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Epithelial Mesenchymal Transition as Targets for Cancer Therapy

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Abstract

Most of the primary epithelial cancers are developed by increased epithelial cell proliferation and angiogenesis. When these cancer cells broke, they shed their contents in to the blood stream as well as in to the lymphatic vessels and stay at sites called as secondary site via metastasis mediated by epithelial mesenchymal transition giving cell a mesenchymal nature that are more prevalent in cancers of various types. Irreversible mutation and reversible epigenetic changes like methylation in DNA, histone modifications, altered miRNA also cause cancer as they are prone to deletion, amplification, recombination. Epithelial mesenchymal transition develops resistance to treatment drugs. Hence, using EMT as targets for cancer will be of much useful and in the present review few targets that could alter EMT is discussed. So, any natural compound that could act on the process of EMT i.e able to inhibit the transition in to mesenchymal cell in order to maintain architecture and adhesive property of cell.

Keywords: Cancer; Epithelial mesenchymal transition; Metastasis; Targets

Abbreviations: EMT: Epithelial Mesenchymal Transition; HGF: Hepatocyte Growth Factor; EGF: Epidermal GrowthFactor; BMPs: Bone Morphogenetic Proteins; MMP: Matrix Metallo Proteinases; FGF: Fibroblast Growth Factor

Introduction

Epithelial Mesenchymal transition (EMT) makes cancer to metastasize as it alters the properties of epithelial cells to mesenchymal cells which are motile and invasive, including angiogenesis (new blood vessel formation) surrounding metastatic cancers. Cancer cells expresses reduced levels of cell adhesion receptors (E-Cadherin, β-Catenin) while expressing more of cell motility receptors (N-Cadherin, Vimentin, Snail 1, alpa smoot muscle actin) as well as metalloproteinase's to promote metastasis causing secondary tumors. The process of motility depends on the cytokines and chemokines released either by cancer cells or by the cells close to tumor microenvironment.

The drug resistance induced by epithelial mesenchymal transition rely on the tumor stage or grade demonstrates direct correlation among EMT and drug resistance both at molecular, phenotypic level [1,2]. Expression of specific transcription factors like snail 1 and 2, ZEB 1 and 2, Twist1and 2 in a normal, untransformed epithelial cell promotes epithelial - mesenchymal transition [3,4] and signaling pathways such as e TGFb, Wnt, Notch, Hedgehog , Ras-MAPK, PI3K/Akt regulate the expression of transcription factors as well as growth factor receptor signaling cascades like the receptors of epidermal growth factor, insulin-like growth factor 1, fibroblast growth factor and hepatocyte growth factor [5]. Y Box binding protein 1 promotes EMT, invasion, metastasis in cervical cancer through snai1 expression [6]. Ni2 a lipid transfer protein otherwise called as PITPNM1 regulates cell migration, invasion in mammary epithelial, breast cancer cells.

Epithelial Mesenchymal Transition Targets

EMT is a normal process takes pace during the developmental stage of embryo in mesenchyme formation during gastrulation, in neural crest delamination, in placenta, somites, heart valves, urogenital tract, secondary palate, as well as during differentiation of tissues and organs. Epithelial mesenchymal transition is induced by any stimuli from tumor microenvironment like collagen, hyaluronic acid in extracellular matrix and also by soluble growth factors such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), Notch, Wnt, tumor necrosis factor-α (TNF-α), and cytokines [7].

Matrix metallo proteinases are key proteins for the tissue development and homeostasis and in cancer it gets deregulated. The link between Matrix metallo proteinases (MMP) and epithelial mesenchymal transition during tumor occurs through increased MMPs, directly inducing EMT in epithelial

cells, facilitate cell invasion, metastasis and generate activated stromal like cells that continue cancer progression via further MMP production. EMT was induced by MMP3 via RAC1B [8]. Similarly, increased expression of MMP2 and 9 (gelatinases) due to changes in αvβ3, αvβ6 integrin activates ECM protein degradation through increased proteases expression and also it activates transforming growth factorβ (TGFβ) a differentiation factor present in the extra cellular matrix in its latent form thus allowing increased signaling by TGFβ promoting colocalization, invasion [8-11].

And also extra cellular matrix proteins (collagen, fibronectin) stimulate remodeling of extra cellular matrix with varied properties and composition an essential criteria for EMT [12,13]. Integrins are transmembrane proteins, connects extracellular matrix to cytoskeleton and activate cell adhesion and migration followed by tumor cell invasion and metastasis. Integrin permit cells to get signals from ECM proteins through integrin-linked kinase (ILK) called PINCH also as LIMS1 and parvin [14]. Since, the epithelial cells are transitioned to mesenchymal cells they lack the interaction with basement membrane and instead communicate with a different extracellular matrix.

This causes reduced expression of epithelial integrins (α6β4) but activate the expression of new integrins (α5β1) that are involved in EMT progression by stimulating cell adhesion to fibronectin [14-16]. E-Cadherin a cell adhesion molecule synthesized in epithelia during embryo and maintains epithelial homeostasis in adult. E- Cadherin suppresses invasion and metastasis. Loss of E- Cadherin causes cancer. Snail 2 or slug a transcriptional repressor represses E-Cadherin expression which simultaneously induces invasion via E-box elements in their promoter [17-19]. E-Cadherin acts as a substrate for MDM 2 (otherwise called as E3 ubiquitin ligase) and gets degraded via ubiquitination [20]. Thus, MDM 2 play an important role in regulating cell adhesion molecule E-Cadherin.

EMT progression is connected to augmented expression of Snail, Twist, Zeb family transcription factors. Snail comprising 264 amino acids with a molecular weight of 29.1kDa has N terminal regulatory region and C terminal DNA binding domain, having 4 zinc fingers of C2H2 class, a conserved domain able to bind with high affinity if the oligo nucleotide contains 5′-CACCTG-3′ sequence [21]. The consensus sequence is absent in the 4th zinc finger. SNAG box is present in the N-terminus carry out the process of repression [22] the region between 82 and 151 is called subdomain which contains nuclear export sequence (NES).

Snail enter in to the nucleus by the phosphorylation of adjacent serine rich sequence, which allows NES available to the transporter, thus it migrate to nucleus. Once snail is phosphorylated, it represses E-Cadherin expression, while increasing mesenchymal marker expression like vimentin, N-cadherin. Snail degrades basement membrane, extracellular matrix–metalloproteinase 2, mesenchymal markers- vimentin and fibronectin, and other transcription factors such as ZEB-1 and LEF-1 [23-25]. Snail disturb the transition from early to late G1 by continuing low levels of Cyclin D and block G1/S transition by maintaining high levels of p21 [26]. Increased expression of snail causes tumor reoccurrence as well as resistance to therapeutic treatment. During hypoxia, HIF 1α bind to hormone response element present between -750 to -643bp of promoter of snail and increases its transcription. NF –kb bind to snail promoter within -194 to -78bp [27] and increases its transcription, While SMAD 2 bind within -631 to -506bp to increase the transcription of snail. HIF1α increases histone deacetylase HDAC3, for deacetylation of Lys4 in histone 3, leading to reduced epithelial gene expression. On the otherhand, in mesenchymal cells, HDAC3 with the help of histone methyl transfer as WDR5 methylates Lys4 of histone 3, leading to increased expression of mesenchymal genes [28]. This dual epigenetic mechanism of HDAC3 promotes epithelial mesenchymal transition.

In tumor cell, TGF β triggers epithelial mesenchymal transition process and its markers are controlled by TGF β signaling. TGFb stimulate the activation of Smad complexes [29-32], Smad3 and Smad4 promote EMT. While Smad2 inhibits EMT of keratinocytes [33]. TGFβ up regulates ATF3 a transcription factor, to increase Snail, slug, twist, HIFα [34,35] in Ras transformed breast cancer cells [36,37]. Snail upregulates Slug [34,35] and Twist [38], Snail and Twist induce ZEB1 [27,39] and Slug [40] and Snail induces ZEB2. Altogether, these factors suppress E-cadherin expession, while increasing the expression of mesenchymal genes causing EMT. Signaling pathways stimulated by TGFβ independently regulate the transcription factors and also it act along with Notch, Wnt, integrins.

In breast cancer cells, TGFb increases miR-155 targeting Rho A, [41] for the dissolution of tight junctions, loss of polarity, miR-491-5 targeting polarity protein Par3, [42] miR-10b induces Twist and also targets HOXD10 for the invasiveness and metastasis to takes place [43]. TGFb expressing homeobox transcription factor CUTL1, induces ligand Wnt-5A expression, activates canonical Wnt signaling involve the movement of b-catenin to nucleus, acting as a transcriptional cofactor of TCF (T-cell factor) [44] thereby eliciting EMT involving GSK-3b by Axin2 an adaptor protein, thus keeping kinase unphosphorylating the transcription factor Snail and further its degradation causing stabilization of snail and its interaction with TCF to promote epithelial mesenchymal transition in pancreatic cancer [44,45].

Notch controls the snail expression directly at transcriptional level and indirectly via lysyl oxidase by locating HIF α to lysyl oxidase promoter to stabilize snail and EMT, followed by invasion in cancer cells [46,47]. Tyrosine kinase receptor ligands, Interleukin-like EMT-inducer, growth factors such as hepatocyte, epidermal, platelet-derived growth factors are stimulated at the time of EMT, augment the transition process and promote cell migration. Growth factors activating receptor tyrosine kinases function via Ras- MAPK or PI3K- Akt in inducing the expression

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of snail [48,49]. TGFb acts as a suppressor by arresting cell cycle as well as promoter by increasing TGFb expression and activates epithelial-mesenchymal transition making tumor cells more invasive and prone to metastases [50].

The epithelial mesenchymal transition was affected by ubiquitin ligases a promoter of poly-ubiquitination, proteasomal degradation of Smads, such as WWP2 [51]. The transcription intermediary factor 1c ubiquitinate Smad4 [52] /replace Smad4 in a Smad2/3 complex, [53] suppresses TGFb-induced EMT [54]. Smad induces high mobility group A2 (HMGA2), a nuclear protein having three DNA binding peptide motifs (AT-hooks) binding to minor grove of DNA for its interaction with other transcription factors including Smad Thus, EMT driven by Snail requires both transcriptional induction of its gene, e.g. via TGFb signaling, but also additional stabilization of the protein via Wnt signaling, depending on the cell type that undergoes the transition.

Conclusion

Cancer is a disease leading to death compared to other diseases as cancer spreads to other distant organs through metastasis. During travelling to distant site most of the tumor cells reside in the blood, lymph and very few settle at specific organ. Epithelial mesenchymal transition is a characteristic feature of cancer cells. 80% of the common cancers are derived from epithelial tissues due to its transition to mesenchymal cells. Transcription factors such as snail, Twist, ZEB 1 are connected to epithelial mesenchymal transition which further increases the invasion and E-Cadherin degration. So, it is essential to study the transcription factors (that are normally absent in epithelial cells), in cancer and also on novel inhibitors from natural resources to inhibit transcription factors that causes resistance to chemotherapy in tumor cells. Hence, study on epithelial mesenchymal transition markers will form an effective tool in search of therapy against cancer and this review presents some important targets of EMT.

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