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• Review

Progress in research on the effects of traditional Chinese medicine on the tumor microenvironment

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ABSTRACT

Tumor microenvironment (TME) has received more and more attention as modern medical research has begun to understand its importance in tumorigenesis. The occurrence, development, metastasis and drug resistance of tumors are closely related to TME. TME is a complicated system, including nontumor cells, their secreted cytokines, extracellular matrix, among other components. The concepts of wholism and multitarget regulation in traditional Chinese medicine (TCM) make it well suited to the regulation of TME. In this paper, the authors reviewed the progress of TME research and the effect of TCM on TME, providing some views of Chinese medicine in antitumor research.

Keywords: tumor microenvironment; medicine, Chinese traditional; Chinese medicine monomer; Chinese medicine compound; research progress

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1 Introduction

With the development of modern medicine, the focus on tumor biology research has been gradually switching from the functional exploration of oncogenes and tumor suppressor genes to the investigation of crosstalk between tumor cells and their microenvironment.[1] As early as 1889, Paget[2] had proposed the so-called "seed and soil" hypothesis to explain the metastatic behavior of cancer cells; the metaphor equates tumor cells with seeds and their growing microenvironment with soil.[3] Conventional cancer studies have mostly focused on single targets or single pathways (the seeds) and treatments that they develop have also emphasized single definite targets. However, the effects are far from satisfactory. Many drugs cannot effectively control the tumor, and in some cases where a tumor can be inhibited at the first, the rapid emergence of drug resistance may lead to decreased efficacy. In consideration of that, the development of a tumor is a multistep, complex processes regulated by many signal pathways and molecules.[4] Therefore, in recent years, more and more studies have focused on the tumor microenvironment (TME). Traditional Chinese medicine (TCM) takes the approach of multitarget and overall-regulation in the treatment of tumors, through the concept of wholism and syndrome differentiation and treatment.[4,5] As TME has become a hotspot in recent cancer research, research on the effects of TCM on

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TME has made certain progress. In this review, we will summarize these effects according to recent studies.

2 An overview of TME

TME is a complex system composed of nontumor cells, cytokines, chemokines and extracellular matrix. The nontumor cells mainly consist of vascular and lymphatic endothelial cells, innate immune cells (macrophages, neutrophils, mast cells, dendritic cells and natural killer (NK) cells, etc.), acquired immune cells (T and B lymphocytes) and various stromal cells, such as smooth muscle cells fibroblasts, and mesenchymal stem cells (MSCs).[6] Tumor development requires energy which is provided by new blood vessels in a process termed "the angiogenic switch." Vascular endothelial cells, which can be activated by vascular endothelial growth factor (VEGF) or fibroblast growth factor-2, are important for the formation of these blood vessels.[7] On the other hand, the formation of lymphatic vessels may be activated by lymphangiogenic factors and provide a channel for metastasis.[8] Macrophages can express different phenotypes or be differentiated according to microenvironmental stimuli and such macrophages vary from pro-inflammatory to anti-inflammatory. More and more evidence shows that macrophages, called tumor-associated macrophages (TAMs), can influence the growth and metastasis of tumors.[9] It is well known that TAMs mainly include two phenotypes: classically activated macrophages (M1) and selectively activated macrophages (M2).[10] Most tumors express the polarized M2 phenotype, which can secrete a variety of chemokines, cytokines and proteases, and promote the proliferation, angiogenesis, invasion and migration of tumors.[9,11] In the meantime, these macrophages may provide an immunosuppressive microenvironment that promotes tumor development and is associated with poor prognosis.[9]

Dendritic cells (DCs) are the major antigen-presenting cells in human body. The ability of DCs to preferentially activate T cells is the foundation of the cancer immunity cycle.[12] DCs may endocytose dead neoplastic cells or cellular debris and transport cancer-associated antigens to the draining lymph node, where T-cell priming and activation can occur.[13] However, TME can affect the DC recruitment, differentiation, maturation and survival, and inhibit antigen presentation of DCs and activation of T cells, leading to immunosuppression or immune tolerance.[14] NK cells, as innate immune cells, should monitor and kill tumor cells before they can proliferate, but in the TME dysfunctional immune cells, such as M2 phenotype TAMs and DC, may inhibit the anticancer effects of NK cells through interfering with their activation.[15,16]

As for acquired immunity, regulatory T cells (Tregs) have gained more and more attention, as Tregs isolated from tumors have a stronger immunosuppressive effect. The biological properties of Tregs comprise of the important mechanisms for the development of tumor and interfere with the body's immune process. Therefore, it is significant to study the influence of TME on Tregs and find way to improve the effectiveness of the human immune system against tumor cells by targeting Tregs.[17]

Cancer-associated fibroblasts (CAFs) are representative cells in the cancer microenvironment, which play an important role in the synthesis, deposition and decomposition of the extracellular matrix. CAFs may secrete growth factors and cytokines and other cell to cell signaling factors, to regulate tumor growth, proliferation and invasion.[18]

Besides various mesenchymal cell types, such as endothelial cells and CAFs mentioned above, MSCs are becoming increasingly appreciated as critical components of the TME, since they serve comparable roles in cases of malignancy. MSCs display avid tropism for developing tumors as their abilities to home to wounded tissues.[19,20] MSCs within TME may exert direct paracrine influences on the cancer cells or indirect promalignant actions through recruitment of endothelial progenitor cells to promote tumor angiogenesis.[21,22] On the other hand, MSCs may differentiate into other types of stromal cells such as fibroblasts in response to the numerous signals and cues present in the TME.[23] Thus MSCs promote tumor proliferation, invasion and metastasis.[20,24]

In addition to the nontumor cells and their secretion of cytokines and chemokines in the TME, research on exosomes is also a point of interest in the field of TME. Exosomes are parts of extracellular vesicles characterized by their distinct biogenesis and small size, and are derived from multiple types of living cells through the endocytic pathway.[25] These vesicles fuse with the cellular membrane in a calcium-dependent manner and are released into the extracellular matrix to form exosomes. Exosomes contain a small amount of cytoplasm and serve as information transfer vehicles; tumor-derived exosomes carry messages from the parent tumor cell to other normal or malignant cells.[26] Cytoplasm excreted from exosomes contains proteins, messenger RNA, microRNAs (miRNAs), DNA fragments and other bioactive components that can mediate tumor angiogenesis, fibroblast differentiation and immune regulation, thus playing an important role in TME.[27,28] Of these, miRNAs have been of particular interest because they may modify transcription and translation as well as directly inhibit or enhance key regulatory proteins.[29,30]

In addition, the chaotic proliferation of cancer cells that places them at a distance from the nearest capillary and the abnormal structure of the new vascular network