this could be accomplished.

Downregulation of E-cadherin surface expression is explained by two mechanisms, which include functioning separately at the post-translational and the transcriptional levels. Activation of Tyrosine kinase signaling occurs in response to various growth factors and during neoplastic progression and can downregulate E-cadherin secondary to phosphorylations of the E-cadherin complex. Scatter factors (such as hepatocyte growth factor [HGF] and epidermal growth factor [EGF]) lead to epithelial cell migration away from cohesive masses secondary to E-cadherin downregulation. The cytoplasmic part of the E-cadherin gets dissociated, which leads to E-cadherin internalization and degradation. This may function in carcinomas, almost all of which have autocrine growth factor signaling loops most often that via the EGF receptor. We have found in prostate carcinoma lines that inhibition of this autocrine EGF receptor loop

(and likely the EGFR-induced HGF/c-met autocrine loop), either by direct disruption of the signaling loop or by second site signaling trans-attenuation, results in E-cadherin re-expression and cell–cell cohesion. Thus, post-translational E-cadherin downregulation represents an available target for counter-regulation by other factors that might be present in the metastatic microenvironment.

Promoter hypermethylation leads to complete shut off of E-cadherin at the translational level in most of the carcinomas, other than prostate carcinomas. A null phenotype is generated usually by deletions or mutations of the coding deoxyribonucleic acid (DNA), which differs from other tumor suppressors. While these latter mechanisms are irreversible by their nature, promoter hypermethylation is readily reversible only by proliferation-linked failure to maintain methylation. There exists one distinction between the normally irreversible tumor suppressors from E-cadherin, which is that loss of the former often occurs early in neoplastic transformation, whereas E-cadherin is related to tumor progression to dissemination. Still, this mode of transcriptional shut off is reversible. In fact, it has been noted that E-cadherin promoter methylation is unstable. Recently, we have found that E-cadherin promoter methylation can be selectively lost in breast carcinoma cells when proliferating in the presence of normal hepatocytes. Thus, the microenvironment of metastatic target organs provides signals that may undo both mechanisms of E-cadherin downregulation. These data provide proof of principle that carcinoma cells may re-express E-cadherin in response to the ectopic organ microenvironment so as to establish connections with the resident, non-neoplastic epithelial cells.<sup>53</sup>

A recent study by Takaishi et al<sup>58</sup> (►Table 2) demonstrated that the squamous cell carcinoma (SCC) cells decrease malignant potential in vitro and in vivo through MET by the introduction of reprogramming factors without the pluripotent-like state. They found that reprogramming factors introduced cancer (RIC) regained epithelial properties through MET and showed reduced cancer malignancy in vitro and in vivo.

Only a handful studies exist in the current literature on MET in oral cancer. Worthy to note is the expression of E-cadherin in lymph node metastases of two of oral squamous cell carcinomas (OSCC) cases in a study by Schwock et al which they attributed to MET following nodal metastasis. Another school of thought states that tumor cells may exist in “quasi-mesenchymal” states, rather than undergoing complete transition.<sup>59</sup>

Hong et al studied induction of MET in OSCC cell lines by inhibiting Akt activity. Decreased nuclear factor- $\kappa$ B signaling and downregulation of snail and twist were observed on Akt inhibition.<sup>60</sup>

A study by Nguyen et al investigated the role of fibroblast growth factor receptor 1 (FGFR1), a cytokine (FGF) receptor that acts as oncoprotein during head and neck SCC (HNSCC) tumorigenesis. Simultaneously, they also observed the effects of PD173074, a known selective inhibitor of FGFR1. HNSCC cases demonstrated a high expression of FGFR1, and this correlated with malignant behaviors. An interesting finding was relative overexpression of FGFR1 in EMT cell lines compared with non-EMT cell lines. Furthermore, on treatment with

PD173074, cancer cells exhibited a morphological change from spindle to cobblestone like.<sup>61</sup>

Chang et al investigated the role of multifunctional signaling modulator, connective tissue growth factor (CTGF) in HNSCC. CTGF acts as either an oncoprotein or a tumor suppressor in different cancer types. Their results revealed that CTGF promoted MET and reduced invasiveness in HNSCC cells.<sup>62</sup>

Recently, a study by Cheng et al investigated the expression of growth differentiation factor-10 (GDF10) (a member of the transforming growth factor- $\beta$  [TGF- $\beta$ ] superfamily) in oral cancer cell lines. They found GDF10 to be downregulated during oral carcinogenesis. GDF10 inhibited EMT; hence, authors suggested the use of TGFBR3, an upstream activator of GDF10 expression, to reversing the process of EMT.<sup>63</sup>

## Conclusion

According to our current knowledge, both EMT and MET are highly significant biological events, not just in physiological, but in pathological circumstances. A better understanding of their induction and regulation may lead to the identification of pathways and factors that can be potent therapeutic targets.

### Funding

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### Conflict of Interest

None declared.

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