

Epithelial Mesenchymal Transitions: Basics, Clinical Applicability & Recent Updates

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Abstract: Epithelial mesenchymal transition is an integral step in embryogenesis and wound healing. In this motile, mesenchymal like cells develop from epithelial precursors. These modified cells have immense plasticity and are governed by interplay between different functional and regulatory molecules. This plasticity has broad implications in the field of cancer research, tumor invasion and metastasis as well as in anti neoplastic therapies. A complete understanding of the molecular mechanism of EMT along with molecular regulators is essential for targeted therapeutic interventions. This article aims to review molecular mechanism of EMT as a whole along with special emphasis on its clinical relevance and its role in anti- neoplastic therapies, prognosis and controversies associated with it.

Keywords: EMT, tumor microenvironment, metastasis, master genes, MET.

I. INTRODUCTION

Elizabeth Hay was the first to describe the epithelial mesenchymal transformation using a chick primitive streak formation model. (E.D., 1995) Later the term transformation was replaced by transition reflecting that the cell was not converting entirely into another phenotype but was only acquiring some properties similar to a cell of a different origin. (Kalluri R, 2003).

Epithelial mesenchymal transition is the conversion of a cell possessing the characteristics of an epithelial phenotype to a cell possessing mesenchymal properties. An epithelial cell is usually polarized, well attached to each other by desmosomes and to the basement membrane by hemidesmosomal junctions. Mesenchymal cells are different from epithelial cells in that they are elongated in shape and possess focal adhesions which allow increased migratory capacity. (Guarino M, 2007).

The conversion of epithelial cell to a mesenchymal phenotype is said to be complete once it achieves properties

like migratory capacity and ability to produce ECM components. The completion of EMT is indicated by the degradation of the basement membrane allowing the converted mesenchymal cell to migrate away from the epithelium from which it originated. Numerous molecular mechanisms are involved in this conversion, like transcriptional factors activation, expression of cell surface receptors, production of matrix degrading enzymes and many more. All these factors can be used as markers to demonstrate the process of epithelial mesenchymal transition. (Thiery J.P., 2006).

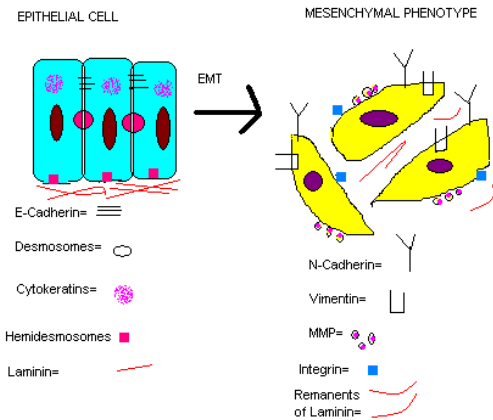


Figure 1: molecular difference between cells during epithelial mesenchymal transition

II. NEED FOR EMT

The need for EMT arises from gastrulation, as this reduces the need for providing different types of cells for forming different tissues and functions. At the end of embryogenesis these factors that were responsible for the transition become dormant. EMT and its reverse process, mesenchymal-epithelial transition (MET), regulate the early stages of development of most animals. EMT is primarily required during gastrulation while MET is seen during somitogenesis, kidney development, and coelomic-cavity formation. EMT is reactivated in the adult as a physiological attempt to control inflammation and to heal damaged tissue. (Locascio A, 2001).

CLASSIFICATION OF EMT:(GHANTA SB, 2012)

Epithelial mesenchymal transitions can be classified into 3 types.

TYPE 1

Seen in embryogenesis, involves the transition of primitive epithelial cells into mesenchymal cells that are motile and is often associated with formation of varied cell types. These cells may later undergo mesenchymal epithelial transition (MET) to produce secondary epithelium.

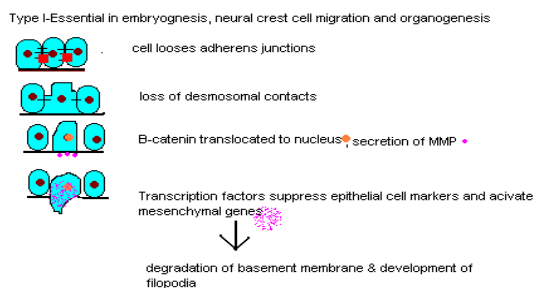


Figure 2: Sequential events in type I EMT

TYPE 2

Seen in wound healing, tissue regeneration and if it continues it takes a pathological path to produce organ fibrosis. Begins in order to repair the damaged tissue resulting in wound healing. However sometimes it continues as inflammation persists resulting in destruction of tissue architecture. Thus, the physiological process of wound healing is now converted into the pathological process of fibrosis.

Figure 3- EMT in healing and fibrosis and pathogenesis of benign tumors like cementifying and ossifying fibromas

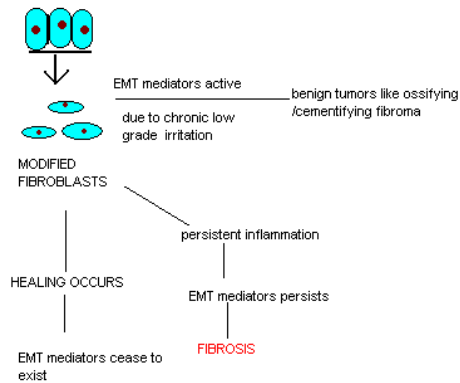


Figure 3: Sequential events in type II EMT

TYPE 3

Seen in neoplasia, and involve cells that have undergone genetic and epigenetic changes that promote clonal expansion and the development of neoplasms. In this type the cells retain a few epithelial characteristics like cytokeratin expression but lose most of the other features like cohesiveness and desmosomal junctions.

figure 4- Role of EMT in Neoplasia & Metastasis

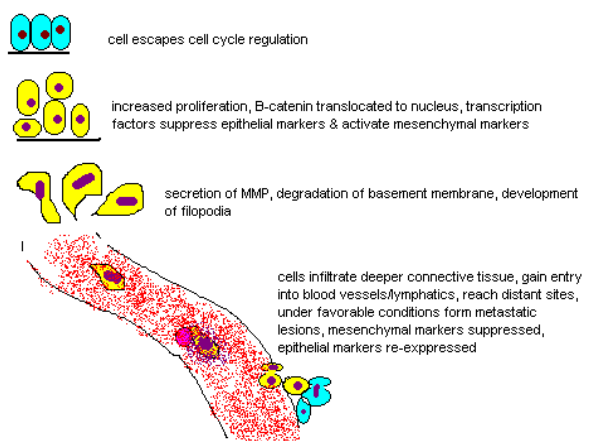


Figure 4: Sequential events in type III EMT

III. MOLECULAR ASPECTS OF EMT

CADHERIN SWITCH

Alteration in the cell surface markers is a primary step in EMT. One of the first steps in EMT is the change in expression of E-cadherin which facilitates cell to cell

adhesion. (Chetana Chandrashekar, 2014) Down regulation of E cadherin is accompanied by up regulation of N-cadherin expression and this transformation is called the “cadherin switch” and is regarded to be a hallmark of EMT (Gravdal K, 2007). Degradation of cell-cell junctions is further facilitated by repression of claudin and occludin expression, and there is loss of zonula occludens 1 (ZO-1) post-transcriptionally. (Chu K, 2008; Nguyen PT, 2011; Tomita K, 2000).

VIMENTIN EXPRESSION

Vimentin is an intermediate filament protein which is found in mesenchymal cells. It has been shown that tumors show high vimentin expression which is directly proportional to the degree of invasiveness. It is one of the most commonly used markers for identifying EMT in cancers (Dal Vecchio AM, 2011). It has proved to be a useful prognostic indicator when used along with E-cadherin/ β -catenin complex at the invasive tumor front in OSCC (Liu LK, 2010).

INTEGRIN SWITCHING

Dysplastic cells need to reach the connective tissue in order to reach circulation. This is achieved by relocation of the cell by alteration in integrin expression. Ramos *et al.* demonstrated that there is an increase in the expression of $\alpha\beta6$ in poorly differentiated squamous cell carcinoma cell lines, this results in fibroblast-like morphology of the cells (Ramos DM, 2009).

EXPRESSION OF PROTEASE

For the tumor cells to be able to move in the extracellular matrix it is important that they express proteases which will help them in degrading the ECM and allow disruption of cell to cell junctions. Most common protease expressed is Matrix Metalloproteinase. The process of migration and invasion is further facilitated by development of cellular modifications such as lamelliopodia, invadopodia and filopodia. They contain actin network which allows for cell motility. The primary difference among these three is the arrangement of the actin filaments, being parallel in filopodia, branched in lamelliopodia and invadopodia. The primary difference between invadopodia and lamelliopodia is that the former possess the ability to degrade extracellular matrix by secretion of lytic molecules like MMP-1,7 & 9 (Blavier L, 2010). TGF- β also activates the small GTPases such as Rho, Rac and Cdc42 that increase the reorganization of actin cytoskeleton which allows for lamellipodia and filopodia formation (Ramos DM, 2009). Vimentin is essential for the maturation of the invadopodia and is often upregulated in the cells with an EMT phenotype.

Marker	Function	Unregulated /Downregulated
α -catenin	Cell adhesion molecule	Downregulated
β -catenin	Cell adhesion molecule	Downregulated
Claudin	Cell adhesion molecule	Downregulated

Cytokeratins	Cytoskeletal filament	Downregulated
N-cadherin	Cell adhesion molecule	Upregulated
Notch-1	Transcription factor	Upregulated
p16INK4a	Cell cycle regulator	Upregulated
Slug	Transcription factor	Upregulated
Snail	Transcription factor	Upregulated
α v beta 6		Upregulated
Vimentin	Intermediate filament	Upregulated
Matrix Metalloproteinase	Protease	Upregulated

Table 1: molecular markers of EMT, their function and role in EMT.(Konrad Steinestel, 2014)

IV. CONTROVERSIES IN EMT

A lot of researchers also do not agree with the role of EMT in invasion as most of the resected specimens histologically show the metastatic deposits as multicellular organizations rather than single cell migration. This can be explained by the soil and seed theory based on which it can be said that EMT is just a transitional state which is acquired by only few cells which helps them to achieve the dynamic configuration required for invasion and metastasis, this has been referred to as “spatial and temporal heterogeneity of EMT” by Voulgari *et al.* (Nieto MA, 2012; Voulgari A, 2009).

Another controversy associated with EMT is that whether EMT is associated with increased or decreased proliferative activity of the involved cell. In normal conditions TGF- β exerts a pro-apoptotic and anti proliferative effect. However experiments have shown that tumor cells that undergo EMT actually show enhanced proliferative activity and decreased apoptosis (Bierie B, 2010; Gore AJ, 2014).

Thus TGF- β has a spectrum of effects which can be identified by loss of Smad 4 in tumor tissue that promotes tumorigenesis (Levy L, 2005).

V. CLINICAL SIGNIFICANCE OF EMT

EMT IN GINGIVAL OVERGROWTH

Medication like phenytoin, nifedipine, and cyclosporine-A are known to produce gingival overgrowth. Siddika *et al.* found that there was diminished expression of E-cadherin and enhanced expression of fibroblast-specific protein-1 (FSP-1) and $\alpha\beta6$ integrin levels. The connective tissue showed increased levels of fibronectin and alternatively spliced fibronectin extra type III domain A (FN-ED-A). These findings support the role of EMT in fibrosis and gingival enlargement.

OSMF

Das et al studied the association of EMT and OSMF by using expression of p63, E-cadherin, β -catenin, N-cadherin and TWIST, immunohistochemically and found that along with progressive maturation in osmf there was increase in thickness of basement membrane along with collagen deposition. Increase in expressions of epithelial master regulator p63 and its oncogenic isoform (Δ N) along with membranous loss of E-cadherin (EMT hallmark) and its associate β -catenin and gain of mesenchymal markers like N-cadherin and TWIST. These changes were indicative of EMT activation in oral sub-mucous fibrosis.(Das RK, 2013).

OSCC

It has been found that there is an alteration in the location of expression of E-cadherin in OSCC especially at the ITF, instead of being localized on the membrane. E-cadherin is expressed diffusely in the cytoplasm of cells at the ITF, as cadherins are functional at the membrane /adherens junctions but not when they are distributed in cytoplasm, indicates a transient shift in location of expression of markers in EMT and this change in expression is directly related with the grade of the tumor. Switch from E-cadherin to N-cadherin also is suggestive of an aggressive phenotype and unfavorable prognosis. It has also been shown that the aggressive subsets of the OSCC cells lose the keratinocyte markers and express mesenchymal molecules specifically at the ITF indicating the role of EMT in progression of OSCC.(Chiba T, 2009; Maeda G, 2007; Miyazawa J, 2004; Uraguchi M, 2004).

Stem cell marker	Function	Utility
CD44	plays a dual role, both as a cell surface adhesion molecule and hyaluronan and osteopontin receptor.	extensively used for cancer stem cell enrichment in various tumors. functionally involved in biological processes, like lymphocyte homing, cancer metastasis and peritoneal colonization.
CD133	glycosylated transmembrane cell surface antigen identified as a marker of various stem and progenitor cells, including haematopoietic stem cells, circulating endothelial precursors, and numerous cancer stem cell populations (lung, liver, prostate, colon, ovary, pancreas, etc.).	Its relevance for cancer stem cell identification has been questioned. Both its expression and glycosylation can change upon cell differentiation.
CD326	pan-epithelial differentiation antigen expressed on the basolateral surface of various carcinomas.	It acts as a homotypical cell adhesion molecule and can modulate various oncogenic signal molecules, like Cadherin - Catenin of c-Myc.
CD33	is a cell surface adhesion molecule of myelomonocytic cells that belongs to the SIGLEC family of lectins and binds	Its specific expression in AML and CML leukaemic stem

	sialic acid	cells could provide a potential therapeutic target.
CD34	CD34 is a cell surface adhesion molecule typical for haematopoietic stem and precursor cells and endothelial progenitors, as well as leukaemic stem cells.	
CD123	CD123 represents the α -chain of the interleukin-3 receptor and is expressed on both haematopoietic stem cells and various normal haematopoietic cell lineages, as well as on leukaemic stem cells.	Its specifically increased expression in AML leukaemic stem cells could provide a potential therapeutic target.
CD29.	CD29 is the β 1 integrin expressed in basal cells of stratified epithelia, e.g. in skin or urothelium, as well as on the corresponding transformed cells..	Its expression has also been reported in mesenchymal stem cells.
CD49f	CD49f is the α 6 integrin expressed on a variety of cells. As a stem cell marker,	it proved to be valuable for purification of normal mammary as well as breast cancer stem cells, cervical cancer stem cells, stem cells of normal urothelium and prostate, as well as bladder cancer stem cells
CD24	CD24 is a membrane sialoglycoprotein that binds glycosylphosphatidylinositol. Due to a specific posttranslational processing and/or membrane transport and insertion,	its expression is low to absent on breast cancer stem cells, whereas it is expressed on normal mammary epithelial stem cells, as well as on pancreatic cancer stem cells.
CD166	CD166 was reported to characterize both the stem cell fraction of colorectal carcinoma and mesenchymal stem cells.	Its high expression on tumor cells might represent a poor prognosis indicator for colorectal carcinoma patients.
CD90	CD90 (Thy-1) is expressed on a wide spectrum of cell types, like T-cells, neurones, endothelial cells and fibroblasts, and, accordingly, is implicated in various biological processes, like T-cell activation, neurite outgrowth, apoptosis, as well as cancer growth.	As a specific cancer stem cell marker, it was used for purification of hepatocellular carcinoma stem cells, and recently also bladder carcinoma stem cells
ALDH1A1	Aldehyde dehydrogenase H1A1 belongs to an extensive family of aldehyde dehydrogenases involving at least 19 genes.	They are involved in various metabolic processes, notably in retinoid metabolism. It seems to be a rather universal marker of various normal and cancer stem cell populations (breast, ovary, bladder, liver, head and neck

		etc.). By virtue of its detoxification activity (e.g. towards cyclophosphamide), it is involved in cancer stem cell chemoresistance.
ABCB1 and ABCG2	ABCB1 (P-glycoprotein = Multidrug Resistance Protein-1 - MDR-1) and ABCG2 (Breast Cancer Resistance Protein - BCRP) are members of an extensive family of ATP-binding cassette (ABC) efflux pumps specifically expressed on both normal and cancer stem cell populations, as well as on chemoresistant tumor cells.	Being a part of stem cell self-protection, their specific expression was extensively used for purification of stem cells as side population (SP).
ABCB5	ABCB5 represents a new member of the ABC family, mapping to the 7p15.3. Basically acting in the same way as ABCB1	useful to identify and purify melanoma stem cells

Table 2: Stem cell markers- their function and clinical applicability(HATINA, 2012)

VI. EFFECT OF EMT ON CANCER THERAPY

Conventional cancer therapy like chemotherapy and radiotherapy are ineffective on cells undergoing EMT. Targeted therapies like EGFR inhibition also prove to be ineffective in presence of ongoing EMT especially when cells exhibit vimentin and fibronectin(Thomson S, 2005) Most of the cells undergoing EMT express stem cell markers like CD44+/CD24-, which in turn activates genes which are associated with angiogenesis, invasion and metastasis. This has been shown to be the chief mechanism in mammosphere formation in breast cancer (Li X, 2008; Shipitsin M, 2007) Lung cancer cells exhibiting EMT like gene expression profile have been found to be insensitive to EGFR and P13K/Akt pathway inhibitors.(Byers LA, 2013).

Thus the stem cell like properties acquired by the tumor cells during EMT allows their self renewal by the activation of signaling pathways like TGF- β , wnt, notch and Hedgehog which is primarily responsible for the resistance of these tumors to antineoplastic therapies (Singh A, 2010).

VII. EFFECT OF EMT ON PROGNOSIS

EMT is brought about in order to produce motile cells that show change in expression of markers thereby becoming refractory to therapy. Prognosis is related to diseases free survival and this in turn is dependent on metastasis, hence a direct link can be drawn between EMT and prognosis (J, 2012). This has been supported in literature by showing that upregulation of EMT related genes in colon cancer is associated with unfavourable prognosis and decreased E-Cadherin expression is associated with higher TNM stage and increased propensity for distant metastasis (De Sousa E, 2013; Jie D, 2013).

Twist and vimentin have been shown to be independent predictors of prognosis in prostate cancer (Behnsawy HM, 2013). Advanced clinical stage along with decreased E-

Cadherin expression and increased Gleason score are indicative of poor prognosis (Whiteland H, 2013).

VIII. EMT AND ANTI NEOPLASTIC THERAPIES

As shown be many studies the tumor tissue is full of cells that have undergone EMT and hence are resistant to conventional therapies, hence the newer therapies are targeted towards EMT rather than tumor cells per se (K, 2008; Kalluri R, 2003). The antineoplastic therapies aim primarily at reducing distant metastasis and this is achieved by targeting EMT master genes. This can be achieved by inhibition of STAT3 signalling pathways, ALK receptor activation via recombinant BMP-7, acts antagonistically to TGF- β leading to re-expression of lost E-cadherin expression.

IX. CONCLUSION

Thus we can say that EMT is a multifaceted process that can be identified by different markers based on the tissue type and physiological expression of molecules. But EMT does form the basis of most pathological process, as it is transient in most tumors. No single marker can be accepted to be a true indicator of EMT or prognosis, the combination varies from tissue type to tumor type. Valuation of the EMT markers gives the clinician a better idea for carrying out targeted therapies which in turn will decrease metastasis and recurrence thereby improving prognosis.

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