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Inflammation, Macrophage in Cancer Progression and Chinese Herbal Treatment

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ABSTRACT

Inflammation is associated with cancer development, and has been recognized as the seventh hallmarks of the cancer. Cancer-related inflammation can be activated by genetic or epigenetic changes in cancer cells (intrinsic pathway) or mediated by tumor-infiltrating immune cells (extrinsic pathway). Immune cells involved in cancer-related inflammation mainly including tumor-associated macrophages or M2 macrophages, neutrophils, dendritic cells, mast cells, and lymphocytes. As major players of the cancer-related inflammation, M2 macrophages, secreting various of growth factors, immunomodulatory cytokines and matrix metalloproteinases, participate in remodeling of extracellular matrix，contribute to cancer invasion and metastasis, angiogenesis, and inhibit anti-cancer immunity. Inflammation has been considered as an important target for cancer therapy. Some Chinese herbal ingredients have been confirmed to be effective in inhibit inflammation related gene expression in cancer cells, such as COX-2 and NF- B. However, there is a shortage of study on Chinese herb or herbal ingredient against extrinsic cancer inflammation, especially in tumor-associated macrophages. Related studies may provide new insight into cancer treatment.

KEY WORDS

Cancer, Inflammation, M2 macrophages, Traditional Chinese Medicine

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INTRODUCTION

Studies on the relationship between inflammation and tumor can be traced back to the 19th century. In 1863, Virchow found inflammation cells, which presented in tumor biopsy specimens, and proposed the hypothesis that tumors might originate from the site of chronic inflammation. It has been cleared now that inflammation is involved in tumor incidence. Inflammation may promote tumor cell proliferation, angiogenesis and tumor metastasis, influence anti-tumor immune responses and even affect the response of tumor cells to drug treatment. In 2009, Mantovani *et al* classified inflammation as the seventh hallmarks of cancer [1-2]. Studies on the relationship between inflammation and tumor have brought far-reaching impacts on diagnosis and treatment of cancer.

1. INFLAMMATION AND TUMOR

Tumor, a complex aberrant cell aggregate, is composed of tumor parenchyma and stroma. Stroma includes extracellular matrix, endothelial cells which constitute blood vessels and lymphatic vessels, and immune cells. The factors involved in tumor inflammation may derive from tumor cells (intrinsic pathway), or mediated by immune cells (extrinsic pathway). Intrinsic pathway of tumor inflammation is related to genetic events in tumor cells. Gene mutations in Ras, MYC and microRNA-155, or abnormal activation of VHL/HIF and NF-κB pathway, may promote cell to express cytokines (such as IL-1 and TNF-α), chemokines (such as CXCL5 and CXCL12) and growth factors (such as colony-stimulating factors), which directly participate in or recruit immune cells to participate in tumor inflammation [2-4].

Immune cells involved in tumor inflammation include tumor-associated macrophages (TAM)-a kind of M2 macrophage, neutrophils, lymphocytes, dendritic cells and mast cells. These immune cells, which are activated by chronic infections (such as HBV, HPV, EBV, H. pylori, etc.) or damaged cells, may produce cytokines, chemokines, adhesion molecules and free radicals to intervene the interaction between tumor cell and extracellular matrix, and participate in tumor initiation, progression and metastasis. In addition, NF-κB, HIF-1α and STAT3 are common transcription factors both in intrinsic and extrinsic tumor inflammation [2].

It has been confirmed that common malignancies such as liver cancer, gastric cancer, cervical cancer, pancreatic cancer, colon cancer and nasopharyngeal cancer are closely related to chronic inflammation. In tumor initiation phase, inflammation produces reactive oxygen species (ROS) and reactive nitrogen species (RNS) which may lead to genetic instability, induce DNA damage and mutations, affect DNA damage repair through post-translational modifications in tumor suppressor genes such as p53 and RB, and promote malignant transformation. Chronic inflammation can also influence the expressions of p16, RUNX3, p53 and other genes by epigenetic mechanisms and involve in malignant transformation [2,5-6]. In the development of tumor, inflammation plays a promoting role, for example, immune cells can secrete cytokines such as IL-1, IL-6 and EGF to promote tumor cell survival, VEGF and IL-8 to promote angiogenesis, TGF-β and MMPs to promote cancer metastasis, IL-10, and TGF-β and CCL17 to suppress anti-tumor immunity. In addition, inflammation can affect the response of hormone treatment and chemotherapy, and targeting inflammatory pathways have some potential effects to improve chemotherapy of cancer [2, 6-8].

2. MACROPHAGES AND CANCER

Macrophage is one of the major cell populations to be involved in inflammatory response. For the high degree of functional plasticity, under the influence of different microenvironments, they could polarize to M1

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Table 1: Chinese herbs or herbal components against cancer-related inflammation.

Compound	Chinese herb	Molecular targets	Ref.
Curcumin	curcuma longa, zedoary turmeric, curcuma aromatica	NF-κB, COX-2,VEGF,TNFα , IL-1, IL-6	34-35
Resveratrol	polygonum cuspidate, grape seed	COX-1, COX-2, NF-κB	34,41
Quercetin	bupleurum, mulberry leaf, inula britannica	MEK/ERK, Nrf2/keap1	36
Silibinin	Silybum marianum	NF-κB, MMP-9, COX-2	37
PC-SPES	eight herbal mixture	COX-2, NF-κB, C/EBPβ	40
Tanshinone I	Salvia Miltiorrhiza Bge	NF-κB, IL-8 ,VEGF	44
Gypenosides	Gynostemma pentaphyllum Makino	MMP-2, MMP-9, urokinase-plasminogen, ERK1/2, NF-κB	45
Berberine	Coptis chinensis Franch, Hollygreen Barberry, Chinese Mahonia	FAK, IKK, NF-κB, u-PA,MMP-2,MMP-9	46
Triptolide	Tripterygium Wilfordii Hook	NF-κB, IAP1, Rac1, JAK/STAT3	47,51
Celastrol		NF-κB, MMP-9	49
Pachymic acid	Poria cocos	NF-κB, MMP-9	50
Ginsenosides	Panax ginseng	EGFR, STAT-3, p38, NF-κB, COX-2 ,iNOS	52,54-55
Tetra-methylpyrazine	Ligusticum chuanxiong.	IFN-γ, IL-2, IL-4, IL-6, IL-10	53

macrophages (classically activated macrophages) and M2 macrophages (alternatively activated macrophages) [9-11]. M1 macrophages can be activated by bacterial products, lipopolysaccharides (LPS), interferon-γ and GM-CSF. M1 phagocytes are characterized by an IL-12^{high}, IL-23^{high} and IL-10^{low} phenotype, and executes classic macrophage functions such as antigen-present, and consequent activation of type I immune response. In addition, M1 macrophages expressed iNOS and M2 macrophages expressed Arg1 could competitively combine with L-arginine to produce NO and ROS, which can promote inflammatory response and clear invading microbes [12-13]. M1 macrophages present anti-tumor activity in lung cancer and positively correlated with prognosis, activated M1 macrophages also can be used for treatment of liver cancer and other cancers [14-16].

M2 macrophages have been divided into at least three subtypes (1): type M2a, induced by IL-4 and IL-13; (2) type M2b, induced by immune complexes in combination with IL-1β or LPS; (3) type M2c, activated by IL-10, TGF-β, or glucocorticoid, and participated to immunoregulation [17]. M2 macrophages are the major cell macrophages in tumor tissue, namely tumor-associated macrophages (TAMs). TAMs express arginase I (Arg-1), which decompose L-arginine to produce L-ornithine, a precursor of proline, and promote collagen synthesis and damaged tissue repair [12-13, 18]. In addition to the induction of cytokines, Wang *et al* recently found that Notch signaling is significant in the determination of M1 versus M2 macrophages polarization, blocking Notch signaling could promote macrophage differentiation into pro-tumor M2 macrophages, while activating Notch signaling promote macrophage differentiation into anti-tumor M1 macrophages [19]. It has been proved in many tumors such as breast cancer and pancreatic cancer, M2 macrophages are closely related with tumor metastasis, showing a negative correlation with prognosis [20-21].

3. TUMOR-ASSOCIATED MACROPHAGES AND CANCER

TAMs are the main cell population involved in chronic tumor inflammation. TAMs are differentiated from monocytes under the induction of cytokines like M-CSF, IL-4, IL -13 and IL-10. In addition, tumor cells secreted cytokines/chemokines such as IL-10, CSF-1, CXCL1 and CCL2, may activate NF-κB and STAT3 signaling pathways and promote

monocytes to differentiate into TAM which highly express IL-10 and Arg-1 and lowly express IL-12, showing M2 macrophage phenotype and function. Tumor hypoxia environment is also involved in the activation of TAM. Tumor hypoxia environment activates HIF-1a signaling pathway, up-regulates CXCL8 and CXCR4 to activate TAM, and promotes NOS2 and ARG gene expression, thus affecting the metabolism of L-arginine [17, 22-24].

TAMs show a poor antigen presenting ability, promote tumor angiogenesis and metastasis, and inhibit anti-tumor immune response [18, 22-24]. TAMs are enriched at the invasive edges of tumors. Tumor cells secretes CSF-1 to stimulate TAMs to express epidermal growth factors, forming EGF/CSF-1 paracrine loop, thereby promoting tumor cells migration; meanwhile, TAMs expressed SPARC/osteonectin, matrix metalloproteinases (MMPs) and chemokines may influence matrix remodeling in tumors, and promotes tumor metastasis. TAM also secretes a variety of proangiogenic factors, such as VEGF, TGF-β, PDGF and FGF, to promote tumor angiogenesis. In addition, TAMs produce immunosuppressive cytokines such as IL-10 and TGF-β, and secrete CCL22 to recruit regulatory T cells (Tregs) to inhibit tumor immunity.

4. CANCER INFLAMMATION AND TRADITIONAL CHINESE MEDICINE

Cancer is a complex disease. Studies conducted from different perspectives may improve the efficiency of cancer therapy. In view of effects of inflammation in tumor initiation and development, inflammatory cells are genetic stable and less prone mutations and drug resistance, inflammation has become a potential target for cancer prevention and treatment [25-26].

Inflammation targets for tumor treatment include COX-2, NF-κB, cytokines and their receptors, chemokines and their receptors as well as M2 macrophages. Present studies mainly focus on non-steroidal and steroidal anti-inflammatory drugs, COX-2 inhibitors, plant extracts and biological therapeutics. It has been confirmed that anti-inflammatory drugs such as sulindac have not only a certain degree of anti-cancer effects, but also can prevent the incidence of colorectal cancer, lung cancer and other tumors in high-risk populations to some degree and may cooperate with current anti-cancer drugs [26-31]. It has been reported anti-inflammatory plant natural products, such as resveratrol, genistein, quecetin, shikonin and epigallocatechin gallate, have been found to have anti-cancer potential [32-33].

Chinese herbs are widely used for cancer treatment. Some anti-cancer Chinese herbal components, such as curcumin, resveratrol, quercetin and silibinin, may inhibit tumor inflammation related gene expression [34-38]. Curcumin and resveratrol showed potential effect for cancer prevention and treatment, to some degree, and a better prospect for clinical application when combing with traditional treatments like chemotherapy [39-42]. PC-SPES, an eight herbal mixture, may down-regulate COX-2 via inhibition of NF-κB and C/EBP β in non-small cell lung cancer cells [43]. Tanshinone I, a major compound of Danshen, reduces interleukin-8 by attenuating the DNA-binding activity of activator protein-1 and NF-κB in human lung adenocarcinoma CL1-5 cells [44]. Anti-cancer effects of Gypenosides, Berberine, Triptolide and Tribulus terrestris Linn have been found associated with down-regulation of NF-κB pathway [45-48]. Inhibitory effects of Pachymic acid and Celastrol on breast cancer cell invasion were found related to down-regulation of NF-κB-mediated matrix metalloproteinase-9 expression [49-50]. In addition, Triptolide may decrease colitis induced colon cancer by interrupting the IL6R-JAK/STAT pathway [51]. Ginsenoside Rg3 may inhibit phorbol ester-induced cyclooxygenase-2 expression, NF-kappaB activation and tumor promotion [52]. Tetra-Methylpyrazine could enhance IFN-γ, IL-2 and T-bet, but reduce those of type 2 cytokines in lung cancer patients [53] Table I.

However, there is a shortage of study on Chinese herb or herbal ingredient against extrinsic cancer inflammation, especially in M2 macrophages. Traditional Chinese Medicine is the unique biomedical resource in China. Many Chinese herbs used to treat inflammatory diseases are also applied for tumor treatment, such as Barbed Skullcap, Hedyotis Diffusa Willd, Solanum Nigrum, rhizoma pardis and Polygonum Cuspidate. In facts, the most frequently used anti-cancer herbs are heat-clearing and detoxifying (Qing-Re-Jie-Du) herbs which are originally used for inflammatory diseases treatment [56-57]. It can be speculated that these Chinese herbs may have effects on inhibiting cancer-related inflammation. Related studies may provide new clue for pointedly apply specific Chinese herb or components against cancer inflammation to enhance the overall efficacy of cancer treatment.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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