Cellular Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review article

The paradox of Th17 cell functions in tumor immunity

Zahra Asadzadeh[a,b,1], Hamed Mohammadi[a,b,1], Elham Safarzadeh[a,b], Maryam Hemmatzadeh[a,b], Ahmad Mahdian-shakib[c], Farhad Jadidi-Niaragh[a,b], Gholamreza Azizi[d,e], Behzad Baradaran[a,b,*]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[d] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[e] Department of Laboratory Medicine, Imam Hassan Mojtaba Hospital, Alborz University of Medical Sciences, Karaj, Iran

ARTICLE INFO

Keywords:
Th17 cells
IL-17 cytokine
Pro-tumor
Anti-tumor
Angiogenesis

ABSTRACT

Immune system acts as a host defensive mechanism protecting against attacking pathogens and transformed cells, including cancer cells. Th17 cells are a specific subset of T helper lymphocytes determined by high secretion of IL-17 and other inflammatory cytokines. Th17 cells increase tumor progression by activating angiogenesis and immunosuppressive activities. They can also mediate antitumor immune responses through recruiting immune cells into tumors, stimulating effector CD8+ T cells, or surprisingly by altering toward Th1 phenotype and producing IFN-γ, so Th17 cells are supposed as a double-edged sword in cancer. A comprehensive approach to indicating the activity of Th17 cells in tumor progression could help in the planning of new therapeutic approaches specially targeting Th17 cells in cancer.

1. Introduction

CD4+ T helper (Th) lymphocytes act as a crucial factors for the arrangement of immune responses because they are able to regulate the function of CD8+ cytotoxic T lymphocytes (CTLs) [1,2], B cells [3], NK cells [4], macrophages, and dendritic cells [5,6]. About 20 years ago, it was found that CD4+ T helper cells are separated into Th1 or Th2 subsets with diverse cytokine profiles and roles [7]. Th1 cells usually secrete interferon (IFN)-γ and their role in autoimmune diseases and immunity against intracellular pathogens is clear. Th2 cells produce interleukin IL-4, IL-5, and IL-13 and take part in humoral immunity against parasites and in allergic reactions [8–10]. Moreover, CD4+ Th cells can be changed into T regulatory (Treg) cells and express forkhead box P3 (FoxP3) transcription factor. They show an anti-inflammatory function and retain tolerance to self-components by contact-dependent prevention or by producing anti-inflammatory cytokines like transforming growth factor (TGF) β, IL-10 [11–14]. The recognition of T helper 17 (Th17) cells, as a third group of T helper cells, altered the typical Th1/ Th2 pattern of T helper cell development [15,16]. Compared with other T-cell lineages, Th17 cells are described through their production of IL-17, expression of special transcription factors, and the performance of particular biological activities [17–19].

Although Th17 cells are important in the pathogenesis of autoimmune diseases and in infectious immunity, the role of these cells and their unique cytokines on cancer growth is still ambiguous. Several studies have indicated that Th17 cells can show antitumor and tumor-promoting properties [20,21]. Th17 cells produce high level of IL-17 that have close association with tumorigenesis. This cytokine can both heighten natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) function to create antitumor effects and increase tumor development through activating tumor angiogenesis, while the definite role of IL-17 in tumorigenesis is not clear yet [22].

In this review, we will investigate the phenotype, generation and role of these cells, concentrating on their production of cytokines, plasticity and on their interactions with other immune cells in the tumor milieu. As a final point, we consider the clinical correlation of Th17 cells in tumor immunology and underline their therapeutic potential.

2. Differentiation and function of Th17 cells

A third lineage of effector T helper cells, called Th17 cells, different from the IFN-γ-producing Th1, IL-4-producing Th2 was identified in 2005 [15,16]. The expansion of Th17 cells is separate from the expansion of Th1, Th2 and regulatory T (Treg) cells. Transcription factors of Th17 cells are unique and their expansion need to different cytokines

* Corresponding author at: Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail address: baradaranb@tbzmed.ac.ir (B. Baradaran).
[1] Zahra Asadzadeh and Hamed Mohammadi contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.cellimm.2017.10.015
Received 29 October 2017; Accepted 29 October 2017

[23]. Th17 cells develop from naïve CD4+ T cells and TGF-β, IL-6, and IL-1β are necessary cytokines for their development and IL-21 and IL-23 are required for their maintenance [24]. Th17 cells have the ability to produce IL-17A, IL-17F, IL-21 IL-22, and CCL20 [17,25]. Th17 cells express RORγt as the first transcription factor [26]. Gene profiling analysis of Th17 cells demonstrates that high expression of RORγt correlates with increasing Th17 differentiation and significantly up-regulation of IL-17, while low expression of RORγt notably reduces the level of IL-17 [26,27]. Yang et al. showed that RORα was over-expressed in Th17 cells [28]. Although loss of RORα had no significant impact on IL-17 production, a defect in both RORγt and RORα entirely suppressed IL-17 production and entirely prevented EAE disease. This indicates that the two receptors synergistically increase the differentiation of Th17 cells [29]. Moreover, STAT-3, the main signal transducer for IL-6, IL-21, and IL-23, was recognized as a vital transcription factor that modulates the development of Th17 cell lineage [30,31]. Another transcription factor that is important in the differentiation of Th17 cells, is interferon regulatory factor 4 (IRF4) that acts not only through the conventional IL-6 and TGF-β pathway but also through the IL-21-mediated pathway [32,33]. Additionally, it was demonstrated that aryl hydrocarbon receptor (AHR), a ligand-dependent transcription factor, plays a main role in the differentiation of Th17 cells [34,35]. Moreover, Ets-1, STAT-5, and the suppressor of cytokine signaling 3 (SOCS3) were shown to negatively control Th17 cell differentiation [36,37]. Th17 cells form ~0.1 to 0.5% of circulating CD4+ T cells in healthy people and their role in clearance of extracellular pathogens are central. Furthermore, they are responsible for the pathogenesis of several immune-mediated diseases, including psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma [38]. Th17 cells promote B lymphocyte-mediated immunity [3], participate in the migration and stimulation of macrophages [39], neutrophils [40], and adjust the activation and development of CD8+ T cells [41,42]. Studies represent a relation between the activity of Th17 cells and the environmental agents, such as toxins and ultraviolet light. The ligand-dependent AHR transcription factor stimulates the differentiation of Th17 cells [35,43]. Some ligands include hydrocarbons, such as dioxins, which are toxic chemical compounds can trigger AHR [44]. According to several studies, the attachment of these toxins, as well as other dietary compounds to AHR, leads to its activation and can cause the differentiation of Th17 cells [45]. Specially, binding of dioxins to AHR augment the production of IL-22, IL-17A, and IL-17F by Th17 cells and can intensify autoimmunity. Besides environmental toxins, exposure to ultraviolet light can also influence the Th17 milieu. It is demonstrated that Phototherapies by means of UV light have a helpful effect in the controlling of aggravating skin diseases such as psoriasis and atopic dermatitis [46,47]. According to previous studies, UV treatment decreases the amount of IL-17 and IL-22 in psoriasis patients [48]. These results show that the environment can influence Th17 cells. Additionally to the formerly stated properties, the expression of dipeptidyl peptidase IV, called CD26, is increased on the Th17 cells surface [49]. CD26 is a multifunctional ectoenzyme that has several various roles in the stimulation and function of T cell [50]. Remarkably, high expression of CD26 on the surface of Th17 cell can induce the production of large amount of IL-17A, which is the hallmark cytokine of Th17 cells [51]. Furthermore, CD26 up-regulation associates with disease activity in human autoimmune manifestations related to the existence of pathogenic Th17 cells, such as rheumatoid arthritis [50], and diabetes [52]. In addition to high expression of the inducible costimulator (ICOS), the IL-23 receptor (IL-23R), and chemokine receptor 6 (CCR6), increased CD26 expression separates Th17 cells from other human T cell lineages [53,54].

3. Th17 cells and cancer (IL-17 function in cancer)

Cancer, as stated by the World Health Organization, is still one of the significant reasons of mortality in the world [55]. Th17 cells show different functions. These cells have important roles in autoimmunity [15,56,57]. They can also promote host protection against infectious pathogens, including definite bacteria, fungi, viruses and protozoa. Moreover, these cells have the ability to maintain barrier immunity at mucosal surfaces, such as the gut, lungs and skin. On base of this, the prevalence of Th17 cells in the mucosal tissues of healthy people is significant [58,59]. Accumulating evidence recommends a close relation of chronic infection and inflammation with tumorigenesis. Recruitment of diverse immune cells, such as αβ T cells, γδ T cells, and natural killer (NK) T cells that have central roles in tumor immunity, occur by local inflammation in the tumor microenvironment [60]. So, the existence of Th17 cells as significant players in the immunopathogenesis of inflammation in a tumor microenvironment, are predictable [61]. Th17 cells are present in many various types of human tumors, including lymphoma [62], myeloma [63], breast cancer [64,65], colon cancer [66,67], gastric cancer [68,69], hepatocellular cancer [70,71], melanoma [64,70], ovarian cancer [39,70,72], pancreatic cancer [70], and prostate cancer [73,74]. Interleukin-17 (IL-17), the most important cytokine of Th17 cells is a proinflammatory cytokine that plays a part in different diseases, including infectious diseases, autoimmune disorders and cancer [22,75,76]. The IL-17 family of cytokines consists of six family members (IL-17A-F) [77]. Although, IL-17A and IL-17F are mainly produced by CD4+ Th17 cells, it should be considered that γ δ T cells [78], natural killer (NK) T cells [79], CD8+ T cells [80], macrophages [81], neutrophils, and eosinophils can produce IL-17 [82]. IL-17 signals through connecting to its transmembrane receptor. To date, it has been recognized that human IL-17 receptor family have five members, defined as IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE [83]. IL -17 cytokines have important roles in cancer and different studies have been done about these cytokines. Although the important role of IL-17A in intestinal tumorigenesis and colorectal cancer (CRC) is well-known, enough information about the function of other IL-17 family members is not available. Al-Samadi et al. studied tissue expression of these cytokines and their receptors in sporadic CRC vs. healthy control. Although IL-17B was augmented in CRC, IL-17C revealed different expression on the basis of the grade of differentiation and IL-17E remained unchanged. In the opposite direction, IL-17F was reduced in CRC compared to healthy control. IL-17RA, IL-17RB, and IL-17RC are all expressed in both healthy control and CRC [84]. Van anh et al. examined whether expression of the membrane-bound form of IL-17A on CT26 colon cancer cells increases or prevents their growth as tumors, and realized that membrane-bound IL-17A significantly promoted their proliferation and tumorigenicity both in vitro and in vivo [85].

IL-17 cytokines are double-edged agents and depending on type of cancer can be as anti- and pro-tumor cytokines [86]. While the details remain dubious, accumulating evidence has revealed that IL-17 might have an oncogenic function by preventing tumor cell apoptosis, diminishing antitumor responses, increasing tumor angiogenesis and stimulating tumor metastasis and invasion [22]. Contrary to oncogenic role of IL-17, remarkable amounts of experimental evidence verify that IL-17 can act as a tumor suppressor during the process of tumorigenesis and metastasis. The first line of document was found from the association of the survival rate of cancer patients with IL-17 expression, which show that the five-year survival rates in gastric adenocarcinoma patients with augmented IL-17 expression are considerably higher than in patients with lower IL-17 expression [87]. While the precise mechanism is yet unclear, it is supposed that IL-17 has an antitumor function by modulating the adaptive immune responses via recruiting T lymphocytes, increasing NK cell action, promoting the production and activation of CTLs [22]. Here, we will summarize dual functions of this cytokine in tumors (Table 1).

4. The paradox of Th17 cell function in tumors

Immune cells, such as CD8+ cytotoxic T lymphocytes (CTL),