Remodeling of extracellular matrix during cancer metastasis (Review)

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Introduction: Metastasis of cancer cells accounts for about 90% of patient mortality, as spread of neoplastic cells to organs such as liver and lung makes their eradication challenging. Cancer cells grow in a dynamic tumor microenvironment consists of various types of stromal cells, lymphatic network and extracellular matrix (ECM). Beside serving as a scaffold, ECM undergoes vast remodeling during different stages of tumorigenesis that influences migration, adhesion, survival, proliferation and differentiation of cancer cells. In present review, we focused on biochemical modifications of ECM associated with migration and invasion of cancer cells.

Methods: Recent review articles included key words extracellular matrix, metastasis, ECM remodeling, cellular deposition and protein composition were extracted from databases Google Scholar, Web of Science, PubMed and Scopus.

Results: Remodeling of ECM, which affects abundance, structure and organization of its components, can be divided into ECM deposition, chemical modifications and proteolytic degradation. Stromal cells are major depositors of ECM components that secret various growth and inflammatory factors such as TGF-α, TGF-β, FGF-2, PDGF and EGF, as well as matrix metalloproteinases (MMPs) and chemokines. Chemical modifications of ECM components, which affect their complexity and three-dimensional topology, include hydroxylation, glycosylation, carbamylation and isomerization of collagen, phosphorylation of fibronectin, MMPs and laminin, sulphation of glycosaminoglycans and cross-linking between collagen, fibronectin and elastin. Degradation of ECM components are mediated by target-specific proteases, such as MMPs, and proteases that specifically cleave at serine, cysteine and threonine residues. The proteolytic enzymes secreted by cancer and stromal cells serve multiple roles during tumor progression; they allow progressive destruction of normal ECM and its replacement with tumor-derived ECM, they release ECM-bound growth factors and thereby increase their bioavailability, and more importantly, they pave the way for cell motility.

Conclusion: Remodeling of ECM not only supports tumor growth, also promotes migration of cancer cells and modifies the ECM in distant organs to

allow for metastatic progression. Deeper understanding of ECM remodeling and its underlying mechanisms would lead to developing therapeutic approaches for cancer patients and/or prevent malignancy.

Keywords: Extracellular matrix, Remodeling, Metastasis, Chemical modification, Proteolytic degradation.