STROMA — REGULATOR OF CANCER CELL PROGRESSION

Recent advances in tumor biology highlighted the active function and importance of stromal cells and the factors that they express during cancer initiation and progression, and have identified the stroma as an important regulator of carcinogenesis. Phenotype and biological features of tumor cells are formed consequently by complex crosstalk between the tumor cells and stroma.

Tumor stroma is a connective tissue composed of cells, blood vessels, nerves and extracellular matrix. Stroma is formed by the elements that are derived from the circulating blood and from adjacent host connective tissues. It is largely a product of the host-tumor cell interactions and from the extracellular matrix. Stroma is formed by the elements that are derived from the circulating blood and from adjacent host connective tissues. It is largely a product of the host-tumor cell interactions and from the extracellular matrix. Stroma is formed by the elements that are derived from the circulating blood and from adjacent host connective tissues.

Certain types of tumors in tissues lining the peritoneal cavity. Stroma, whereas in medullary breast carcinoma and many lymphomas it is minimal. Differences in stromal content among different tumors are largely qualitative. For example, some histological types of breast carcinoma are characterized by the abundance of elastic tissue along with collagen. Others, such as medullary breast carcinoma, provoke an extensive lymphocytic infiltration. Even within a single tumor there may be significant variations in stromal composition from one area to another. Leukemia and ascitic tumors are also embedded in stroma, which consists of plasma and peritoneal exudates, respectively. Clones of leukemic cells commonly induce stroma analogous to that of solid tumors in the bone marrow, and analogous to ascitic tumors in tissues lining the peritoneal cavity. Stroma, thereafter, at once provides a lifeline that is necessary for tumor growth and imposes a barrier limiting for the moment the dissemination of tumor cells.

Emphasizing the central role of stromal factors in tumorogenesis, recent advances in the understanding of the differentiation of multipotent stromal cells and their communication pathways between tumor and multipotent stromal cells were identified: growth factors, molecules of extracellular matrix, and proteases.

Cancer cells produce a line of growth factors, such as transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), the epidermal growth factor receptor (EGFR) ligand and vascular endothelial growth factor (VEGF). These proteins affect fibroblasts, and epithelial and endothelial cells. The endothelial cells produce connective tissue growth factor (CTGF), which together with TGF-β and PDGF not only attract stromal cells to the tumor site but also induce them to provide a supportive environment for the cancer cells. Expression of CTGF in steroid hormone-sensitive tissues, such as ovary and endometrium stroma, is regulated by the levels of estrogen and progesterone, determining the hormone dependence of tumors. Under the influence of TGF-β and PDGF stromal fibroblasts develop into myofibroblasts. Tumor-induced stromal growth is accompanied by the production of additional growth factors by these myofibroblasts, such as insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), CTGF and VEGF, which further enhance stromal growth.

The organization and architecture of the extracellular matrix (ECM) are rather dynamic. The metabolism of ECM molecules (synthesis balanced by degradation) is an important aspect of tissue homeostasis. The proteins and other ECM molecules embedded in the neoplastic tissue favor cell proliferation, production of inflammatory cytokines, angiogenesis and migration of cells into ectopic tissue compartments. As the predominant cell in stroma, the fibroblast is responsible for the elaboration of most connective tissue components in the ECM, including collagens and structural proteoglycans, as well as various classes of proteolytic enzymes, their inhibitors and various growth factors. The architecture of tumor-associated ECM is fundamentally different from that of preexisting stroma. Being the immediate environment of the tumors as well as of non-transformed cells, the ECM provides cues to the cells, thereby regulating their proliferation and morphology. The dense meshwork of ECM can be a hurdle to cell migration, especially for the basement membrane, which is impermeable for cells.

The third way of communication between tumor and stromal cells is supported by proteases. The proteases are involved in modifying tumor — stroma interaction through activation or inactivation of various cytokines and growth factors and modification of adhesion molecules favoring tumor growth. Within this group of proteins, two families of proteases are very important: the matrix metalloproteinases (MMPs) and the cathepsines. On the basis of the ECM components the MMPs can be divided into collagenases, gelatinases and stromelysins. Cathepsines are the other important class of proteases in the complex interplay between tumor and stroma. These proteases are divided into the aspartic, cysteine and serine cathepsins. It is known that latent forms of MMP-2 and -9 being of special importance in modulating ECM properties are activated in ECM by chymase and superoxide radicals that are formed in mitochondria of tumor cells and/or produced by neutrophils. Eventually various proteases modify the tumor — stroma interaction by regulating the functions of proteases-activated receptors, which results in tumor growth and subsequent invasion.

An understanding of the differentiation of multipotent stromal cells and their communication pathways with tumor cells will be helpful to design future pharmacological approaches for cancer treatment. New anti-cancer therapies targeting stromal cells can be developed. More data is needed to clarify how stromal cells modulate carcinogenesis and to evaluate the safety of these cells in cell-mediated gene strategies.

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