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Review article

Chemopreventive agents targeting tumor microenvironment

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ABSTRACT

Recent studies have shown that tumor development and progression depend not only on the perturbed genes that govern cell proliferation, but is also highly determined by the non-tumor cells of the stromal compartment surrounding the tumor called tumor microenvironment (TME). These findings highlight the importance of targeting the microenvironment in combination with therapies aimed at tumor cells as a valuable approach. The innate and adaptive immune cells in the TME interact among themselves and also with the endothelial cells, pericytes and mast cells of the stromal compartment through various autocrine and paracrine manner to regulate abnormal cell proliferation. Direct cytotoxic killing of cancer cells and/or reversion of the immunosuppressive TME are to be considered as better strategies for chemoprevention and chemotherapy. With a growing emphasis on a "hallmark targeting" strategy for cancer therapy, the TME now appears as a promising target for cancer prevention using natural products. Clarification on the nontumor stromal cells, the mediators involved, interactions with immune response cells, and immune-evasive mechanisms are needed in order to manipulate the characteristics of the TME by natural pharmacological agents to design effective therapies. This review will provide a glimpse on the roles played by various non-tumor cells in tumor progression and their intervention by pharmacological agents.

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1. Introduction

Research in recent years focuses on cancer as a problem of tissue organization. According to the tissue organization field theory (TOFT), proliferation is the default state of cells, as in unicellular organisms or in the developing embryo and carcinogenesis results from alternation of normal tissue structure and the microenvironment rather than from genetic or cellular damages [1]. The tumor-associated stroma, or tumor microenvironment (TME), harbors two types of cells: the first type represents the cells like fibroblasts and endothelial cells that normally constitute a part of tissue parenchyma before the onset of tumorigenesis whereas the second type includes immune/inflammatory cells, including T- and B-cells, macrophages, neutrophils, mast cells and bone marrow-derived cells that are recruited from distal sites into the stroma after the onset of tumorigenesis. The process of crosstalk between stromal non-tumor cells and tumor cells has been broadly termed as immunosculpting or immunoediting [2]. The tumor-stroma cross talk

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is elicited by contact-dependent mechanisms involving cell–cell and cell–ECM adhesion molecules and contact-independent mechanisms involving soluble molecules such as growth factors (chemokines, cytokines) and soluble subcellular organelles (microvesicles and exosomes). Further, this tumor-stroma crosstalk adopted two different pathways namely an efferent pathway characterized by the tumor induced reactive response in the stroma and an afferent pathway where the modified stromal cells affect tumor responses.

Stromal cells support tumors in various ways starting from the recruitment of endothelial progenitors and their activation to form functional vessels, to secretion of a large amount of cytokines and soluble factors affecting cancer cell behavior [3].Moreover, micro environmental stimuli, such as those involved in the epithelial-mesenchymal transition (EMT) and hypoxia, indirectly contribute to chemoresistance by inducing a cancer stem cell like-phenotype [4]. As an integral part of cancer cells, tumor stromal cells play a vital role in neovascularization, invasion, and metastasis; and also its interaction with immune cells "shift the equilibrium towards an immunosuppressive environment favoring the tumorigenesis". Hence strategies that attempt to exploit cellular targets within the tumor stroma have potential advantages over traditional approaches. However, recently some anticancer agents are being tested for their impact on tumor stromal cells but a focused and elaborated research using these agents is really needed to bring a fruitful outcome in anticancer research. This review addresses the key roles played by the stromal cells in tumor progression and their intervention by pharmacological agents.

2. Tumor associated macrophages

Macrophages infiltrating tumor tissues are termed as tumor associated macrophages (TAM). TAMs express a broad repertoire of growth factors like production of endothelial growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF-β) that promotes proliferation of tumor cells, increase resistance to apoptotic stimuli and stimulate angiogenesis. TAM also produces various immune-suppressive factors, including prostaglandin E2 (PGE2), indoleamine 2, 3-dioxygenase (IDO) and interleukin 10 (IL-10) that contribute to immunosuppression [5]. Immunosuppression is caused due to TAM derived cytokines and proteases, such as TGF-β, IL-10, and arginase 1 [6–8]. Deregulation of T-cell receptor (TCR) signal due to which there is induction of unresponsive CD8 + T-cell is caused by arginase1 [9]. Conversion of M1 to M2 phenotype of macrophage is caused by TGF-β which results in immunosuppression [10]. TAM derived proteolytic molecules such as plasmin, urokinase-type plasminogen activator (uPA), cathepsin B and matrix metalloproteases (MMP) can directly remodel the extracellular matrix (ECM) [11]. Pro-tumoral function of TAM such as activation of inflammatory response causes neoplastic transformation and progression (Fig. 1). These findings represent TAM as possible target for anticancer agents. Present TAM-targeted approaches mainly concentrate on four aspects: (i) inhibiting macrophage recruitment; (ii) suppressing TAM survival; (iii) enhancing M1 tumoricidal activity and (iv) blocking M2 tumor-promoting activity. Tyagi et al., [12] reported that silibinin a proven chemopreventive agent inhibits TAMs present in TME. It has also been found to exhibit angiopreventive effects against lung tumorigenesis. Bisphosphonates are also now being tested to target TAMs in the TME [13]. Germano et al., [14] reported that trabectedin a marine origin chemotherapeutic agent inhibits the local differentiation of tumor-recruited monocytes to fully mature macrophages and causes depletion of mononuclear phagocytes *in vivo*. *In vivo* results have shown that macrophage depletion around tumor discourages paracrine signaling by TAM thereby preventing further tumor growth. In line with these findings studies conducted by Coscia et al., [15] reported that zoledronic acid at clinically achievable doses decreased tumor vascularization and also the number of tumor-associated macrophages with their reverted polarization from M2 to M1 phenotype and substantiated the hypothesis that zoledronic acid inhibits spontaneous mammary carcinogenesis by targeting the local microenvironment.

The antitumor activity of nitrogen containing bisphosphonates observed in preclinical models and in clinical trials is likely mediated indirectly through uptake of these drugs by TAMs and possibly other myeloid lineage cells, leading to their functional impairment and depletion, rather than by direct effects on tumor cells *per se* [13]. Cannabidiol (CBD) a member of the cannabinoid family and one of the constituents of *Cannabis sativa* is shown to modulate cytokine production from tumor cells which lead to less recruitment of total macrophages and M2 macrophages into the primary and secondary tumor sites. This

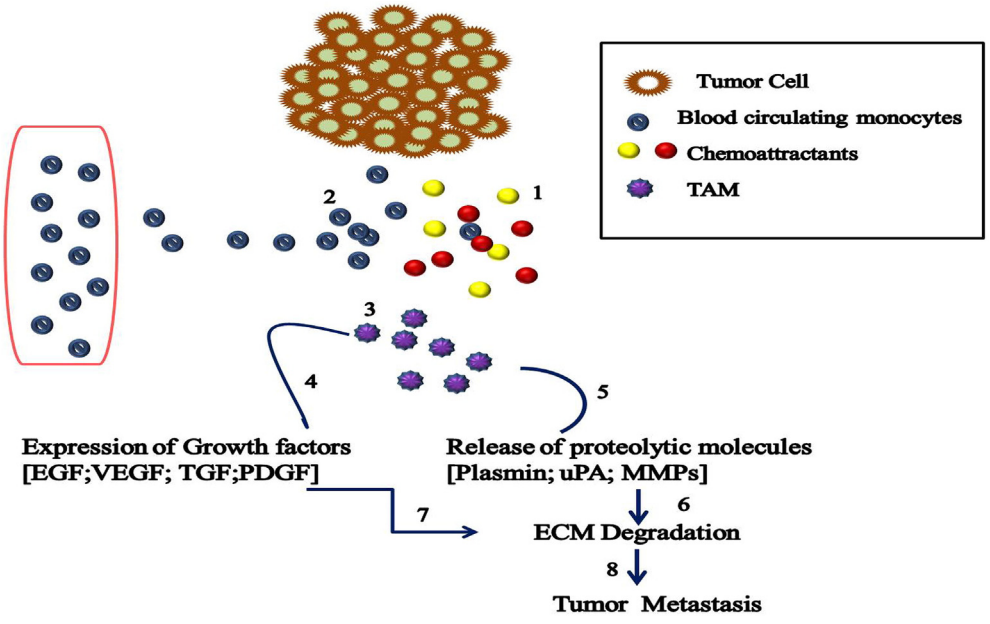

Fig. 1. Role of TAMs in tumorigenesis. 1. Tumor cells and stromal cells secrete chemoattractants like CSF-1, MCPs, MIP1 α. 2. Tumor infiltration of monocytes. 3. Differentiation of monocytes to macrophages. 4. TAM expresses growth factors. 5. TAM releases proteolytic molecules. 6. Proteolytic molecules cause ECM degradation. 7. Tumor cells exploit TAM mediated ECM degradation. 8. Tumor cells invade locally to cause distant metastasis.