Epithelial Mesenchymal Transformation

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Abstract: The epithelial-mesenchymal transition (EMT) defined as a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to transform into mesenchymal cells. Some signaling events activated transcription factors (Wnt, TGF-β, and FGF family members) that mediate EMT. EMTBeginning of metastasis needs invasion, which is allowed by EMT. Carcinoma cells in primary tumor lose intercellular adhesion mediated by E-cadherin repression and break through the basement membrane with increased invasive properties, and enter the bloodstream through intravasation. After then, when these circulating tumor cells (CTCs) exit the bloodstream to form micrometastases, they undergo its reverse process for clonal outgrowth at these metastatic sites.

Keyword: Epithelial-mesenchymal transition, carsinogenesis, metastases

INTRODUCTION

The term "epithelial mesenchymal transformation" (EMT) was defined for the first time by Elisabeth Hay in the year 1995. The term "transition" has been used in lieu of the word "transformation" since the event is not a neoplastic but a reversible process [1-3]. EMT is the gain of mesenchymnal characteristic by a cell of epithelial origin. EMT has an important role in embryogenesis, embryo transplantation, organ development, tumor invasion, and metastasis [4-10]. It has not been only defined in the liver but also in the kidney, fetal tissues, and serious membranes [11, 12]. The some changes in malign cells and their microenvironment that cause to disintegration of intracellular linking. EMT plays a major role in many levels of development, including gastrulation, in this process the ends with many different tissues. Although an epithelial cell gains a mesenchymal characteristic in time but also the contrary is also possible, that is to say a mesenchymal cell may also be transformed into an epithelial cell. However, this "mesenchymal epithelial transformation" was first defined in the kidney [13-15].

EMT was shown both *in vivo* and *in vitro*. This transformation happens as a result of the loss of intercellular links (E-cadherin), re-arrangement of cytoskeleton, and the gain of migration capability and extracellular matrix protein secretion capability by an epithelial cell. It is thought that it has an important role especially in the acquisition of a migration capability, tumor invasion and metastasis of neoplastic cells. Transformation of epithelial cells into mesenchymal cells occurs with the changes including the phases such as activation of transcription factors, expression of specific cell surface proteins, expression and reorganization of cytoskeleton proteins, synthesis of extracellular matrix proteins, and expression of specific micro-RNA. Three sub-types of EMT has been defined. Type 1 plays a role in EMT embryo transplantation and embryogenesis, type 2 in organ fibrosis, and type 3 in tumor invasion and metastasis. It is thought that type 2 is especially effective in the fibrosis of solid organs such as liver, kidney, and lungs [16-19].

In the cells undergone EMT, the cytokeratin and E-cadherin that are specific molecules for epithelial cells are substituted by extracellular matrix proteins synthesized by mesenchymal cell gained the mobility capability in time. Meanwhile, intermediary cells having both functions are called as "cells undergone partial EMT". It is thought that two cell types have undergone epithelial mesenchymal transformation in adult human liver: hepathocytes and cholangiocytes [20-23].

In damaged liver, TGF β1 secreted from monocytes and macrophages together with the damage has a critical importance in the activation of fibrogenic myofibroblasts. Hepatic myofibroblasts are profibrogenic, proinflammatory, proangiogenic, and contractile cells with high proliferative capability, produce type I collagen, and contribute in fibrous scar such as other extracellular matrix proteins. Although it

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is anticipated that these cells originate from the transdifferentiation and the activation of the HSHs or the fibroblasts in the portal area underlie as explained before, it is also thought that mesenchymal stem cells of bone marrow origin has a contribution.

Another way is that the hepatocytes or cholangiocytes undergo an epithelial mesenchymal transformation. In mesenchymal transformation process, E-cadherin distribution and functions in hepatocyte cytoplasmic membrane are damaged depending on impaired TGF-ß regulation. Intercellular links of the epithelial cells are affected and adhere to mesenchymal cells through integrins rather than other hepatocytes being its hepatocyte neighbor. It is suggested with these steps that a cell previously behaving like an epithelium functions as a mesenchymal cell and thus participates in the fibrosis process [24, 25].

It is expected that the key points still unknown about EMT should be solved with the studies to be carried out and especially with rat models and molecular studies. What are the triggering mechanisms in EMT, details of signal pathways, and reasons sensitizing the cells to this kind of signals? As a result, the proofs belonging to all of this process and the amount of the contribution of EMT to the fibrosis and resulting cirrhosis development are the subjects that must be still investigated.

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