Stromal Players In Carcinogenesis

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ABSTRACT

Tumor cells alter the surrounding stroma and in turn, the stromal cells may promote cancer progression and invasion. This is carried out by stromal cell like carcinoma-associated fibroblasts (CAFs), tumor associated macrophages (TAMs), endothelial cells (ECs), leucocytes, and bone marrow derived cells. While none of these cells are themselves malignant, owing to their environment and owing to their interaction with each other and directly/indirectly with the cancer cell, they acquire an abnormal phenotype and altered function. In this review paper, we will discuss in detail the various cellular and molecular components of stromal environment, their effect on cancer cells, and aspects of targeting this environment for control of cancer.

Introduction

Cancer is the number one cause of death in the United States for people less than 75 years old. Every year, more than 11 million people are diagnosed with cancer throughout the world and it may likely increase to 16 million by 2020. In 2005, cancer accounted for 7.6 million deaths from a total of 58 million deaths worldwide¹. As a result, a re-evaluation of our basic assumptions concerning the nature of cancer and how to better assess risk, prevent, and medically manage is a high priority². Recent advances in tumor biology have revealed that a detailed analysis of the complex interactions of tumor cells with their adjacent microenvironment (tumor stroma) is mandatory in order to understand the various mechanisms involved in tumor growth and the development of metastasis³. The tumor microenvironment is an evolving concept that defines the behavior of cancer not by the genetics of the tumor cells alone, but by the surrounding milieu that the tumor cells need for survival, growth, proliferation and metastasis⁴. The stroma consists of a compilation of cells, including fibroblasts/myofibroblasts, glial, epithelial, fat, immune, vascular, smooth muscle, and immune cells along with the extracellular matrix (ECM) and extracellular molecules. While none of these cells are themselves malignant, due to their environment, their interactions with each other, and directly or indirectly

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with the cancer cells, they acquire an abnormal phenotype and altered function. This abnormal interplay consisting of cell–cell contact and active molecular crosstalk further drives the cancer stroma phenotype, and may result in permanent alterations in cell function.

**CELLS OF THE STROMA**

Cells within the stroma include fibroblasts, vascular, glial, smooth muscle, epithelial, and fat cells, and cells of the immune system. The most widely studied to date are the fibroblasts, immune cells, and the vascular cells, which we will focus on in this review.

**Fibroblasts**

In normal tissue, fibroblasts are the predominant cell type in the connective tissue stroma and are the primary producers of the non-cellular scaffolds—the extracellular matrix (ECM). Fibroblasts are responsible for the deposition of the fibrillar ECM—type I, type III, and type V collagen and fibronectin—and contribute to the formation of the basement membrane by secreting type IV collagen and laminin. Quiescent fibroblasts undergo activation and become myofibroblasts during wound healing and fibrosis where both conditions share the requirement for tissue remodeling, as originally described by Giulio Gabbiani in 1971.

**CANCER-ASSOCIATED FIBROBLASTS (CAFs)**

These cancer-associated fibroblasts (CAFs) are functionally and phenotypically distinct from normal fibroblasts that are in the same tissue but not in the tumor environment. CAFs directly stimulate tumor cell proliferation by contributing various growth factors, hormones and cytokines. CAFs associated with incipient neoplasia exhibit a pro-inflammatory signature, leading them mainly to over express SDF-1, IL-6 and IL-1b, as well as to recruit proangiogenic macrophages and promote tumor growth.

**Immune cells**

Monocytes/macrophages, neutrophils, and lymphocytes are recruited to and reside in the tumor stroma. Macrophages exhibit an array of diverse functions that depend on factors encountered in their microenvironment. Their distinct effector phenotypes can be considered as a spectrum ranging from pro-inflammatory or host defense (M1), to anti-inflammatory or regulatory (M2) phenotype. The relative balance of macrophage subsets is likely to
influence disease\(^9\). M1 and M2 polarized macrophages display a number of distinct features\(^10\).

### TUMOR-ASSOCIATED MACROPHAGES (TAM)

Origin and accumulation of TAMs is by

1. Tumor-derived chemo attractant, later identified as chemokine ligand - 2 (CCL2) - which plays a role in their recruitment\(^11\)
2. Molecules such as VEGF, PDGF, TGF-\(\beta\) and M-CSF are chemotactic for monocytes/macrophages and also promote macrophage survival and differentiation (primarily M-CSF)\(^10\)
3. Macrophages and tumor cells produce matrix proteases which are able to degrade the extracellular matrix (ECM); cleavage of ECM proteins liberate bioactive degradation products, including chemotacticants such as fragments of fibronectin and fibrinogen, in addition to other growth and angiogenic factors\(^12\). TAMs play role in tumor progression as: Angiogenesis, Matrix remodelling (TAMs-derived proteases), Suppression of anti-tumor immune responses.

Based on this, M1 macrophages are generally considered as potent effector cells, which defend the body against the attack of pathogens, and tumor cells. On the opposite extreme, M2 macrophages have poor antigen presenting capacity and thus play a role in immunosuppression and angiogenesis, thus hijacking the local immune system away from anti-tumor functions\(^9,10\). Many investigations have shown that differentiated mature TAMs exhibit their phenotype and functions, which are more akin to M2 macrophages\(^13\). Indeed, under many aspects, TAM summarizes a number of functions expressed by M2 macrophages: Tuning of inflammatory responses and adaptive immunity, tissue remodeling and repair, promotion of angiogenesis. Nevertheless, studies have reported that TAM isolated from a murine fibrosarcoma also expressed Interferon (IFN) - inducible chemokines: CXCL9 and CXCL10, via alternative Signal transducers and activators (IRF-3/STAT1) activation pathway. Many are the factors expressed in the tumor microenvironment that have the potential to promote the differentiation and polarization of recruited monocytes into M2 macrophages. These include the growth and differentiation factor macrophage colony-stimulating factor (M-CSF) and prostaglandin 2 (PGE-2) Transfroming growth factor beta (TGF-\(\beta\)), IL-6 and IL-10\(^10\). Thus, it can be said that most of macrophage in tumors are of M2 phenotype or TAM are similar to M2 macrophage.

### ENDOTHELIAL CELLS

The endothelium is the thin layer of cells that lines the inner surface of blood and lymphatic vessels, forming an interface between circulating blood and lymph in the lumen and the rest of the vessel wall. The cells that form the endothelium are called ECs. Tumors require the formation of a complex vascular network to meet the metabolic and nutritional needs for growth\(^5\).
Various forms of ECs in tumor microenvironment are circulatory endothelial cells (CEC) and endothelial progenitor cells (EPC). Recently, exocytic procoagulant endothelial micro particles (EMP) have also been identified.14

**Role of EC in tumor progression**

Elevated numbers of CEC have been variously described in lymphoma, melanoma, and glioma patients, as well as in breast, colonic, gastric, esophageal, renal cell, ovarian, cervical, carcinoid, testicular, prostate, and head and neck cancer patients, reflecting the perturbation of vascular endothelium in cancer disease.14,15 However, the clinical significance of CEC in cancer is still poorly understood. Clarity of CEC as mere markers of altered vascular integrity, or direct contributors to the neoplastic process and its associated complications is not known. In case of EPCs, in addition to the physical contribution to newly formed capillaries the angiogenic cytokine release of EPCs may be a supportive mechanism to improve neovascularization as well.16 This idea was supported by a recent report by Gao et al, who found that although only 12% of the new blood vessels showed incorporation of EPCs, blocking EPC mobilization caused severe angiogenesis inhibition and significantly impaired tumor progression. Moreover, in the same study, gene expression analysis of EPCs revealed up-regulation of a variety of key pro-angiogenic genes.16,17

**THERAPEUTIC TARGETING OF TME**

1. Targeting CAFs: TGF-β is one of the fibroblast supplied factors involved in suppression of epithelial transformation.
2. Targeting TAM’s: (NSAIDs), the selective COX-2 inhibitors, in the prevention and treatment of cancers associated with chronic inflammation, and
3. Targeting the tumor vasculature: One way to reduce pericyte coverage is to block the signaling pathways involved in recruiting pericytes to ECs.

**CONCLUSION**

TME is essence of cancer, which is the invasion metastasis cascade. Therapeutic targeting of cellular/molecular components in events of TME might be Relevant. Targeting reversible events in TME that contribute to tumor progression continues to hold great clinical promise.
REFERENCES

1. World Health Organization. 2006