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PRO-TUMOR AND ANTI-TUMOR FUNCTIONS OF IL-17 AND OF TH17 CELLS IN TUMOR MICROENVIRONMENT

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Summary. The current review reveals the seven subclasses of CD4+ T helper cells, i.e. Th1, Th2, Th9, Th17, Th22, regulatory T cells and Tfh, the cytokines produced by them and their role in tumor microenvironment. Main attention was paid to IL-17 and Th17 cells. IL-17-producing cells were described, among which were Treg17 cells and Tc17 cells. The transcription factors, engaged in the activation of Th17 cell differentiation were reviewed. It was shown that Th17 cells might possess regulatory functions in tumor microenvironments that directs toward immunosuppression. The reciprocity between Treg and Th17 cells is realized when the production of a large amount of TGF-β in tumors causes Treg cell differentiation, and the addition of IL-6 shifts the differentiation of naïve T cells to Th17 cells. The main pro-tumor role of IL-17 is the promotion of tumor angiogenesis through stimulation of fibroblasts and endothelial cells. The antitumor functions of IL-17 are associated with enhancement of cytotoxic activity of tumor specific CTL cells and with angiogenesis that provide channels through which immune cells might invade tumor and promote antitumor immunity.

Key words: *IL-17, Th17 cells, tumor microenvironment*

INTRODUCTION

The deteriorated immune response plays a decisive role in tumorigenesis and tumor progression. Central role in anti-tumor immunity take different subsets of $CD4^+$ T helper (Th) cells, which regulate the function of antigen-specific effector cells, of antigen-presenting cells and cells of the innate immunity [1, 2].

$CD4^+$ cells play a central role in the function of the immune system by orchestrating $CD8^+$ T cells and macrophages functions against a wide variety of pathogens and by helping B cells to produce antibodies [3]. Over 20 years ago, two main subsets of $CD4^+$ T helper cells were identified in both mice and humans which were named as type 1 Th (Th1) and type 2 Th (Th2) lymphocytes [4]. Recently, Th17 T lymphocyte subset has been most intensively studied, being crucial for host defense against extracellular pathogens and contributing to tumor progression [5].

In present days, CD4 T-helper cells are classified into seven major subsets according to their expression profile of transcription factors and secreted cytokines: Th1, Th2, Th9, Th17, Th22, regulatory T cells (Treg) and follicular Th (Tfh) cells [4, 6, 7, 8, 9]. The first two subsets, Th1 and Th2, were identified in the 1980s [9], when Th1-Th2 hypothesis for regulation of immune response became clear [10, 11].

The identification of Th1 and Th2 as two different subsets clarified the phenomenon of helper $CD4^+$ T lymphocytes to modulate a separate immune response against various pathogens [12]. Th1 cells are characterized by the secretion of IFNγ, which induces the cell-mediated inflammatory response, and were involved in immunity against intracellular pathogens [13]. Th2 cells produce mainly IL-4, IL-5, and IL-13, helping B cells, and are involved in the immune defense against extracellular pathogens [13, 14]. Effector Th cells are engaged in the pathologic immune response, and Th1 cells are linked to the cell-mediated autoimmune diseases, while Th2 cells play an important role in allergy [13].

The differentiation of Th1 cells is mainly induced by IL-12 [13] and could be further enhanced by IFNγ. Th2 cells develop in the presence of IL-4 [15]. Th1 and Th2 negatively regulate each other through actions of their specific cytokines, as IL-12 represses the development of Th2 cells, whereas IL-4 inhibits Th1 cell generation. Th1 initiating cytokines induce the transcription factors T-bet and STAT4, whereas Th2 cells are associated with the action of STAT6 and GATA3 [16].

A population of IL-9 producing cells has been described in the late 1980s [17]. IL-9 was described as a Th2-associated cytokine, involved in "Th2 – like" inflammation. IL-9 has a number of important functions in the immune system: it promotes the survival and proliferation of T lymphocytes and mast cells. Th9 cells are dependent upon TGF-β and IL-4 signalling. IL-25 induces the production of IL-9 and IL-10 cytokines by Th9 lymphocytes [18]. The transcription factors STAT6, PU.1, IRF4 and GATA3 are responsive for IL-9 production [19]. Elevated production of IL-9 plays an important role in autoimmune processes, allergy and anti-tumor immunity [7].

IL-22 belongs to the IL-10 cytokine family and is expressed by innate lumphoid cells and adaptive lymphocytes [4]. Like IL-9, IL-22 could be produced by various types of activated T cells, including Th17, $CD8^+$ cells, and innate immune cells. T cells expressing IL-22, but not IL-17 or IFN-γ, have been described as a distinct subset termed Th22 [20]. Th22 cells are differentiated from naïve $CD4^+$ T cells, in-

duced by TNF-α and IL-6 and further promoted by IL-1β. The production of IL-22 is increased in several autoimmune diseases and in various tumors [21, 22, 23].

A subset of T helper cells residing in B cell follicles – Tfh, had been described [24]. Tfh cells differentiate under the influence of IL-6 and IL-21, and this differentiation is regulated by STAT3 and Bcl-6 [24]. Tfh cells play an important role in maintaining B cell memory and antibody production [7].

Regulatory T cells (Treg) are a unique subset of $CD4^+$ T cells that control activation, proliferation, and effector functions of different populations of immune cells – other T cells, B cells, NK cells and antigen-presenting cells [25]. Activated Treg cells produce the anti-inflammatory cytokines IL-10 and TGFβ, that suppress the development of functional immune reactions in different pathologic conditions including tumor microenvironment [6, 26, 27]. They could suppress the function of other effector T cells and antigen-presenting cells by cell-cell interactions, thus maintaining the peripheral tolerance [6, 7, 16, 26]. The differentiation of Treg is induced by TGFβ [28] but is inhibited in the presence of proinflammatory cytokines, such as IL-6 and IL-12. Treg differentiation requires the expression of transcription factors FoxP3 and STAT5 and the expression of CD25 [29].

IL-17 is the founding member of a new cytokine family composed of six cytokines - IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F (ML-1) and five receptors IL-17RA, B, C, D and E [17]. IL-17 is secreted primary by Th17 cells as a homodimer or heterodimer [30]. In addition to Th17 cell differentiation, IL-17 secretion could also be induced by IL-6, IL-1β, TGF-β, and IL-23 secreted by other cell types such as invariant NKT cells (iNKT cells), gamma-delta (γδ)-T cells, neutrophils and Paneth cells [31, 32, 33], and also by recently described $IL17^+FoxP3^+ROR\gamma t^+$ Tregs (Treg17 cells) [34], and $CD8^+IL\text{-}17^+$ (Tc17 cells) [35]. Moreover, human inflammatory dendritic cells (infDCs), derived from monocytes, stimulate memory $CD4^+$ T cells to produce IL-17 [36].

Human IL-17 is produced predominantly by activated $CD4^+$ T cells and has several biological activities including induction of IL-6, IL-8, and prostaglandin E2 (PGE2), as well as enhancement of intercellular adhesion molecule (ICAM)-1 expression in fibroblasts and keratinocytes. In addition, IL-17 induces secretion of tumor necrosis factor (TNF)-α, IL-1β, and stromelysin by macrophages [26, 37]. IL-17R has a single trans-membrane domain with a long cytoplasmic tail [32]. IL-17R receptor signaling may trigger activation of NF-κB transcription factor and may regulate ERK1, ERK2, c-Jun N-terminal kinase and p38 MAPK [26].

Th17 cells are recently discovered subset of $CD4^+$ Th cells that are differentiated independently of the classic Th1/Th2 programme, and are characterized by the selective production of IL-17A and IL-17F. Differentiation of Th17 from naïve $CD4^+$ T cells needs the combined and consecutive actions of IL-6, TGF-β, IL-21, IL-23/IL-1β [33, 38, 39]. These cytokines initiate the activation of STAT3 and induce the

expression of the main regulator of Th17 cell differentiation orphan nuclear receptor RORγt (mice) or RORc (human), as well as of RORα and other transcription factors, necessary for the maximal expression of IL-17 and IL-22 [40, 41, 42]. Development of Th17 cells is suppressed by IFN-γ and IL-4 that promote Th1 and Th2 cells, respectively [43]. TGF-β alone, in absence of other proinflammatory cytokines like IL-6, induces FoxP3$^+$ regulatory T cells instead of Th17 cells, which shows the close relationship between Th17 and Treg cells [44]. Activated Th17 cells secrete IL-17A, IL-17F, IL-21, IL-22 and TNF-α, which then promote tissue inflammation by induction of other proinflammatory mediators and recruitment of leukocytes to the site of inflammation [45]. Evidence for the existence of Th17 cells in humans have been recently given by two major studies [5, 41].

TH17 CELLS IN TUMOR MICROENVIRONMENT

Tumor microenvironment comprises of inflammatory/immune cells, stromal cells and blood microvessels from the host, that are responsible for tumor generation and development. Tumor microenvironment can promote the production, recruitment and activation of Th17 cells [46]. The function of Th17 cells is still under investigation. Compared with mouse Th17 cells, the main reasons for the development of human Th17 cells have not been well studied [47]. Recent studies reported that IL-1 was critical for human Th17 cell differentiation, and the presence of IL-1, IL-6 and IL-23 in tumor milieu was determinant for human Th17 cell production [48]. Recently, it was announced that TGF-β was also required for Th17 cell differentiation [42]. Moreover, tumor cells and tumor-derived stromal cells, such as fibroblasts and APCs (dendritic cells and monocytes) are responsible for Th17 cells generation, because of secretion of proinflammatory cytokines IL-1, IL-6, IL-23 and TGF-β that formed the optimal cytokine milieu for differentiation and expansion of Th17 cells [48, 49, 50].

It has been supposed that the development of tumor-infiltrating Th17 cells may be a general feature in cancer patients with ovarian cancer, breast cancer, melanoma, and colorectal cancer [46]. Previous reports have shown an increased expression of IL-17 mRNA in tumor probes from prostate and colorectal cancer patients [51]. In addition, a recent study in gastric cancers showed that increased numbers of Th17 cells were correlated with cancer stages, a fact that explained the contribution of Th17 cells to cancer development [52].

Recent reports demonstrated that tumor-infiltrating Th17 cell clones (derived from melanoma, breast and colon cancers) after stimulation with OKT3 secreted large amounts of IL-8, IL-17, and TNF-α, small amounts of IL-6, and also moderate amounts of IL-10 and TGF-β1 [46], showing that Th17 cells might possess regulatory functions in tumor microenvironments [46, 53].

Some authors examined the phenotypes of tumor-infiltrating Th-17 cell clones by flow cytometry, and CD4$^+$CD25$^+$ Treg cells and naïve CD4$^+$ T cells were used as

controls [46]. It was established that all Th17 clones uniformly expressed the memory phenotype $CCR7^+CD62Ldim/+CD45RA\text{-}CD45RO^+$. In addition, Th17 cells had minimal or no expression of the cytotoxicity-associated markers, CD56, granzyme A, and Fas ligand as well as inhibitory molecule PD-1, similar to those expressed on $CD4^+CD25^+$Tregs and naïve $CD4^+$ T cells [46].

It was shown that tumor-derived Th17 cell clones also expressed CTLA-4, CD25, and FoxP3, which are characteristics of $CD4^+$ Treg cells, therefore these tumor-infiltrating Th17 cells may have plasticity and overlap phenotypically with Treg cells [46]. The same authors also established that tumor microenvironment of melanoma, ovarian, breast and colon cancers used to secrete MCP-1 and RANTES from tumor-derived fibroblasts, factors that strongly attracted Th17 cell migration. In addition, other authors showed that tumor microenvironment used migratory mechanisms to recruit not only Th17 cells but also Treg cells, in order to block immunosurveillance and immune destruction of cancer cells [54, 55, 56, 57]. It was also shown that cell culture supernatants from melanoma, breast cancer and colon cancer contained chemokines such as IL-8 involved in the preferential recruitment of CCR6-expressing Th17 cells in tumor site [46, 58]. Some tumor cells (melanoma and colon cancer cells) were determined to secrete Th17 chemoattractant CCL20 as well [57]. Tumor cells and tumor-infiltrating macrophages secreted also CCL22 that attracted $CCR4^+CD4^+$Tregs at tumor site [54]. These studies suggested that Th17 cells, $CD4^+CD25^+$ Treg cells, as well as other T cell lineages, shared common chemokine receptors and trafficking receptors [2, 57]. In addition, tumor cells used the same migratory mechanisms as the inflammatory microenvironment to block immunosurveillance and immune destruction of tumor cells in tumor microenvironment [46].

Recent studies demonstrated a Th1/Th17 subset (IL-17+IFN-γ^+) that exclusively co-expresses IFN-γ and IL-17 and that was often identified in infectious and autoimmune diseases and in some tumors [59, 60]. Moreover, human $CD4^+$Treg cells can also be changed into IL-17-producing Th17 cells ($IL\text{-}17^+/FoxP3^+$) and Th17 cells were shown to express FoxP3 and RORγt ($ROR\gamma t^+/FoxP3^+$) [61]. It was reported recently that in parallel with Treg cells, $IL\text{-}17^+CD4^+$ and $IL\text{-}17^+CD8^+$ T cells appeared in multiple tumor microenvironments, and the number of these cells was elevated during tumor development [62, 63, 64].

In summary, it might be concluded that tumor-infiltrating Th17 cells have no direct immunosuppressive activities. However, because of secretion of moderate amounts IL-10 and TGF-β, and because of expression of some Treg cell markers such as CTLA-4, FoxP3 and CD25, Th17 cells possess developmental plasticity as other T cell lineages, and might have dual functions performing regulatory as well as effector roles in tumor microenvironments.

REGULATION OF TH17 CELL DIFFERENTIATION IN TUMORS

It has become clear that IL-17-producing Th17 cells and Treg cells share a common pathway. Although TGF-β favors differentiation of naïve T cells into Tregs, simultaneous presence of both TGF-β and IL-6 promotes the differentiation of Th17 cells. Naive T cells entering tumor site are exposed to the influence of TGF-β and IL-6, a condition favoring Th17 cell differentiation [32]. Moreover, TGF-β favors tumor growth by antagonizing Th1 differentiation and CTL activities such as perforin production [65]. Besides, upon stimulation with TGF-β and IL-6, $CD8^+$T lose their cytotoxic activity and start secretion of IL-17 [66]. Th1 or $CD8^+$ T cells expressing IFN-γ, inhibit angiogenesis and induce MHC class I molecule expression in tumor cells, thus favoring anti-tumor immune response [67]. In contrast, IL-17 favors angiogenesis and tumor growth, therefore replacing IFN-γ with IL-17 in tumor microenvironment the immune surveillance is blocked. In addition, the presence of tumor cells secreting TGF-β and IL-6 causes local polarization of $CD8^+$ T cells into IL-17 secreting state (Tc17). Therefore, IL-17-producing CD8+ T cells may promote tumor growth [68].

Another cytokine with pro-tumor functions and stimulating Th17 cell expansion is IL-23. IL-23 is in reciprocal relations with IL-12, the latter induces IFN-γ secretion and anti-tumor immunity. In tumors, where IL-12 production is reduced, the secretion of IL-23 is increased [69]. IL-23 is not required for induction of Th17 cell differentiation but it is necessary for Th17 function [70]. IL-23 overexpression in tumors is associated with reduced growth and metastasis [71]. It was shown that the stimulation with prostaglandin E2 (PGE2), the most abundant prostanoid in epithelial cells, leads to an increase of IL-23 and to a decrease of IL-12 production in tumors and to an expansion of Th17 cells there [68, 60, 72]. Except its pro-tumor functions expressed by promotion of Th17 cells, IL-23 possesses anti-tumor functions as well. For example, IL-23 mediates myeloid infiltration presented by dendritic cells, macrophages, and granulocytes and promotes the differentiation of $CD8^+$ T cells [32, 69].

RECIPROCITY BETWEEN TREG AND TH17 CELLS

The production of a large amount of TGF-β in tumors causes Treg cells differentiation, and the addition of IL-6 shifts the differentiation of naive T cells to Th17 cells. Therefore, IL-6 is referred to as a key factor in determining Treg/Th17 reciprocity [32]. Moreover, IL-2 promotes Treg cells expansion and in parallel inhibits Th17 cell generation [61]. Retinoic acid metabolites, secreted by dendritic cells in tumor microenvironment, reduce Th17 cell differentiation (but not Th1 cell differentiation) through inhibition of IL-6 and promote TGF-β activity [61, 73]. FoxP3 binds to RORγt and RORα in order to regulate each others activity reciprocally [74]. In the absence of FoxP3 in the milieu, RORγt activity and Th17 cell differentiation are stimulated.

Although FoxP3 alone inhibits the secretion of IL-17, recent reports showed that there exists functional plasticity between Treg cells and Th17 cells, in tumor microenvironment [75]. In addition, $FoxP3^+IL\text{-}17^+CD4^+$ T cells (Treg/Th17) were observed in the presence of TGF-β and IL-6 in tumor microenvironment [76]. The origin and function of these dual $FoxP3^+IL\text{-}17^+CD4^+$ T cells were unknown, probably they existed in the early stage of transition between Treg and Th17 cells [77]. Some authors reported increased levels of Tregs in peripheral blood, regional lymph nodes and within tumor-infiltrating lymphocytes in tumors [78]. Tregs were the largest population of $CD4^+$T cells in progressive tumors, and Th17 cells existed in parallel with Tregs within tumor tissues [61]. Therefore, the regulation of Treg/Th17 proportion determines tumor progress and regression.

PRO-TUMOR FUNCTIONS OF IL-17 AND TH17 CELLS

The functions of IL-17 in the tumor microenvironment contribute predominantly to tumor progression. IL-17 has a direct effect on proliferation and survival of tumor cells, which express IL-17R and respond to that cytokine [52].

The main pro-tumor role of IL-17 is the promotion of tumor angiogenesis through stimulation of fibroblasts and endothelial cells [55]. For example, the number of Th17 cells positively correlates to microvessel density in several tumors [26]. Something more, IL-17 significantly increases the production of many angiogenic factors such as VEGF, keratinocyte-derived chemokine (KC), macrophage inflammatory protein 2 (MIP-2), nitric oxide (NO), PGE1 and PGE2 [26, 79]. Many cancer cells express high levels of TGF-β, a cytokine that enhances tumor growth and metastasis by stimulating angiogenesis [80]. IL-17 induces VEGF that in turn stimulates TGF-β and thereby initiates VEGF-mediated angiogenesis [78]. Moreover, IL-17 induces the secretion of IL-6 and PGE2 and enhances ICAM-1 expression in fibroblasts. All these molecules have major role in angiogenesis and tumor invasion [32].

IL-17 induces the secretion of IL-8 that promotes the angiogenic signals of endothelial cells. That cytokine increases the proliferation and survival of endothelial cells and of tumor cells and potentiates the neutrophil recruitment at tumor site [81].

In addition, IL-17 stimulates the secretion of proangiogenic chemokines such as CXCL5, CXCL6 and CXCL8 in tumor cells and epithelial cells and inhibits the secretion of angiostatic chemokines by fibroblasts [82]. Thus, IL-17 may shift local biologic balance between angiogenic and angiostatic chemokines toward a predominance of angiogenic activity.

ANTITUMOR FUNCTIONS OF IL-17

A lot of reports have described tumor inhibitory effects of IL-17 [19]. It was shown that Th17 cells were more effective than Th1 cells in elimination of a large

established melanoma [83]. However, Th17-mediated immune response in tumors is dependent on IFN-γ that is produced by NK cells and by Th1 $CD4^+$ T cells [1]. Th17-polarized cells also secrete cytokines, determining the Th17 phenotype, such as IL-17F, IL-22, IL-21 and CCL20. In addition, it has been shown that IL-17 enhanced CTL activity [84]. Different mechanisms have been proposed to explain the IL-17 enhancement of cytotoxic activity of tumor specific CTL cells. It has been shown that IL-17 induced the secretion of the stimulating inflammation cytokine IL-6 from a variety of cells at tumor site [85]. Moreover, IL-17 induced IL-12 production from macrophages [86]. Both cytokines IL-6 and IL-12 have been associated with the induction of CTL cells. Something more, IL-17 promotes the maturation of dendritic cell progenitors (expressing costimulatory molecules and MHC class II), a fact that might lead to further improvement in T cell priming by tumor cells producing IL-17 [32]. Although IL-17 has been shown to promote tumor growth by inducing angiogenesis, the same process provided channels through which immune cells might invade tumor and promoted antitumor immunity.

In conclusion, we might state that the pro-tumor and anti-tumor functions of IL-17 and Th17 cells are functions of cytokines, chemokines and growth factors, secreted by tumor cells, stromal cells and T lymphocytes in tumor microenvironment. These factors regulate the plasticity in differentiation of T cells – from cytotoxic $CD8^+$ T cells in IL-17^+/$CD8^+$ T cells (Tc17) or from $CD4^+$ $FoxP3^+$T cells in IL-17^+/$FoxP3^+$ Tregs (Treg/Th17) through reprogramming gene expression in T lymphocytes.

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