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Review Article

Epithelial–mesenchymal transition-related factors in solid tumor and hematological malignancy

Yi-Sheng Chou [a,b,c], Muh-Hwa Yang [a,b,*]

[a] Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC
[b] Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
[c] Division of Hematology and Oncology, Department of Medicine, Lo-Hsu Foundation, Lotung Poh-Ai Hospital, Luodong, Yilan, Taiwan, ROC

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Abstract

The epithelial–mesenchymal transition (EMT) process plays pivotal roles in regulatory mechanisms of embryogenesis and wound healing physiologically, and organ fibrosis, cancer progression, and metastasis pathologically. EMT is classified as primary, secondary, and tertiary during embryonic development. EMT contributes to repair of tissue injury and fibrogenesis by re-epithelialization and regeneration of fibroblasts, respectively. The hallmarks of EMT include loss of contact inhibition, remodeling of extracellular matrix, and reorganization of cytoskeleton, along with expression of mesenchymal markers and reduction of epithelial markers. Cancer cells acquire stemness, migration and invasive capability, evade apoptosis, and initiate metastasis to distant organs. Several EMT regulators including Snail, Zeb1, Zeb2, and Twist in solid tumor and Sox4, distal-less homeobox gene 4 (*DLX4*), Prdm14, Bmi1, and the forkhead box family in hematological malignancy are reviewed with regard to their signaling pathways, regulatory mechanisms, and clinical interactions.

Keywords: epithelial–mesenchymal transition; hematological malignancy; solid tumor; transcription factor

1. Introduction

The epithelial–mesenchymal transition (EMT) is the process of conversion of cells from a differentiated epithelial state into a dedifferentiated migratory mesenchymal phenotype, which is crucial for regulatory mechanisms in embryogenesis, cancer metastasis, organ fibrosis, and wound healing.[1]

2. Physiologic EMT

During embryogenesis, EMT is classified as primary, secondary, and tertiary.[2] In the process of primary EMT, the first EMT incident in the embryo occurs during gastrulation when cells from the epiblast move to a primitive streak in the midline and undergo EMT to form the mesoderm and the ectoderm.[3] Another primary EMT process occurs during the generation of neural crest cells, when epithelial cells become neural crest cells and migrate to form neural tubes, which develops into the central nervous system in mammals.[4]

During embryogenesis, transient epithelial structures including the notochord, somites, somatopleures, and splanchnopleures also undergo secondary EMT to generate mesenchymal cells, which subsequently differentiate into specific cell types, such as those of connective tissue, hematopoietic stem cells, endocardium, muscle, and neural arches. The mesenchyme of liver and islets of Langerhans also develop through secondary EMT from the liver diverticulum and pancreatic bud, respectively.[5,6] The physiologic event involving tertiary EMT is the formation of mesenchymal cardiac jelly from endothelial cells located in the

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* Corresponding author. Dr. Muh-Hwa Yang, Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: mhyang2@vghtpe.gov.tw (M.-H. Yang).

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atrioventricular canal and the outflow tract in the heart, which becomes the endocardial cushion.[7]

In addition to embryogenesis, EMT also participates in the physiologic repair of tissue injury, that is, the re-epithelialization of wounds. Keratinocytes assembling around the border of a wound will undergo phenotypic conversion to an intermediate "metastable" phenotype and then acquire mesenchymal characteristics including loss of cell–cell adherence and polarity, and gain in migratory activity.[8] The ovarian epithelial cells also utilize EMT to assume a fibroblast-like phenotype in the postovulatory phase and reside in the ovary mesenchyme, which promotes tissue repair in response to ovulation.[9]

3. Pathologic EMT

During renal fibrogenesis, interstitial fibroblast can originate from progenitors of tissue fibroblasts (bone marrow derived) migrating in the circulation to repopulate in peripheral organs; however, they also can originate *de novo* from the epithelium through the EMT process to generate a much larger number of fibroblasts.[10] It is not a unique process for renal fibrogenesis, and hepatocytes, lens epithelium, endothelium, and cardiomyocytes can contribute to tissue fibrosis in a similar manner. In a murine animal model, hepatocytes derived from cirrhotic liver demonstrated features of EMT including mitogen-activated protein kinase-dependent increased expression of vimentin and type I collagen, suggesting the involvement of EMT in the mechanism of hepatocellular carcinoma genesis.[11] Cardiac fibrosis was associated with the recruitment of fibroblasts from endothelial cells undergoing EMT.[12] For patients receiving peritoneal dialysis, mesothelial cells go through EMT to transform into cells with epithelioid morphology, resulting in peritoneal fibrosis, and eventually, dysfunction of the peritoneal membrane.[13]

4. EMT in solid tumors

Accumulated evidence suggests that EMT plays pivotal roles in cancer progression and metastasis, but the effects of EMT on human tumors remain inconclusive.[14,15] Cancer cells acquire their stem cell-like property, that is, the capability of metastatic colonization and resistance to treatment, through the process of EMT to promote deposition of extracellular matrix.[2]

In the invasive front of tumor of colon carcinoma, migratory tumor cells at the edge will display morphological features of EMT, including loss of E-cadherin and basement membrane.[16] Similar phenomena were also observed in papillary thyroid carcinoma, in which EMT was associated with tumor invasion and nodal metastasis.[17]

Several hallmark processes are crucial in EMT, including loss of E-cadherin and polarity but increase of N-cadherin and vimentin. Upon initiation of EMT, loss of E-cadherin promotes invasion during carcinoma progression and E-cadherin is repressed by EMT-related factors either directly or indirectly. Snail, Zeb, E47, and KLF8 directly bind to the promoter of *CDH1*, which encodes E-cadherin and down-regulates the expression of E-cadherin,[18,19] whereas Twist, goosecoid, E2-2A, E2-2B, and FoxC2 indirectly transcriptionally inhibit E-cadherin.[20,21]

5. Direct regulators of EMT

5.1. Snail

Snail is of enormous significance in physiologic EMT, such as in gastrulation and formation of neural crest. Snail1 is one of the repressive transcription factors directly binding to the promoter of *CDH1*. In breast carcinoma, the expression of Snail1 was associated with repression of E-cadherin and lymph node metastasis.[22]

Snail1 interacts with Suz12 and Ezh2 and recruits polycomb complex 2 to repress CDH1.[23] Snail1 binds to the E2-box [C/A(CAGGTG)] on the promoter with its C-terminal domain or interacts with histone deacetylases with its SNAG sequence in the N-terminal domain.[24,25] The translation of Snail1 messenger RNA (mRNA) can be activated by Y box binding protein 1 in breast carcinoma,[26] and its nuclear localization is promoted by LIV1, which is a downstream signaling target of signal transducer and activator of transcription 3.[27] Many post-translational modifications have been found, such as the p21-activated kinase 1 regulating the level of subcellular localization by phosphorylation of Snail[28] and glycogen synthesis kinase 3β (GSK3β)-mediated phosphorylation facilitating the ubiquitin-dependent degradation of Snail.[29] By contrast, *Lox2* counteracts GSK3β and stabilizes Snail.[30] The cooperative corepressors may be required for Snail to function; for example, these corepressors are required for the SMAD protein to bind to Snail to form a repressive complex inhibiting transforming growth factor-β (TGF-β)-induced EMT.[31]

5.2. Zeb1

The expression of Zeb1 can be induced by Snail1,[32] but its function is independent of Snail because it is associated with repression of *CDH1* in the absence of Snail in colon carcinoma, which implies that the inducers of EMT are dependent on the cellular context.[33]

5.3. Twist

Twist belongs to the category of basic helix–loop–helix factor transcription factors. Besides being a master regulator of embryogenesis, Twist also induces EMT and metastasis and is associated with poor survival in invasive breast ductal carcinoma, endometrial cancer, hepatocellular cancer, and melanomas.[34–37] Downstream targets of Twist include platelet-derived growth factor receptor-α, Akt2, Snail1, and Snail2. Twist is upregulated by nuclear factor-kB (NF-kB), hypoxia-inducible factor 1-α, and SRC-1/PEA3.[38–42] Twist represses E-cadherin and upregulates N-cadherin and vimentin, which are the hallmarks of EMT.