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EDITORIAL

Inflammation, cytokines, the IL-17/IL-6/STAT3/ NF-κB axis, and tumorigenesis

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Correspondence: Xiao-Wu Chen Department of General Surgery, The First People's Hospital of Shunde, Southern Medical University, I Penglai Road, Shunde, Foshan 528300, Guangdong, People's Republic of China Tel +86 757 2221 8555 Fax +86 757 2222 3899 Email drchenxiaowu@163.com

Shu-Feng Zhou Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, 12901 Bruce B Downs Boulevard, Tampa, FL 33612, USA Tel +1 813 974 6276 Fax +1 813 974 9885 Email szhou@health.usf.edu In the recently published paper by Xie et al¹ in the journal of Drug Design, Development and Therapy, the authors have evaluated interleukin (IL)-17-driven inflammatory responses in 17 cases of human colon adenocarcinomas, 16 cases of human normal colon tissues adjacent to the resected colon adenocarcinomas, ten cases of human ulcerative colitis tissues from biopsies, and eight cases of human benign colon polyps. The authors have observed that human colon adenocarcinomas contained the highest levels of IL-17, which was significantly higher than the IL-17 level in the adenomas, ulcerative colitis, and normal colon tissues ($P \le 0.01$). The levels of IL-17 receptor A (IL-17RA) were also the highest in human colon adenocarcinomas, followed by adenomas and ulcerative colitis. The increased level of IL-17 and IL-17RA was accompanied with increased IL-17-driven inflammatory responses, including activation of extracellular signal-regulated kinase 1/2 and c-Jun N-terminal kinase pathways, increased expression of matrix metalloproteinase (MMP)-9, MMP-7, MMP-2, B-cell lymphoma, and cyclin D₁, decreased expression of Bcl-2-associated X protein, and increased expression of vascular endothelial growth factor (VEGF) and VEGF receptor expression that were associated with increased angiogenesis.1 These data suggest that IL-17-driven inflammatory responses contribute to the initiation, growth, development, and metastasis of colon cancer. IL-17 and its related signaling pathways may serve as promising novel targets in the development of drugs for the prevention and treatment of colon cancer.

The relationship between IL-17 and tumor growth was first reported in 1999 by Tartour et al² who showed that IL-17 served as a tumor growth factor in nude mice, although its mechanism remained unclear. Currently, six IL-17 family members have been identified, including IL-17A (namely IL-17), IL-17B (also named IL-20), IL-17C, IL-17D (also named IL-27), IL-17E (also named IL-25), and IL-17F.3 IL-17A binds the receptor complex IL-17RA-IL-17RC to drive inflammatory gene expression. IL-17 is a cytokine produced by Th17 cells, a T helper cell subset developed from an activated CD4⁺ T cell that is characterized by the expression of intracellular retinoic acid-receptor-related orphan receptor yt and signal transducer and activator of transcription 3 (STAT3). Th17 cells secrete IL-17A, IL-17F, IL-21, and IL-22 to fight extracellular bacteria and fungi by stimulating epithelial cells to produce chemokines and cytokines, which drive the immune response. Other cells, including $\gamma\delta T$ cells, natural killer (NK) cells, NK T cells, mast cells, and granulocytes can also secrete IL-17. Phosphorylation of STAT3, the downstream signal of IL-6 and IL-21, is a key process in the differentiation of Th17 cells in the presence of transforming growth factor (TGF)-β1.4

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IL-17 plays an important role in inflammation, immunity, and autoimmunity and has been associated with many immune-related/autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, asthma, allograft rejection, autoimmune hepatitis, and inflammatory bowel disease.⁵⁻⁷ IL-17 has proinflammatory effects on a panel of cellular targets, such as epithelium, endothelium, and monocytes/macrophages. IL-17 can stimulate the production of a variety of cytokines such as IL-1β, IL-6, tumor necrosis factor (TNF)- α , and TGF- β , chemokines such as IL-8, and prostaglandins from macrophages, endothelial cells, epithelial cells, and fibroblasts, resulting in and amplifying inflammation.4,6,8-11 IL-17-triggered release of IL-6 will consequently activate the STAT3 pathway, which will further activate the nuclear factor (NF)-KB pathway.^{3,5} IL-6 promotes the differentiation of Th17 cells, and IL-17 amplifies IL-6 production in the tumor.

STAT3 is a critical signaling molecule that is involved in the formation of the tumor microenvironment through regulating downstream proinflammatory cytokines and factors promoting tumor growth, progression, and metastasis.^{8,12–15} Constitutively active phosphorylated STAT3 can regulate the differentiation and maturation of Th17 cells to secrete IL-17, which in turn positively feeds back to STAT3 signaling and induces more IL-17 production.8,12-14 IL-17 promotes the recruitment and infiltration of myeloid-derived suppressor cells (MDSCs), such as CD11b+Gr1+ cells, to the tumor environment; IL-17 also augments the development and function of MDSCs.⁴ Furthermore, IL-17 produced by MDSCs recruits T regulatory cells at tumor sites via upregulation of chemokines CCL17 and CCL22 and enhances their suppressor function via upregulation of CD39 and CD73.4 MDSCs produce nitric oxide and reactive oxygen species (ROS) and suppress T-cell function through modification of T-cell receptors, inhibition of Janus kinase 3 and STAT5, inhibition of major histocompatibility complex class II expression, and induction of T-cell apoptosis.16,17 Meanwhile, IL-17 can enhance the growth of vascular endothelial cells and influence the angiogenic progress by increasing the secretion of cytokines, such as TNF-α, IL-8, and VEGF.⁴ IL-17 promotes the invasion of cancer cells via upregulating the expression of MMP-2 and MMP-9 and downregulating the expression of tissue inhibitor of MMP-1 and MMP-2.4 The increased expression of chemokines by IL-17 attracts neutrophils but not eosinophils.

IL-17 plays a dual role in serving either as a promoter or antitumor factor depending on the type of tumors and the existence of host immune system. In mice, IL-17 promotes an antitumor cytotoxic T-cell and NK-cell response, leading to tumor regression of fibrosarcoma, hematopoietic immunogenic tumor, and lung melanoma; IL-17A has showed a protective effect against chronic lymphocytic leukemia development by promoting immune system-mediated tumor rejection.^{4,6,9,10} Adaptive transfer of Th17 cells reduced tumor growth because Th17 cells developed into Th1 cells in vivo and produced interferon (IFN)-y and promoted the activation of cytotoxic T lymphocytes.^{4,6,9,10} On the other hand, IL-17 promotes tumorigenesis, proliferation, angiogenesis, and metastasis of many types of tumors.^{4,6,9,10} IL-17^{-/-} mice have been used to determine the endogenous IL-17A functions with regard to tumor progression. One study using B16 melanoma cell lines has showed that IL-17A promoted tumor growth via angiogenesis and induced IL-6 production, which in turn activated oncogenic STAT3, upregulating prosurvival and proangiogenic genes.¹⁴ However, another study using MC38 colon cancer cell lines has showed that IL-17A inhibited tumor growth through antitumor immunity.¹⁸ IL-17 has been detected in various tumors, including breast cancer, gastric cancer, colorectal cancer, cervical cancer, brain tumor, intrahepatic cholangiocarcinoma, and hepatocellular carcinoma.4 The sources of Th17 cells in cancer may include the trafficking of circulating Th17 cells to tumors and locally induced Th17 cells. The recruitment of Th17 cells is mainly mediated by CCR2-CCL2, CCR4-CCL17/CCL22, and CCR6-CCL20 pathways.⁴⁻⁷ The Th1 cytokines, such as IFN-y, and Th2 cytokines, such as IL-4, regulate the differentiation and development of Th17 cells.^{4,6,9,10} The number of Th17 cells gradually increases in the tumor microenvironment during tumor development, and this increase is positively associated with poor prognosis in patients with cancer.4

In the 19th century, Dr Rudolf Virchow observed the infiltration of leukocytes in tumor tissues, offering the first indication of a potential link between cancer and inflammation. Up to date, there is enough evidence that inflammation plays a critical role in tumor initiation, growth, and development.^{19–23} A key role for inflammation in carcinogenesis is generally accepted by cancer scientists, and it has become evident that an inflammatory microenvironment is an essential component of all types of tumor. It is known that only a minority of cancers (<10%) are caused by germline mutations, while the vast majority (90%) are ascribed to somatic mutations and environmental factors.^{20,22–26} Many cancers are associated with certain forms of chronic inflammation and 15%–20% of cancers are linked to chronic infections.^{20,22–26}

It is now well established that the induction of inflammation by bacterial and viral infections increases cancer risk. Chronic Helicobacter pylori infection is associated with gastric cancer and mucosa-associated lymphoid tissue lymphoma; Chlamydia trachomatis infection increases the risk of cervical cancer;27 enterotoxigenic Bacteroides fragilis infection promotes colon tumorigenesis.²⁸ Viral infections by highrisk human papillomavirus (HPV) subtypes, such as HPV16 and HPV18, are causal to the development of cervical, anal, and genital cancers.^{29,30} Infections with hepatitis B or C viruses increase the risk of hepatocellular carcinoma;³¹ the Epstein-Barr virus can cause lymphomas and nasopharyngeal cancer;³² human herpes virus 8 (also known as Kaposi sarcoma-associated herpes virus) causes Kaposi sarcoma;³³ HIV infection has been linked to a higher risk of developing Kaposi sarcoma and cervical cancer;³⁴ human T-lymphotrophic virus-1 has been linked with adult T-cell leukemia/lymphoma;35 Merkel cell polyomavirus causes Merkel cell carcinoma.36 Schistosomiasis is associated with the development of bladder cancer;³⁷ Opisthorchis viverrini and Clonorchis sinensis infection are linked to increased risk of cholangiocarcinoma.38 Microorganisms may manipulate and/or collaborate with cellular signaling pathways to promote an inflammatory microenvironment that facilitates cancer development.

Another type of chronic inflammation that precedes tumor development is caused by immune deregulation and autoimmunity.^{20,22–26} A typical example is inflammatory bowel disease, which significantly increases the risk of colorectal cancer. Chronic inflammation associated with infections or autoimmune disease precedes carcinogenesis and can contribute to it through induction of oncogenic mutations and activation of oncogenes, inactivation of tumor suppressors, genomic instability, early tumor promotion, and enhanced angiogenesis.^{20,22–26} Prolonged exposure to environmental irritants (eg, smoking or asbestos) or obesity can also result in low-grade chronic inflammation that precedes tumor development. Particulate materials from tobacco smoke and other environmental irritants can precipitate chronic obstructive pulmonary disease, a condition associated with higher lung cancer risk.^{39,40} The precise mechanisms that underlie the association of obesity with increased risk for tumors, including mammary, renal, esophageal, gastrointestinal and reproductive cancers, remain elusive. The obese setting provides a unique adipose tissue microenvironment with concomitant systemic endocrine alterations favoring both tumor initiation and progression, and considerable metabolic differences are induced by tumor cells in the stromal vascular fraction that surrounds them.⁴¹

The inflammatory response can promote angiogenesis, oncogene mutation, tumor progression and metastasis, immunosuppression, and genomic instability. Cancer therapy can also trigger an inflammatory response by causing trauma, necrosis, and tissue injury that stimulate tumor reemergence and resistance to therapy.¹⁹ Most solid tumors trigger an intrinsic inflammatory response that builds up a protumorigenic microenvironment. Other tumors, for instance lung cancer, can promote inflammation through active secretion of proinflammatory molecules, such as the extracellular matrix component versican, which activates macrophages through Toll-like receptor 2.^{21,23}

The tumor microenvironment is a complex ecology of cells that evolves with and provides support to tumor cells during the transition to malignancy, which facilitates inflammation initiation, development, and amplification.^{22,42,43} As a result of different forms of inflammation, the tumor microenvironment contains innate immune cells, including macrophages, neutrophils, mast cells, MDSCs, dendritic cells, and NK cells and adaptive immune cells (T and B lymphocytes) in addition to the cancer cells and their surrounding stroma consisting of fibroblasts, endothelial cells, pericytes, and mesenchymal cells.^{20,22,44} These different types of functional cells communicate with each other by means of direct contact or cytokine and chemokine production and act in autocrine and paracrine manners to shape the tumor environment. The expression of various immune mediators and modulators as well as the abundance and activation state of different cell types in the tumor microenvironment dictate in which direction the balance is tipped and whether tumor-promoting inflammation or antitumor immunity will ensue.^{42,43} In established tumors, this balance is profoundly tilted toward protumor inflammation, since the tumor rarely regresses spontaneously without therapeutic intervention.

The primary immune cells found within the tumor microenvironment are tumor-associated macrophages (TAMs) and T lymphocytes.^{21,23,42,43} TAMs promote many important features of tumor progression, including angiogenesis, tumor cell invasion, motility, and intravasation as well as at the metastatic site, stimulation of tumor cell extravasation, and persistent growth.^{45,46} TAMs express an array of effector molecules that inhibit the antitumor immune responses; this includes cell surface receptors, cytokines, chemokines, and enzymes that can suppress CD4⁺ and CD8⁺ T-cell effector function directly or indirectly by recruitment of natural regulatory T cells to the tumor microenvironment, as well as by inducing the CD4⁺ regulatory fraction cells and sustaining their survival.⁴⁶ TAMs can also suppress T-cell activity

by the depletion of L-arginine in the tumor microenvironment. They also modulate therapeutic response and induce multidrug resistance.⁴⁷ Mature T cells are divided into two major groups based on the T-cell receptors they produce: $\alpha\beta$ and $\gamma\delta$. $\alpha\beta$ T cells are further classified into CD8⁺ cytotoxic T cells and CD4⁺ Th cells, including Th1, Th2, Th17, and T regulatory cells, as well as NK T cells with four different groups.^{22,42,43,48} Similar to TAMs, the tumor-promoting activity of T cells are mediated by cytokines, whereas both cytokines and cytotoxic mechanisms mediate the antitumorigenic function of T lymphocytes. TAMs and T cells in tumors may represent useful therapeutic targets for the development of new interventions.

The cytokines and chemokines produced by various effector cells in the tumor microenvironment play a critical role in tumor initiation and development.^{22,43} Different cytokines can either promote or inhibit tumor development, growth, and metastasis. Several cytokines, such as macrophage migratory inhibitory factor, TNF- α , IL-4, IL-6, IL-10, IL-12, IL-17, IL-23, and TGF-β, have been shown to either promote or inhibit tumor development.^{22,43} Malignant cells or inflammatory cells in the tumor microenvironment can produce TNF- α , and TNF- α signaling can promote cell survival, angiogenesis, progression, and metastasis. Other effects of TNF-a include impairment of immune surveillance through T-cell suppression and inhibition of the cytotoxic activity of activated macrophages. IL-6, a pleiotropic inflammatory cytokine, is considered a key growth factor for both malignant and immune cells.49,50 IL-6 acts intrinsically on tumor cells through numerous downstream mediators to support cancer cell proliferation, survival, and metastatic dissemination. IL-6 can also act extrinsically on other cells within the complex tumor microenvironment to sustain a protumor milieu by supporting angiogenesis and tumor evasion of immune surveillance.49,50 IL-10 is an immunosuppressive and anti-inflammatory cytokine that is also linked with inflammation-associated cancer. IL-12 is a cytokine that promotes cell-mediated immunity by promoting Th1-type cytokine responses, enhancing the lytic activity of NK/lymphokine-activated killer cells, augmenting specific cytotoxic T-lymphocyte responses, and inducing the production of IFN-y while it suppresses the development of Th2type cytokine responses and humoral immunity.⁵¹ IL-23 can activate STAT4 through IL-23 receptors distributed on the membrane of T cells, NK cells, monocytes, and dendritic cells; it is involved in the inflammatory response through promoting MMP-9, enhancing angiogenesis and suppressing CD8⁺ T-cell infiltration; IL-23 can induce and promote the differentiation of CD4⁺-naïve T cells to Th17 cells that produce IL-17A, IL-17F, IL-21, and IL-22.⁵¹ TGF- β can inhibit epithelial cell cycle progression and promote apoptosis, contributing to tumor initiation and progression inhibition, but TGF- β also promotes epithelial-to-mesenchymal transition that has been associated with increased tumor cell motility, invasion, and metastasis.^{52,53} Various cytokines can activate downstream effectors such as NF- κ B, STAT3/4, and SMADs, therefore controlling the immune and inflammatory milieu to either favor antitumor immunity or enhance tumor progression.^{12,22,42}

The biochemical mechanisms of how inflammation initiates and promotes tumor development is not fully understood. An inflammatory microenvironment can augment mutation rates and the proliferation of mutated cells. Activated inflammatory cells generate mutagenic ROS, reactive nitrogen intermediates, and other products that can induce marked DNA damage and genomic instability.^{22,24,25} Inflammatory cells may utilize proinflammatory cytokines such as TNF- α to stimulate ROS accumulation in neighboring epithelial cells. Cytokines offer malignant cells a continuous supply of growth and survival signals in an initially hostile microenvironment.^{42,43} A panel of growth factors and cytokines produced in the tumor microenvironment can confer a stem cell-like phenotype upon tumor progenitors or stimulate stem cell expansion, thereby enlarging the cell pool that is targeted by environmental mutagens. An inflammatory environment also promotes epithelial-to-mesenchymal transition. In most cases, cancer-promoting cytokines act in a paracrine manner, while some cancer cells produce their own cytokines (eg, IL-6).42,43

To date, there is enough evidence indicating that inflammation can influence every step of tumor initiation, development, and progression as well as the response to therapeutic intervention. In the past decade, we have learned a great deal about the complicated mechanisms by which cancer and inflammation interplay, and clearly we should consider inflammation as a new therapeutic target in cancer treatment. Modulation of inflammation may be also a useful approach to reduce cancer risk. Prevention is a much better and more economical way to fight cancer than treating an advanced disease. More studies are warranted to explore how inflammation induces and promotes tumorigenesis and if antiinflammatory therapies should be integrated into current cancer treatment regimens.

Because IL-17 plays an important role in the initiation and development of cancer, it represents an interesting target in cancer treatment. Anti–IL-17 monoclonal antibodies have been tested for the treatment of inflammatory autoimmune conditions, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease.54,55 In January 2015, the US Food and Drug Administration approved the use of secukinumab (trade name CosentyxTM), an IL-17 inhibiting monoclonal antibody, for the treatment of moderate-to-severe plaque psoriasis. Ixekizumab (anti-IL-17 monoclonal antibody) and brodalumab (IL-17RA monoclonal antibody) has been shown to be effective in the treatment of patients with moderate-to-severe plaque psoriasis. The anti-IL-12- and IL-23 antibody ustekinumab can also be used to effectively treat psoriasis by reducing IL-17.56 There is preliminary evidence from animal studies that inhibition of IL-17 can induce tumor regression.^{4,57} Further studies are certainly needed to explore the role of IL-17 in tumor biology, pathology, diagnosis, and treatment.

Disclosure

The authors have no conflicts of interest in this work.

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