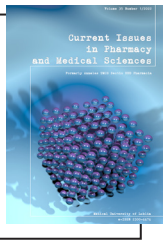
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Epithelial-mesenchymal transition

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ABSTRACT

The process of epithelial-mesenchymal transition (EMT) occurs in both physiological and pathological states, and there are increasing links between EMT and tumor progression. During this process, dynamic changes in cell organization and function occur that promote migration and invasion. A better understanding of the mechanism of plastic EMT may help develop novel targeted therapies that can help treat cancers of varying degrees of malignancy. Our review helps to systematize knowledge of the molecular and biochemical mechanisms involved in the EMT process in both tumor and physiological backgrounds.

INTRODUCTION

Epithelial-mesenchymal transition (EMT) is a biological process in which polarized epithelial cells acquire phenotype typical for mesenchymal cells. The plasticity of these changes is regulated by epigenetic changes through modification of histones that are involved in the regulation of transcription factors. There are three types of EMT: type I associated with embryo implantation and gastrulation and organ development, type II associated with wound healing and tissue regeneration, and type III found in tumor cells and probably associated with metastasis. The process of EMT is complex and involves activation of transcription factors, expression of specific surface and cytoskeleton proteins, as well as extracellular matrix degrading enzymes. The resulting mesenchymal cells are involved in tissue repair and certain pathological processes such as tissue fibrosis, increasing tumor invasiveness and metastasis, but these processes are not yet well understood. Each developing cell has a characteristic phenotype [1-3].

Types of EMT

The EMT process can be observed under different biological conditions, depending on its purpose. There are three types of EMT:

1. Type I and II EMT

Type I EMT is associated with implantation and gastrulation of embryos, mesoderm and endoderm formation, as well as organ development. Embryogenesis is a complex process by which both EMT and mesenchymal–epithelial transition (MET) are needed to ultimately produce specialized cell types and organ organization. Type I EMT does not cause fibrosis and does not show an invasive phenotype leading to systemic spread of cells in the circulation [1,2].

Type II is associated with wound healing, tissue regeneration and organ fibrosis. It usually begins with repair processes, when fibroblasts and related cells are produced to rebuild tissues after injury. It has been observed during fibrosis in kidney, liver, lung, and intestine. In cases of organ fibrosis and persistent inflammation, EMT may act as a response to inflammation, leading to possible organ damage [4-6].

2. Type III EMT and their role in cancer metastasis

Cancer metastasis is believed to account for about 90% of all cancer deaths. The first step in metastasis formation is the separation of cells from the primary tumor. Cells detaching from the primary tumor are known as 'circulating tumor cells' (CSCs), and their presence is considered one of the key conditions for metastatic colony formation [1,4,5]. Considering the plasticity of tumor cells, they can adopt a hybrid phenotype (some are completely mesenchymal, while others maintain some epithelial characteristics), which can provide tumor cells with increased adaptability and better survival in different environments. The enhanced motility of mesenchymal cells resulting from the EMT process is probably one of the reasons for the increased ability of tumors to metastasize. Type III EMT has been noted to be involved in metastasis. It occurs in tumor cells in which genetic and epigenetic changes have occurred, and this is particularly true for genes that promote clonal growth of tumor cells. The cells resulting from type III EMT have the ability to migrate, and when they reach their target site, they are similar at the histopathological level to the original tumor from which they formed [1,7,8]. EMT types and their functions are shown in Figure 1.

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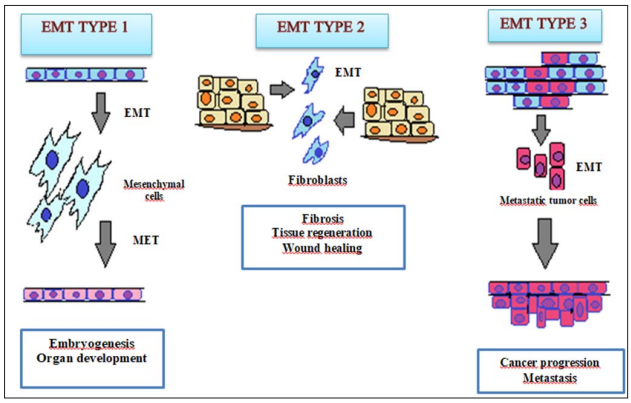


Figure 1. Types of EMT

CTCs cells

During the epithelial-mesenchymal transition in cancer, circulating tumor cells are formed. Both EMT-inducing transcription factors such as SNAI1, SNAI2, ZEB1 and Twist and extracellular molecules found in the tumor microenvironment such as TGF-β and VEGF-A, HGF, FGF, Wnt and Notch are responsible for regulating the EMT process. This highly specialized regulatory network also becomes involved in the generation of CTCs [9].

For the past decade, research on CTCs has expanded due to the significant role of these cells in metastasis. There are several stages in the formation of CTCs. The first step is the detachment of cells from the tumor mass, followed by the movement of cells into blood and/or lymphatic vessels and infiltration of the basement membrane and nearby tissues. They then form new colonies of tumor cells. These cells display increased invasiveness and promote the survival of metastatic cells [10].

Isolation of human CTCs remains a technical challenge. To date, two methods have been developed: biochemical and biophysical. Biochemical isolation allows the detection and identification of biomarkers, while biophysical isolation makes it possible to differentiate between the physical properties of CTCs and blood cells. However, currently, we are observing rapid development of methods based on microfluidics, which is a promising new innovative method for extracting these cells. In the last decade, it has been shown that detection and counting of CTC cells is needed to evaluate prognosis, chemo-resistance and therapeutic efficacy. Moreover, molecular evaluation of CTCs is important to identify the direction of transformation of tumor cells. The molecular characteristics of CTCs are different depending on the subpopulation. Determining the expression of EMT markers in CTCs is clinically important [9-11].

Identification of CTC markers is an alternative to tumor biopsies and allows monitoring of therapy progress and treatment effectiveness. Therefore, it is worth studying genotypic and phenotypic characteristics to know the phenotype of the cell. An example is advanced breast cancer where an increased number of mitotic CTCs was found which correlated with shorter survival. Additionally, studies indicate that the presence of CTCs is important for invasion and metastasis in prostate cancer, gastric cancer, colorectal cancer and non-small cell lung cancer [9].

EMT Markers

During the EMT process, there is a decreased expression of epithelial markers and increased expression of mesenchymal markers as a result of regulation by transcription factors. The markers can be divided into 3 types: epithelial markers, mesenchymal markers and EMT regulators. The characteristic and function of each marker is shown in Table 1.

Table 1. Classification of EMT markers

Marker	Phenotype	EMT type	Characteristic and function
E-cadherin	Epithelial	1,2,3	• transmembrane glycoprotein • forms Ca^{2+} – dependent adhesive bonds • increased expression of E-cadherin – increased invasiveness of cancer cells [1,5,6,12]
Syndecan 1 (SDC-1)	Epithelial	1,3	• cell membrane proteoglycan • involved in the regulation of cell mobility, proliferation and differentiation • silencing the expression of SDC-1 in epithelial cells – induction of the mesenchymal phenotype [6,13]
Laminin	Epithelial	1,2,3	• glycoprotein of the extracellular matrix degraded during EMT • contributes to cell growth and migration; metastasis formation • laminin I is lost in EMTs types I and II, increased levels of laminin V are observed in EMTS types II and III – activation of a specific cellular signal transduction pathway depends on laminin isoforms [6]
Collagen IV	Epithelial	1,2,3	• a major extracellular matrix protein • maintains stable morphology of epithelial cells by interacting with catenin • together with integrins, promotes cell adhesion and mobility • influences gene expression, translocation, adhesion, apoptosis and cell proliferation [5,6,13]
Fibronectin (FN1)	Mesenchymal	1,2	• glycoprotein • important role in cell migration, differentiation, proliferation and growth • increased expression of FN1 in cancer cells – a bad prognostic factor • decreased expression of FN1 – blocking of the cell cycle, reduced mobility of metastatic tumor cells [6,14]
N-cadherin	Mesenchymal	1,2	• associated with increased invasive potential and poor prognosis • N-cadherin downregulation – reduces invasion, migration, epithelial transition to mesenchymal form • N-cadherin overexpression- increases efficiency of tumor cell colony formation; expression of stemness factor [6,15]
Vimentin	Mesenchymal	1,2	• a major component of the intermediate filament (IF) family of proteins • responsible for cellular integrity and stress resistance • vimentin filaments during EMT process – protects tumor cells from mechanical stresses – enables cell migration through narrow cell spaces • increased vimentin expression-positive correlation with tumor growth, invasion and poor prognosis [6]
Slug and Snail	Other major players	1,2,3	• consist of the Snail1 (Snail), Snail2 (Slug) and Snail3 (Smuc) transcription factors • increased expression of Snail – increased cell mobility and invasiveness; decreased epithelial markers and increased mesenchymal markers [6]
TWIST	Other major players	1,2,3	• one of the basic transcription factors having a helix-loop-helix domain in its structure • used as a diagnostic or prognostic factor • low expression of Twist 1 – tumor initiation • high Twist 1 expression – prerequisite for EMT induction; associated with high-grade or highly aggressive tumors [6]
ZEB1 and ZEB2	Other major players	1,2,3	• homeobox ZEB – a family of transcription factors consisting of ZEB1 and ZEB2 • induce EMT by inhibiting E-cadherin expression • ZEB1 is involved in the development of oncogenesis • influences therapy and patient response to treatment [6]

CONCLUSION

To date, it has been determined that EMT occurs in three different biological environments, and the mechanisms of EMT induction and progression are different. In recent years, studies have shown that EMT occurs during cancer progression and is a key mechanism involved in metastasis. In conclusion, a deeper understanding of molecular mechanisms may improve the efficacy of therapeutic trials, controlling cancer progression, treatment resistance and disease relapse. Considering the rapidly changing phenotype of cancer cells and changes in gene expression and signaling pathways, further detailed studies of the EMT process are needed.

INFORMED CONSENT

The authors declare that informed consent was not required.

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