Role of Th17 Cells in Tumor Immunity: A Double Edged Sword

Yan Wang¹, Changle Chen²

Abstract

Objectives: Th17 cells are another CD4+ T cell group after the discovery of the Th1, Th2 cell subsets, which can secrete IL-17A and IL-6. Th17 cells play a role in autoimmunity, inflammation and maintaining immune stability. Seldom studies are about the role of Th17 in tumor, research progress of Th17 cells in tumor immunity was described in this paper. Methods: we search the latest research in the world related to progress of Th17 cells in internet, and describe the progress of Th17 cells in tumor immunity. Results: The role of Th17 cells in tumor immune response is diverse. Some researchers have found that Th17 plays an anti-tumor immune response, while in other studies. Th17 cells play the opposite role. The role of Th17 cells in the local tumor seems to have two sides. Conclusions: The role of Th17 in tumor immunity is not very clear until now. Conflict idea exists in research reports. Are Th17 cells exerting regulatory roles in tumor site like Treg cells? It remains to be explored further. With more scientists in the field of Th17 research, the role of Th17 cells in tumor immunity will be further revealed.

Key words: Th17 cells; Tumor; Immunity.

1 Introduction

Th17 cells, the production of a distinct profile of effector cytokines, including IL-17 (or IL-17A), IL-17F, and IL-6, and have probably evolved to enhance host clearance of a range of pathogens distinct from those targeted by Th1 and Th2. Th17 cells produce IL-17, can cause inflammation in tissue[1 2]. The function in maintaining stability and inflammatory has been gradually known by people. More and more studies were about the protection effect of mucosal surfaces against pathogenic microbes (viruses, fungi and bacteria).

2 Th17 differentiation

Th17 cells develop via a pathway separate from Th1 and Th2, but with several notable parallels to the Th1 lineage that have led to some confusion over the role of the Th1 cells in autoimmunity. TGF-β has double function in differentiation of Th17 and Treg cells, which establishes a link between Th17 and Treg. TGF-β is necessary for differentiation of both Th17 and Treg cells, but at the presence of IL-6 it can inhibit the production of TGF-β induced Foxp3+ regulatory T cells, while promote the growth of Th17 cells[3-4]. Kuchroo and coworkers on also found that Treg cells can be transformed into Th17. TNF-α, also play important role in polarization of Th17 cells. TGF-β has a dual function in T cell polarization by directing the differentiation of both Th17 cells and Tregs pending the polarizing cytokines. TNF-α, present within the tumour microenvironment, has also been implicated in Th17 polarization[5].

¹School of Medical Instrument and Food Engineering, University of Shanghai for Science and Technology, Shanghai 200093, P. R. China
²Shanghai Qigong Institute, Shanghai 200030, P. R. China
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In the malignant tumor, fibroblasts and antibody secreting cells (APCs) secrete a large number of cytokines IL-1β, IL-6, IL-23, TNF-α and TGF-β, is the key cytokine of Th17 cell differentiation and proliferation. Under the action of TGF-β, IL-6, or T, IL-21 cells differentiate into Th17 cells, secreting expression of IL-17 and IL-21 and ROR.

### 3 Th17 cytokines-IL-17A
IL-17A is the hallmark cytokine of Th17 cells and along with IL-17F, with which shares the greatest homology, is also produced by γδT cells, natural killer (NK) T cells, neutrophils and eosinophils[6-7]. IL-17A/F signals through IL-17RA, a type I transmembrane protein ubiquitously expressed[8]. IL-17RA activates mitogen activated protein kinases (MAPK) and nuclear factor-kB (NF-κB) via TNF receptor associated factor-6 (TRAF6) and has also been found to physically associate with the NF-κB activatory protein (Act1) (Shalom-Barak et al., 1998; Schwandner et al., 2000). Knock down of Act1 was subsequently shown to abrogate IL-17 induced inflammatory gene expression as well as NF-κB activation[9].

A large body of evidence suggests that IL-17A and IL-17F mediate local tissue inflammation by inducing the release of pro-inflammatory and neutrophil mobilizing cytokines and chemokines.

In vitro experiments have shown that IL-17A and F stimulate the production of several CXC chemokines, CXCL1, CXCL2 and CXCL5 in mouse fibroblasts and epithelial cells IL-17 has been well studied over recent years in inflammatory diseases, but what about its role in tumour development and malignant progression? IL-17A expression has been detected in several human tumours including prostate, breast and gastric cancer[10-12]. However, the specific role of IL-17 in cancer is still elusive.

### 4 Relationship with Th1, Th2, and Treg
As a basis for understanding recent advances in Th17 development and function, we first highlight features of Th1, Th2, and Treg development and function for comparison. For Th1, Th2, and Treg lineages, key transcription factors have been identified that specify the genotypic and phenotypic characteristics of these lineages. Thus, T-bet specifies Th1, GATA-3 specifies Th2, and Foxp3 specifies Treg development. Is there an analogous factor that links TGF-β and IL-6 signaling to Th17 development?

Almost certainly, therefore, the Th17 lineage evolved to control certain classes of pathogens not covered by Th1 and Th2. Given the growing association of IL-23 and/or IL-17 to host protection in a number of bacterial infection models, it is likely that Th17 cells evolved to cope with a range of extracellular bacterial pathogens[4-13] as well as to contribute to homeostatic maintenance of mucosal tissues such as the gut, which are colonized by abundant commensal bacterial species. Researchers found that DLL4+DC can promote the differentiation of Th17 and Th1 cells[14].

Tregs are found at high frequencies in the tumour microenvironment and have been shown to have a critical role in hampering anti-tumor immunity[15]. More interestingly, the Th17 and Treg differentiation programs are reciprocally related. This suggests a dynamic interaction between Treg and Th17 cells in the tumor microenvironment. Indeed, several studies have shown that naive (CD45RO−) and memory (CD45RO+) Tregs can be induced to secrete IL-17 in the presence of IL-2, IL-1β, IL-6, IL-21, or IL-23[16].

In line with the notion of a Treg-Th17 transition at tumor sites, a subpopulation of CD4+Foxp3+IL-17+
cells can be detected in humans. These cells co-express CD25, Foxp3, IL-17 and RORγt and maintain a suppressive function via a cell-cell contact mechanism. Whether these coexpressors derive from Treg or Th17 cells has not been demonstrated but they appear to represent a transition stage between Treg and Th17 cells. The plasticity of Tregs and the cytokine milieu at tumor sites may therefore allow an initial shift towards the IL-17 producing subpopulation and subsequently the development of Th17 cells. Cytokines in tumor loci such as IL-6, IL-1 and TGF-β can affect the differentiation of Treg cells and Th17 cells, that is, more Treg cells or more Th17 cells in tumor environment.

The remarkable balancing act of adaptive immunity-how to facilitate the targeted destruction of pathogens without excessive collateral damage to self-is nowhere better exemplified than in the shared use of TGF-β in controlling the newly described Th17 effector lineage and adaptive Treg development. It is perhaps fitting that TGF-β should be central to this yin/yang interplay, given its complex and often apparently inconsistent biology[17].

Several animal and human studies have implicated CD4+ T helper 17 (Th17) cells and their downstream pathways in the pathogenesis of central nervous system (CNS) autoimmunity in multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD), challenging the traditional Th1-Th2 paradigm. Th17 cells can efficiently cross the blood-brain barrier using alternate ways from Th1 cells, promote its disruption, and induce the activation of other inflammatory cells in the CNS[18].

5 The conflict role Th17 cells in tumor immunity
Conflicts in the literature concerning whether Th17 cells actively enhance or inhibit the progression of tumours are more likely to be apparent than real. The biological impact of Th17 cells will depend critically on the cancer analyzed, and the source of tissues under analysis and will be the resultant of two principal opposing effects. The first is that Th17 cells in vivo are capable of significant levels of polarization and this is well established in the case of Th1/Th17 cells; these cells appear to promote an anti-tumour effect by enhancing adaptive immunity against tumour antigens. Polarisation to FoxP3-positive Tregs has also been demonstrated in vitro, but the extent to which this occurs in human cancers is currently unknown. Studies have indicated that the increase of Th17 cells in tumor loci is related to the high expression of CXCR4, CCR6 and Th17 in CD161 cells, which play an important role in the migration of Th17 cells to the tumor microenvironment[19].

5.1 Promote tumor growth
The high expression of IL-23A is associated with GC. IL-23A can promoted GC cells growth by inducing the secretion of IL-17A in tumor microenvironment. Our results suggest that the serum concentration of IL-23A is a good biomarker of poor clinical prognosis in GC patients[20].

53 patients with hypopharyngeal cancer were included. The expression levels of Th1-, Th2- and Th17-associated cytokines in hypopharyngeal cancer tissues and pericarcinoma tissues were detected. The relationship between Th1, Th2, or Th17 infiltration and metastasis was studied. Our results showed that the mRNA and protein expressions of Th1 cytokines were lower, while the expressions of Th2 and Th17 cytokines were higher in tumor tissues, and the intensity of expression was strengthened with clinical stage increasing. Cancer tissues had higher level expressions of Th2 and Th17 cytokines than that of pericarcinoma tissues. From the above data, we speculated that high expressions of Th2- and Th17-associated cytokines in hypopharyngeal carcinoma may contribute to cancer development and metastasis[21]. Scientists reported that in a diethyl nitrosamine (DEN) induced hepatocellular carcinoma
mouse model, IL-17A deficient (KO) mice have 20% less tumor incidence than wild-type mice. Th17 cytokine-IL-17A plays important role in development of hepatocellular carcinoma[22]. In a study of gastric cancer, scientists found that the cytokine IL-17 secreted by Th17 cells can promote tumor angiogenesis by activating angiogenic factor VEGF[23]. The high expression of IL-23A is associated with GC. IL-23A can promoted GC cells growth by inducing the secretion of IL-17A in tumor microenvironment. The results suggest that the serum concentration of IL-23A is a good biomarker of poor clinical prognosis in GC patients[24].

5.2 Inhibit tumor growth

In a ladder cancer recurrence research, scientist found the recurrent incidence in patients with Th17/Treg ratio 〈1 was higher than those ratio 〉 2. The results shows Th17 can delay tumor recurrence and inhibit tumor growth in tumor environment[25].

6 Conclusion

Through searching and reading the related papers of Th17 cells. The role of Th17 cells in tumor immunity was discussed. The role of Th17 in tumor immunity is not very clear, the present research reports were conflicting results, whether Th17 cells in the tumor plays an important regulatory role like regulatory Treg cells remains to be explored further. With more scientific research workers entering in the field of Th17 research, the role of Th17 cells in tumor immunity will be further revealed.

References


