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Editorial
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Targeting Epithelial to Mesenchymal Transition: a Critical Prerequisite to Manage Cancer Stem Cell Fate and Metastasis

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Editorial

Cancer is a complex multi-factorial disease of cells consisting of transformation, uncontrolled proliferation of the cells having invasive and infinite survival capacities. Tumor microenvironment plays a critical role in cancer cells' destiny[1]. The tumor and the surrounding microenvironment are closely related and interact constantly[2] .Tumors can influence/manipulate the microenvironment by releasing extracellular signals, promoting tumor angiogenesis and inducing peripheral immune tolerance[3] . Hence, the concept of tumor microenvironment is an integrated and essential part of cancer biology.

Clonal evolution or stochastic model suggests that serial procurement of mutations causes tumor cell heterogeneity and contributes to cancer development. Tumor heterogeneity is classified as intertumoral or intratumoral and reflects genetic and phenotypic diversity[4] .Treatment of cancers consist of multiple cell clones results in elimination of the sensitive clones, whereas the resistant clones remain and undergo expansion. Additionally, functional heterogeneity exists at the cellular level. This intercellular heterogeneity is generated by a hierarchy of cellular differentiation originating from cancer stem cells (CSCs) and lineage conversion known as trans-differentiation. Tumor heterogeneity is also associated with plasticity that results from epigenetic regulation and is affected by the tumor microenvironment and therapeutic stress[5] .

Transformed and differentiated cancer cells can undertakes the process of epithelial-mesenchymal transition (EMT) to exhibit CSCs properties. EMT, a complex reprogramming process of epithelial cells, plays crucial role in tumor invasion and metastasis[6]. The well-characterized features of EMT include loss of epithelial markers (E-cadherin and α-catenin), gain of pluripotent mesenchymal cell markers (fibronectin, vimentin, and N-cadherin), and the attainment of migratory and invasive properties, elevated resistance to apoptosis and augmented production of extracellular matrix constituents[7]. Various signalling pathways can induce EMT. Alterations in genes associated with developmental pathways such as Wnt, Hedgehog and Notch are common in various cancers and have been shown to help promoting EMT[8]. Studies show that EMT is controlled by a group of transcriptional repressors, such as Zeb-1/2, Twist, Snail, and Slug. Upon activation, these repressors recruit histone deacetylases to the E-box elements of the E-cadherin promoter, resulting in transcriptional silence of E-cadherin expression[9]. Emerging evidence suggests that there is a strong relationship between CSCs and EMT[9,10]. CSCs are the cells found within the tumors that possess characteristics associated with extensive proliferation, multilineage long life differentiation, high propensity for invasiveness and metastasis, self-renewing property and are found to be highly resistance to conventional cancer therapies.

By undergoing EMT, cancer cells lose cadherin-mediated cell-cell adhesion and gain motility which facilitates invasion into the extracellular matrix leading ultimately to metastasis. CSCs may generate tumors through the processes of self-renewal and differentiate into multiple cell types. These cells are proposed to persevere in tumor foci as a discrete population and cause relapse and metastasis by giving rise to new tumors.

Therefore, development of specific therapies targeting CSCs holds promise for the improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease[11]. Common signaling pathways shared between normal stem cells and CSCs undergo aberrant activation or dysregulation to give rise to CSCs. Certain cytotoxic drugs, short hairpin RNA molecules, antibodies, which primarily affect Wnt[12], notch[13], hedgehog[14] and other signaling pathways responsible for maintenance of CSCs' stemness, can be used to target CSCs[15]. However, ABC drug transporter proteins, commonly expressed in CSCs, are efflux pumps that protect the cells from chemotherapy conferring multiple drug resistance to the CSCs.

Hence, targeting molecular activators of EMT, such

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the (PI3K)/AKT, Wnt/β-catenin, Notch, TGF-β, and NF-κB pathways, and downstream transcriptional regulators of EMT, including Twist, Zeb1/2, and Snail family members, could prevent cancer cells from undergoing EMT and gaining an invasive phenotype.

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