



## Epithelial and Mesenchymal Transition Pathway (EMT) and Hepatocellular Carcinoma: A Mini Review

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### Introduction

Liver is the second largest and highly metabolic organ which involves in the detoxification, host defense mechanism and also in the transportation of various biomolecules from liver to other organs. Another distinctive feature of the liver is its regenerative capacity. The huge burden of metabolism, detoxification mechanism and pathological conditions like chronic liver diseases like cirrhosis and fibrosis, the structural and functional features of liver would be challenged and affected that may result in the progression liver cancer and very much known as "Hepatocellular Carcinoma (HCC)".

HCC is the third most common cancer with approximately 500,000 new patients diagnosed every year mainly due to lack of prognosis. The prevalence of HCC is more common in males than in females in the Asian and African countries. Long term consumption of alcohol, Hepatitis B or C infection, and obesity are well reported causative factors for the development of HCC [1-4]. HCC develops as sequential steps initiating from dysplastic lesions to advanced molecular heterogeneity. Therefore, the heterogeneity of HCC derives from various causes like chronic liver malfunction, genetic and epigenetic variations, expression patterns and phenotypic differentiation of hepatic cells in the tumor microenvironment [5]. The major heterogeneity of HCC is increased by changes in the transformation of epithelial cells, commonly described as Epithelial to Mesenchymal Transition (EMT). The EMT pathways have been identified earlier during embryonic development and tissue regeneration mechanisms. Recently, the activation of EMT pathway during HCC has been reported from both clinical and experimental observations [6,7].

### Mechanisms of epithelial-to-mesenchymal transition pathway

The cancer progression undergoes homeostatic imbalance through disrupting the cellular junctions, which leads to loss of cell to cell contact. This mechanism will lead to transformation of tumor cells from epithelial to mesenchymal phenotype and transported from their site of origin to distant site to form secondary tumour progression and called as metastasis. The process of metastasis is a multistep process which involves local invasion, intravasation, transport, extravasation, and colonization. Another important event during metastasis is the gain of mesenchymal phenotype by the hepatocytes and epithelial cells are profoundly called as "Epithelial to Mesenchymal transition". Therefore, these two processes, metastasis and EMT, are highly interrelated through the transformation of benign epithelial cells to malignant mesenchymal cells which are capable to affect the distant organs to progress to secondary tumor environment. EMT pathway was first elaborated by Hay in 1995 using chick as an experimental model [8]. EMT pathway can be broadly classified into three types as follows: Type 1 takes place during developmental stage, Type 2 EMT pathway occurs during the period of wound healing, inflammation, fibrosis and tissue regeneration and Type 3 EMT pathway has been involved in promoting metastasis in epithelium derived carcinoma [9,10]. Recent experimental and clinical studies have highlighted the dynamic role of EMT during metastasis in the progress HCC [11-13].

Epithelial-to-Mesenchymal Transition (EMT) is a loss of epithelial nature and acquires morphological and functional phenotypes of mesenchymal cells as a spindle-shaped appearance and migrating from the place of origin to distant location. Therefore, remodeling of epithelial cell surface and cytoskeletal organization would result in the loss of the apical-basal polarity to transform into mesenchymal cells. Epithelial cells have cell-cell contacts to maintain normal homeostasis due to its polarity and cell shape. The epithelial phenotype was maintained by the presence of adherent junctional proteins like E-cadherin,  $\alpha$  and  $\beta$ -catenins and cytokeratins, tight junctions mediated by claudins and occludins and desmosomes. The loss of cell-cell contact remains as the initiating factor of EMT process which further leads to the loss of the cellular phenotype to my fibroblast with the expression of mesenchymal markers like N-cadherin, Vimentin,  $\alpha$ -Smooth Muscle Actin,  $\alpha$ V $\beta$ 1

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integrins and MMPs [14-16].

The downregulated expression of E-cadherin is accounted as a critical event during tumor progression. Therefore, the specific loss of E-cadherin leads to the relocalization and degradation of certain junctional proteins like  $\beta$ -catenin, zonula occludens-1, occludin, and claudin, which are considered as an initiating factor to induce EMT and metastasis [17,18]. However, the loss of E-cadherin is usually compensated by the expression of N-cadherin, which enables epithelial cells to establish dynamic interactions with neighboring mesenchymal cells. EMT pathway also exhibits the rearrangement of the cytoskeletal architecture with the down-regulation of cytokeratins and up-regulation of vimentin, S100A4 and  $\alpha$ -smooth muscle actin [19,20]. As a consequence, the cross talk between various molecular pathways like wnt/ $\beta$ -catenin [21], MAPK [22], Notch pathway [23], NF- $\kappa$ B [24], PI3K/Akt pathway and Hippo signaling pathway [25,26] and EMT govern the process of HCC progression. The activation of these molecular pathways also results in the activation of transcription factors such as the basic helix-loop-helix protein-Twist, zinc finger transcription factor- Snail, Slug and Zeb-1/2 [27].

These transcriptional factors down regulate the expressions of junctional proteins like E-cadherin, claudins, occludins and ZO-1 proteins [28]. Recently, Brachyury (a transcription factor) initiates the EMT pathway of HCC by altering the expression of E-cadherin, Slug and also Akt/mTOR to promote tumour metastasis [29]. Yoshida and Saga have reported that activation of EMT in cancer stem-like cells is highly responsible for tumour heterogeneity and resistance to various treatment strategies [30,31,6]. Tanaka and his group have investigated the role of proteoglycans like serglycin, syndecan-1, glypican 3, agrin, collagen XVIII/endostatin, versican, and decorin in the origin and development of HCC [32]. Reports have shown that Transglutaminase 2 influences the progression of EMT during both cancerous and fibrotic conditions [33]. Another, research article showed that the promotion of EMT was activated in the hepatic stellate cells through TGM2/VHL/HIF-1 $\alpha$  pathway [34]. Therefore, the above discussed biomarkers of EMT with regard to the progression of HCC revealed the promising therapeutic targets to develop cellular and molecular machinery based therapies to treat HCC.

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