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Th17 cells associated cytokines and cancer

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Abstract. – Cancer is one of the most common malignant tumors, which is a serious threat to human life. However, the etiology of cancer is not entirely clear. Under the action of tumorigenic factors, tissue cells lose normal regulation, resulting in abnormal proliferation and differentiation, so as to form a tumor. Cytokines promote the development of chronic inflammation, which may affect the development of cancer, and Th17 cells are a kind of immune cells which are closely related to the tumor. Therefore, this article focused on the role of Th17 cells and its related cytokines in tumor, which is very important for understanding the mechanism of tumor development. This will provide a direction for immunotherapy and gene-targeted therapy of cancer.

Key Words:
Th17 cell, IL-17, IL-21, STAT3, Cancer.

Introduction

Tumorigenesis is a multistage process. It is initiated by mutations that activate oncogenes or inhibit tumor suppressor genes[1]. However, tumor cells often need additional factors from the microenvironment to support their lives, maintain their growth, and lead metastases to distant organs. Cancer-associated fibroblasts and myofibroblasts, generate useful metabolites to sustain cancer progression, produce cytokines to improve cancer cells' invasiveness[2]. The tumor microenvironment, which is mainly composed of tumor cells, stromal cells, and tumor-infiltrating immune cells, is absolutely different from normal tissue environments. This unique microenvironment strongly inhibits immune responses against tumor cells by soluble mediators and contact-dependent mechanisms. It is well known that the immune cells have complex interactions in the tumor microenvironment[3,4].

Inflammation, Immunity and Cancer

Compelling evidence has shown that inflammation is important to tumor development through contribution to the proliferation, migration and survival of cancer cells. Those cells would result in tumor invasion and metastasis. There are two aspects that determine the direction of this malignant process, T lymphocytes and related cytokines modulate immune responses in the tumor microenvironment, the balance between destructive inflammation and protective immunity[5]. It was demonstrated without doubt that inflammation improves tumorigenesis through the activation of NF-κB and STAT3 pathway[6-8]. However, it is very clear that the immune system plays a dual role in cancer development and progression[9,10]. It can eliminate malignant cells. Meanwhile, it can actively improve the growth, invasion and metastasis of malignant cells[11]. It is thought that inflammation in the tumor microenvironment may have played critical roles in the tumor-associated immune response[12]. Intriguingly, immune responses have contradictory roles in tumor development. On the one hand, immune responses are critical to immune surveillance for prevention of tumor development. Numerous studies demonstrate that antitumor immune responses can prevent and eliminate tumors. On the other hand, immune responses, especially in a form of chronic inflammation, can help tumor development in many cases[13].

Source and Differentiation of Th17 Cells

A newly identified CD4+T cell subset, the Th17 cells lineage, which characterized by the production of IL-17, was described on the basis of developmental and functional attributes that are obviously different from those of classic Th1, Th2 and Treg cells lineages. It plays a significant role in inflammation, autoimmune diseases, as well as acute graft-versus-host disease[14,15]. Th17 cells are

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defined as CD4+T lymphocytes secreting massive amounts of interleukin 17A (IL-17A), expressing the transcription factor retinoic acid receptor-related orphan receptor gamma t (ROR-γt), which is likely to act as a molecular determinant for their polarization[16]. In addition, Th17 cells produce IL-21 and IL-22, depending on the differentiation/environmental conditions secrete variable amounts of TNF-β, IFN-γ, and/or GM-CSF[17]. Th17 cells help B lymphocyte-mediated immune response, make a contribution to the migration and activation of macrophages, neutrophils. They also regulate the activation and expansion of CD8+T cells[18-21]. One of the most distinct characteristics of Th17 cells is their high degree of plasticity and their prominent capability to boost other cells, whether pro-inflammatory effector cells such as Th1 or immunosuppressive FoxP3+ Treg cells[22].

Recent work suggests that mouse and human Th17 cells' differentiation are both dependent on the transcription factor ROR-γt, but there is no agreement at present on the cytokines that improve their differentiation. Hirota et al[23] has clearly recognized that IL-6 and transforming growth factor beta (TGF-β) as Th17-promoting cytokines in mice. While *in vitro* experiments, it has also indicated that IL-1β, IL-6 and IL-23 are necessary for the differentiation of human Th17 cells.

It is proved that IL-1β has a significant role in mouse Th17 cells' differentiation, the differentiation of human Th17 cells required low doses of TGF-β, while high doses of TGF-β can inhibit both human and mice[24]. Acosta-Rodriguez et al[25] found that human Th17 cells originated in response to the combined activity of IL-1β and IL-6, while Wilson et al[26] shown that the activity of IL-1β or IL-23 alone was crucial. In addition, cytokines alone cannot improve the generation or differentiation of Th17 cells from naive CD4+T cells. In the case of IL-1β, IL-6 and IL-23, the presence of any two of the three or all three are there, Th17 cells grew faster[27]. Th17 cells' development was considered to rely on a combination of transforming growth factor-β (TGF-β), IL-6, and IL-21[28,29]. Nonetheless, IL-4 can suppress Th17 cells development independently of IFN-γ[30]. Their data also showed that unlike naive CD4+T cells, mature Th17 effector cells can resistant to the inhibitory effects of IFN-γ and IL-4. Therefore, the inhibitory effect of IFN-γ and IL-4 on Th17 cells would probably play an important role in the early stage of the Th17 cells differentiation process.

The differentiation of Th17 cells requires the expression of ROR-γt[31]. The transcription of ROR-γt leads to up-regulation of IL-17A and IL-17F. ROR-γt identified as a Th17-specific transcriptional regulator. When IL-6, IL-21 and IL-23 presents, the expression of FoxP3 is restrained while RORγt expression is induced, leading to produce the Th17 cells rather than Treg cells. Some studies have proved that STAT3 activation, neither STAT4 nor STAT6 signaling is central to both mice and human Th17 cells' development[32]. STAT3 acts as the major IL-6 receptor-dependent transcription factor in the Th17 cells' development. As STAT3 plays an irreplaceable role in tumor-associated inflammation and IL-23 has been implicated in the promotion of tumor growth, it is conceivable that Th17 cells could be involved in carcinogenesis[33,34]. Nevertheless, the role of TGF-β in Th17 cells polarization has been in questions. Although TGF-β is necessary for the production of IL-17 by Th17 cells, it may not be essential for the Th17 induction[35]. Thus, more in-depth studies are needed to determine the role of TGF-β in the differentiation of Th17 cells.

Th17 Cells and Cancer

Newly discovered CD4+ IL-17+ cells, also named Th17 cells can generate the cytokine IL-17, which has been proved to play an essential role in the pathogenesis of autoimmune disorders and infectious diseases[36,37]. It is proposed to be related to tumor pathogenesis and progression of multiple types of cancers, including lung cancer, breast cancer and pancreatic cancer[38-40]. Although the mechanism of Th17 cells to promote tumor growth was still not clear. The increase of Th17 cells in the tumor microenvironment is gradually becoming treated as one of cancers' general characteristic[41]. Tumor cells can proliferate infinitely, evade apoptosis, promote angiogenesis, invade tissues, and metastasize. At the same time, the non-tumor components in the tumor microenvironment can contribute to regulating these complicated processes[42]. Immune cells are one of the most significant components of the tumor microenvironment. A lot of evidences illustrated that the number of tumor infiltrating lymphocytes in the microenvironment of certain tumor types is related to the prognosis of cancer patients. CD4+ T cells play a significant central role in regulating the immune response by coordinated the functions of other immune cells. It has been advised that Th17 cells themselves do not have the ability to kill tumor cells directly. Th17 cells

stimulate tumor residential cells to generate CCL2 and CCL20, which propels the recruitment of dendritic cell, granulocyte, CD4+ T cell, CD8+ T cell, and NK cell to the tumor site to perform the killing effect[43].

Th17 lymphocytes represent a highly heterogeneous cell population that can flexibly differentiate into immunosuppressive Treg cells or effector pro-inflammatory Th1 cells, depending on the environment[44]. Since Treg cells can inhibit anti-tumor immune responses and further promote the development of a tumor, while Th1 cells can enhance anti-tumor immunity, therefore Th17 cells have been reported to exhibit both pro- and anti-tumor biologic activities. In theory, Th17 cells can play the following two opposite roles. Some show a positive effect that Th17 cells are involved in tissue inflammation through the induction of surrounding cells like fibroblasts, macrophages, endothelial and epithelial cells. These surrounding cells can release cytokines such as IL-8, IL-6, COX-2, MMP-1, MMP-3, CXCL1, NOS-2. They are also involved in angiogenesis, tumor proliferation, invasion and metastasis. While others depict an inhibitory influence of Th17 cells on tumor growth[45].

Although the results of studies show that the roles of Th17 cells in the carcinogenesis is still conflicting, the emerging data show that not all Th17 cells play a role in the same way[46]. Wakita et al[47] has illustrated that γδ T cells, rather than αβ T cells, were the major cellular source of IL-17. IL-17 produced by tumor-infiltrating γδ T cells improves tumor development by inducing angiogenesis. It was reported that although the differentiation processes of Tc17 cells and Th17 cells are different, they have a similar developmental pathway[48]. For instance, TGF-β, IL-6 and IL-21 could stimulate the differentiation of both Tc17 and Th17 cells. In addition, studies have demonstrated that Tc17 cells may display suppressed cytotoxic function, which is similar to the function of Th17 cells in autoimmune diseases, infection and antitumor immunity.

Functions of Interleukin-17

IL-17 was first cloned in 1993 and identified as cytotoxicity T lymphocyte-associated antigen (CTLA)-8. Along with the research, it is newly defined as a pro-inflammatory cytokine which is mainly produced by activated CD4+ T-helper cells (also known as Th17 cells), macrophages and CD8+T cells[49]. However, the results of some studies have shown that γδ T cell is a significant source of IL-17. These cells are also shown to express IL-23R and also secrete IL-21 and IL-22[50]. The IL-17 family has six members, IL-17A, B, C, D, E, F, respectively. A major mechanism of IL-17 to regulate the expression of target gene is the activation of NF-κB[51].

Since IL-17 can induce tumor cells and stroma cells to secret IL-6, the activation of STAT3 induced by IL-6 was proposed as a pro-tumor mechanism of IL-17[52]. Thus, the role of IL-17 in the development of tumor may be determined by the tumor microenvironment and the stage of tumor development. Th17 cells and IL-17 have been considered to be a poor prognostic indicator in many cancers and a favorable prognostic indicator in other cancers[53-56]. Some researches proved that at least in the presence of IL-6, TGF-β and IL-23, human γδ T cells differentiated into IL-17-producing cells. However, it has been demonstrated that CD4+T cells were the main cellular source of IL-17 in human ovarian cancer tissues[57]. Thus, for human beings, it is possible that the IL-17-producing cell subsets may vary among organs for different types of cancer.

Even though IL-17 has been identified in many tumors, the exact role of IL-17 in carcinogenesis and tumor progression is still controversial. Many studies have shown that IL-17+T cells get enriched in the tumor microenvironment. It's believed that the expression of IL-17 increased in several human tumors, such as esophageal cancer, gastric cancer, hepatocellular carcinoma, breast cancer, ovarian cancer and prostate cancer[58-62]. More importantly, IL-17 promotes tumor-cell proliferation and migration *in vitro*, promotes tumor-cell growth *in vivo*. Nonetheless, the fact that IL-17 and IL-17-producing cells were found to be effective against tumor in colon, ovarian cancer, and acute leukemia patients[63,64]. These inconsistent findings may vary depending on the tumor microenvironment, Th17 cells with different heterogeneity and different stages of the diseases.

It has been reported recently that IL-17 promotes tumor growth through angiogenesis[65]. The levels of IL-17 positively correlated with STAT3 activity in tumors. Further, IL-17 promotes STAT3 activation in tumors cells, leading to a rise in anti-apoptotic and angiogenic genes. IL-17 induced the activation of STAT3 in tumor cells through an intermediary factor, not a direct effect[52]. Besides that, IL-17 prohibits tumor growth through the antitumor immune response in immunocompetent mice. It remains disputed

whether IL-17 improves or prohibits cancer progression. The combination of IL-17 and IFN-γ increases the secretion of potent anti-angiogenic factors such as CXCL9 and CXCL10 by cancer cells. The levels of CXCL9 and CXCL10 were related to effector T cells and promoted the good prognosis in patients with ovarian cancer[66]. However, IL-17 induces tumor cells to produce IL-6, which in turn promotes tumor growth in a STAT-3-dependent pathway[67]. IL-17 is involved in angiogenesis. IL-17 up-regulates production of various angiogenic factors, such as vascular endothelial growth factor (VEGF), prostaglandin E1 (PGE1), PGE2 and macrophage inflammatory protein-2 (MIP-2) by fibroblasts and tumor cells. IL-17 also promotes angiogenesis through stimulation of vascular endothelial cell migration, leading to tumor progression. The microvessel density and other angiogenic factors such as VEGF and PGE1 are related to tumor development and progression. These factors are the indictors of survival in patients with gastric cancer.

The Role of Interleukin-21 in Cancer

IL-21 is a pleiotropic cytokine that binds to the IL-21 receptor (IL-21R). It comprises of the common cytokine receptor γ chain and the specific IL-21R subunit[68]. It is not only produced by Th17 cells, but also by follicular helper T (Tfh) cells and natural killer (NK) T cells. The IL-21 receptor is expressed by various directed hematopoietic immune cells, including T cells and B cells, NK cells and dendritic cells (DCs), as well as on tissue cells including endothelial cells and fibroblasts[69]. IL-21R is dominantly produced by B cells. It shares the common cytokine receptor γ chain with IL-2 family cytokines. Those cytokines include IL-4, IL-7, IL-9, and IL-15. In addition to its γ chain, IL-21R contains a different α-chain[70]. In NK cells, IL-21 can stimulate cell propagation and the expression of effector molecules. Further, it can extend the life of NK cells by inducing the expression of telomerase[71-73].

What attracts people is that IL-21 also acts as an autocrine cytokine of activated T cells. It induces the differentiation of both human and murine naive CD4+T cells into Th17 cells when transforming growth factor-β presents[74]. The mechanism of IL-21 promoting the differentiation of Th17 cells is to induce the expression of IL-23R as that of IL-6. IL-21 can effectively regulate both innate and adaptive immune responses. It possesses broadly pleiotropic functions. It has been linked to autoimmune disorders, allergies, and inflammatory diseases. Moreover, many researchers have intensively studied the role of IL-21 in the pathogenesis of cancer. It has been found that the expression of IL-17, IL-21 and IL-23 mRNA is largely up-regulated in tumor tissues compared with adjacent normal tissues. What's of vital importance is that, the expression level of IL-21 mRNA in tumor tissues demonstrated a strong correlation with that of the IL-17 mRNA. Those researchers also tested other cytokines such as TGF-β and IL-6, but did not find a correlation as strong as that of IL-17 and IL-21[75].

Signal Transducer and Activator of Transcription 3 (STAT3) and Cancer

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor which has a crucial role in many fundamental cellular processes including cells growth, development and homeostasis. Under physiological conditions, various growth factors or cytokines can activate STAT3 mediated by receptor-associated JAK kinases, as well as by non-receptor Tyr kinases[76]. STAT3 is produced by different subsets of activated CD4+T cells and NK-T cells. It plays a role in a variety of cells, including the enhancement of the immune response to adaptive T cells, antibodies production, and NK cells maturation and activation[77].

The activation of STAT3 correlates with IL-22 transcript expression in CD4+ T cells. STAT3 is necessary for the development of Th17 cells and the differentiation of Th17 cells in early stage[78]. The lack of activation of STAT3 not only affects the expression of IL-22, but also interferes with the number of CD3+ CD4+ RORγt+ IL-17+ IL-22+ cells (Th17 cells)[79].

STAT3, as the main IL-6 receptor-dependent transcription factor, can promote the development of human and mouse Th17 cells after its activation. STAT3 gene mutations can cause Th17 cells deficiency in humans. Targeted knockout of STAT3 gene in T cells completely inhibits the development of Th17 cells in mice[80]. However, STAT3 also drives a negative-feedback loop that restricts the formation of IL-17–producing T cells. This negative-feedback loop may act as a protective mechanism to prevent excessive proliferation of Th17 cells in inflammatory responses[81]. In the local tumor microenvironment, STAT3 activation leads to the expression of pro-inflammatory cytokine IL-23. The elevated

levels of IL-23 were related to a poor prognosis of many human carcinomas[82,83]. For example, high serum levels of IL-23 can be detected in patients with breast cancer and the survival rate is low[84]. STAT3 activation in tumor cells and tumor-associated inflammatory cells is of vital importance in tumor progression. It would promote tumor angiogenesis, suppressing antitumor immunity and prolong tumor survival. Therefore, we can regard the STAT3-signaling pathway as a potential target for therapeutic intervention in autoimmunity, chronic inflammatory diseases and cancer.

Other Cytokines

Hirano et al (Nature 1986; 324: 73-76) Kishimoto discovered Interleukin-6 (IL-6) in 1986 as a B cell stimulatory factor driving IgG production. IL-6 is one of the important factors in the synthesis of acute phase reactive proteins, such as C-reactive protein. However, Yang et al[85] clearly demonstrated that another major role of IL-6 is to regulate the differentiation and activation of T cells. They have recognized IL-1β and IL-6 as the initial cytokines for the activation of human Th17 cells. IL-6 is a STAT3 activator and is elevated in various types of cancers. IL-17 has been reported to stimulate inflammatory cells as well as fibroblasts to product IL-6 and activation STAT3 by a positive feedback loop[86]. Experiment results proved that IL-6 is expressed in breast cancer patients, the expression levels of this cytokine are positively linked to the number of Th17 cells. In the breast cancer microenvironment, IL-6 may improve differentiation and expansion of Th17 cells[87].

The discovery of IL-23 in 2000 was dependent on the computational detection of p19, which is a new sequence with homology to IL-6[88]. IL-23 is an IL-12 family cytokine including two different subunits, one is the p40 subunit shared with IL-12, and the other is the unique subunit p19. Initial differentiation of Th17 cells requires the stimulation of IL-6 and TGF-β, while IL-23 is not only widely regarded to be essential for Th17 cell survival and expansion, but also important to the pathogenesis of Th17 cells[74]. Actually, IL-23 has been found to over-express in various types of tumors, including lung, breast, colon and ovarian cancers. It's able to stimulate angiogenesis by up-regulating the expression of IL-17 and matrix metalloproteinase 9 (MMP9). On the contrary to the pro-tumor effects of IL-23, several reports have depicted that IL-23 has anti-tumor effects. Overexpression of IL-23 in tumor cells inhibited tumor growth and metastasis. It is probably that the functions of IL-23 in tumor progression may rely on the types of tumors, the immune status of the host, and the source of IL-23 being produced[89].

Conclusions

Tumor development is a complex and dynamic process. The presence and interaction of stromal cells, endothelial cells, lymphocytes and other cells in the tumor tissue constitute the tumor microenvironment. Inflammation and cytokines produced by inflammatory cells are thought to be significant components of tumor microenvironment. CD4+T cells are key components of cellular immunity and they are almost participated in all stage of immune response. Uncommitted (naive) CD4+ T cells can differentiate into specific lineages, such as Th1, Th2, Th17 and Treg, by the effect of different local cytokine milieu[90]. Moreover, human Th17 cells express the transcription factor retinoid-related orphan receptor (ROR)-γt and generate the pro-inflammatory cytokine IL-17. IL-17 seems to be able to coordinate and regulate local inflammation through up-regulation of other pro-inflammatory cytokines and molecules. These cytokines and molecules control immune functions in a complex, tightly regulated enviroment. Perturbations of this network may result in immune dysfunction, chronic inflammation and ultimately carcinogenesis[91].

Since Th17 cells are the pathogenic of many chronic inflammatory diseases, it is of vital importance for us to understand how these cells are regulated by each other. Although increasing amount of IL-17-producing T cells have been found within certain tumors, whether IL-17 promotes or inhibits cancer progression is still disputed. Thus further investigations are needed to more clearly understand the polarization process of Th17 cells in tumor.

Statement of Interests

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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