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Roles of genetic and microenvironmental factors in cancer epithelial-to-mesenchymal transition and therapeutic implication

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ABSTRACT

Epithelial-to-mesenchymal transition (EMT) is a process in which epithelial cells lose their cell-cell contacts resulting in the formation of mesenchymal cells with migratory properties. Increasing evidence indicate EMT plays a key role in the invasion, metastasis and therapeutic resistance of cancer and maintenance of the phenotype of cancer stem cells (CSCs), which makes the prognosis of patients worse. The progression of cancer from epithelial tissue towards a malignant phenotype is driven by multiple factors that remodel the tissue architecture. This review summarizes and analyzes current studies of genetic and microenvironmental factors in inducing and maintaining cancer EMT and therapeutic implications. This will enable a better understanding of the contribution of EMT-associated factors to cancer progression and highlights that genetic factors and tumor microenvironment responsible for EMT could be used as attractive targets for therapeutic intervention.

1. Introduction

Epithelial-to-mesenchymal transition (EMT) is a process in which epithelial cells lose their cell-cell junctions and acquisition of front-rear polarization resulting in the formation of mesenchymal cells with migratory properties. Activation of this EMT program confers cancer cells the potential to invade adjacent tissues and migrate to distant organs (Fig. 1). These more aggressive cancer cells change their cell morphology, lose epithelial adhesion, the most important of which is E-cadherin, begin to express mesenchymal marker vimentin and transcription factors, including snails, Slug, Twist, Zeb1. In addition, these cancer cells also secrete increased amounts of matrix-degrading proteases, such as matrix metalloprotease family, to degrade the extracellular matrix and enhance the movement ability. The EMT has caused the plastic changes in tissue architecture, and the crosstalk between tumor cells and various cells in the stroma or specific molecules in the extracellular matrix (ECM). Moreover, cancer cells undergoing an EMT have been found to show increased resistance to apoptosis and chemotherapeutic drugs and to acquire traits of cancer stem cells [1–3]. Multiple kinds of genetic factors and tumor microenvironment (TME) have been suggested to play important roles in promoting cancer invasion and metastasis associated with mesenchymal state. Previous studies have shown that certain types of repressive transcriptional factors bind to E boxes in the E-cadherin promoter and inhibit E-cadherin transcription and then induce mesenchymal phenotype, suggesting a key role of EMT-related factors in tumor invasion and metastasis [4,5].

Therefore, understanding what factors are involved in inducing and maintaining EMT and underlying mechanism is crucial, because it can help us to develop valuable biomarkers for the prognosis of cancer patients and even provides new ideas for a more effective therapeutic approach against cancers. The aim of the present review is to summarize and analyze the current body of literature on the role of genetic and microenvironmental factors in EMT and to emphasize these factors could be exploited as the potential targets for therapeutic intervention.

2. Roles of genetic factors in cancer EMT

2.1. Cancer stem cells

Many experimental conclusions have supported that aberrant activation of EMT can promote the invasion and metastasis of cancer cells associated with malignant progression and stem cell-like characteristics. In addition, several lines of evidence have supported that not every tumor cell in a tumor has tumor initiation potential. The viewpoint that cancer progression is driven by cancer stem cells (CSCs) has become popular. The CSC theory points that CSCs possess three defining characteristics: a higher tumorigenicity than non-stem cancer cells *in vivo*, the ability to self-renew and the ability to regenerate the phenotypic heterogeneity of the parental tumor. CSCs have thus been

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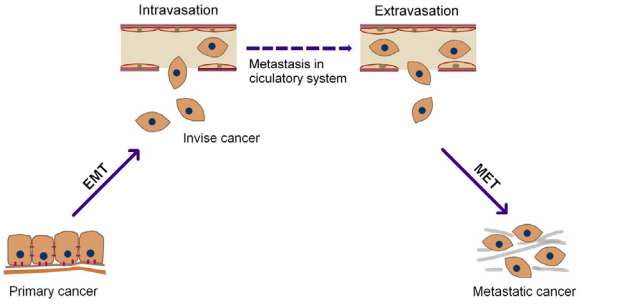

Fig. 1. Functional roles of EMT and MET in cancer. After EMT, cancer cells gradually loss cell-to-cell junctions and degrade extra cellular matrix, finally become mesenchymal-like cells with migratory properties. These cancer cells then invade and migrate to surrounding tissues from primary cancers, intravasate into the circulatory system. Mesenchymal-like cancer cells extravasate the circulatory system in metastatic sites and undergo MET, leading to metastasis of cancers.

implicated both in initiating and sustaining primary cancer growth and in driving metastases of cancer cells to distal sites [6–8].

Recent studies have highlighted the crucial relationship between EMT and properties of CSCs in neoplastic tissues. The induction of an EMT in human mammary epithelial cells has resulted in mesenchymal phenotypes and stem cell properties. Moreover, stem cell-like cells derived from these neoplastic cells formed mammospheres and expressed EMT markers [9]. EMT appears to be a critical mechanism for the induction of cancer cells with stem-like properties, and EMT of non-stem cancer cells could be a source of CSCs [10]. Van der Horst et al. [11] found that mesenchymal liver cancer with malignant phenotype exhibited CSC characteristics, such as tumorsphere formation. Furthermore, transforming growth factor beta (TGFβ) induced mesenchymal cell and CSC characteristics through the upregulation of Snail and Nanog homeobox (Nanog). These results indicate a close relationship between the EMT and stem cell properties in neoplastic cells.

A number of functional molecules seem not only to promote CSC phenotype but also to induce mesenchymal characteristics. Bone morphogenetic protein-2 (BMP-2)-induced spheres displayed up-regulation of stemness markers, an increase of drug resistance, hallmarks of CSCs and expression of mesenchymal phenotype activators p-Smad1/5, Snail and N-cadherin in the colon cancer cells [12]. Ectopic expressions of Oct4 and Nanog in lung adenocarcinoma increased the percentage of stem-like subpopulation, enhanced drug resistance, and promoted cancer EMT. Furthermore, knockdown of Oct4 and Nanog suppressed the expression of Slug, reversed the EMT process, blocked the tumorigenic and metastatic ability [13]. Thus, inducing the mesenchymal properties in human cancer cells enhanced their self-renewal capabilities and promotes acquisition of cancer stem cell-like properties.

2.2. EMT-related signaling pathways

The EMT process can be induced and regulated by various signaling pathways, including Notch, Wnt, Hedgehog, Signal transducer and activator of transcription 3 (STAT3), TGFβ, Wnt/β-catenin, Nuclear factor-kappaB (NF-κB), etc. Activation of these diverse signals upregulate the expressions of a variety of EMT transcription factors which show the capacity to induce EMT in many types of human cancers (Fig. 2). Roles of EMT-related signaling pathways in cancer EMT are listed in Table 1.

2.2.1. Notch1

Emerging evidence suggests that activation of the Notch1 signaling induces mesenchymal phenotype in a variety of cancers. Overexpressing Notch1 in MCF7 and MCF10A cells showed mesenchymal phenotype and displayed CSC-like properties. Moreover, the

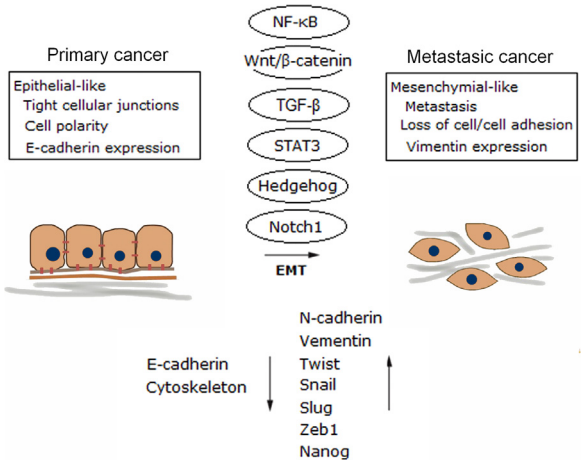

Fig. 2. Signaling pathways inducing and regulating EMT in cancer cells and EMT-related transcription factors. Multiple signaling pathways were involved in cancer EMT including NF-κB, Wnt/β-catenin, TGF-β, STAT3, Hedgehog, Notch1, etc. In the process of EMT, primary cancer lost epithelial markers such as E-cadherin and cytoskeleton, gain mesenchymal markers such as N-cadherin, vimentin and twist and increase invasion and metastasis.

expression levels of the E-cadherin and occludin were decreased, while the expression levels of the N-cadherin and vimentin were increased in breast cancer cells overexpressing Notch1 [14]. E-cadherin and cytokeratins were downregulated by the activation of Notch1, meanwhile, Slug and Snail were upregulated in epithelial ovarian cancer cells. Furthermore, inhibition of Notch by DAPT (a γ-secretase inhibitor) decreases Slug and repression of E-cadherin [15], indicating that Notch is required, at least in part, for TGFβ-induced EMT. Wang et al. [16] also indicated that Notch-1 expression was upregulated in chemoresistant prostate cancer PC3-TxR and DU145-TxR cells, whereas the E-cadherin expression was downregulated in these cells comparing with their parental cells. These data indicate that activation of Notch signaling promotes the EMT and tumor growth by regulating expression of EMT markers and transcription factors.

2.2.2. Hedgehog

Hedgehog (Hh) signaling plays key roles in control of embryonic development, stem cell maintenance and injury repair. Since EMT is an important biological factor responsible for cancer cell invasion, metastasis, drug resistance and tumor recurrence, aberrant activation of Hh signaling is considered the driving factors of tumorigenesis and malignant progression associated with EMT in multiple kinds of human tumors. Previous data showed that the invasion and malignant progression of breast cancer was driven by Hh signaling [17]. Data from Lei et al. [18] showed the role and function of non-canonical Hh signaling in hypoxia-induced EMT and invasion in pancreatic cancer cells. This result indicated that hypoxia induced mesenchymal phenotype as well as invasion, was largely driven by activation of Hh signaling pathway in pancreatic cancer cells. Both Hh pathway and EMT were active in pancreatic cancer cell line Panc-1 tumorspheres. In addition, inhibition of Hh signaling by SMO knockdown inhibited the chemoresistance, EMT, self-renewal, invasion and metastasis of pancreatic CSCs, suggesting that blocking Hh signaling may be beneficial in the treatment of pancreatic cancer [19].

2.2.3. STAT3

STAT3 is a key regulator of cell survival, development and tumorigenesis of human cells. STAT3 proteins are latent transcription factors located in cytoplasm in an inactive state [20]. Driven by the upstream signal, STAT3 phosphorylation, activated STAT proteins translocate to the nucleus where they initiate transcription of its target genes [21]. Through the extensive interactions with crosstalk with other signaling