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Review/Praca poglądowa

The role of Th17 cells in tumor immunity

Znaczenie limfocytów Th17 w odporności przeciwnowotworowej

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ABSTRACT

CD4+ T helper (Th) cells play an important role in modulating immune responses. Th17 cells are a newly established Th subpopulation. Th17 cells differentiate in the presence of TGF-β and IL-6 in mice or IL-1β and IL-6 in humans, depending on the transcription factor RORγt. IL-23 stabilizes the Th17 cells phenotype and helps Th17 cells acquire effector functions. Th17 secretes IL-17, IL-21, and IL-22, which play significant role in the immune response against viruses, extracellular bacteria and fungi, as well as in the pathogenesis of inflammatory diseases. The systemic and local activity of IL-17 and Th17 seems to be an important part of development of autoimmune reaction. Th17 cell subpopulation has been described in many types of cancer, including gastric cancer, melanoma, breast cancer, and ovarian cancer, but it remains unclear whether Th17 cells promote or inhibit tumor progression and the mechanism of their involvement in tumor immunity is unknown.

This review summarizes the current knowledge on the role of Th17 cells in tumor immunity.

Introduction

Since 1989 when Mosmann and Coffman showed that murine CD4+ T cells differentiate into two subsets of reciprocal patterns of cytokine secretion and function, defined as CD4+ T helper type 1 (Th1) and Th2, a great progress in understanding of Th cells and certain effector cytokines utilized by Th cells has been observed. This classic division was changed by the discovery of a new CD4+ helper T cells population which is characterized by the high expression of IL-17, named CD4+ T helper type 17 (Th17). More recently, the new Th subsets such as Th9 and Th22 cells, which play roles in the modulation of host immune responses, were discovered [1–3].

Th17 cell differentiation

After the discovery of Th17 cells, many studies have been focused on the mechanisms that lead to the differentiation of CD4+ cells. At least several cytokines and their combinations, the presence of which determines the formation and

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maintenance of Th17 phenotype in animal models and in humans, are already known.

In mice, transforming growth factor-β (TGF-β) and IL-6 are crucial for Th17 differentiation. Notably naïve T cells stimulated by TGF-β only, without the involvement of IL-6, are developing in the direction of regulatory T cells by the activation of the transcription factor FOXP3. Therefore, IL-6 is an essential factor for the differentiation of naïve T cells into Th17 as it increases the expression of IL-23R and subsequently inhibits the activity of FOXP3. IL-23 is not needed for the early development of mice Th17 cells, but seems to be involved in the expansion and survival of the Th17 cell subpopulation [4–6].

In humans, Th17 cells differentiate under similar conditions, but with little more cytokines in a microenvironment. In vitro studies on CD4+ cells taken from the cord blood have shown that an optimum environment for this process requires the presence of IL-1β, IL-6, IL-21, and IL-23. The formation of human Th17 cells in comparison with the murine cells depends to a greater extent on the presence of IL-23 as well as the pro-inflammatory cytokines such as IL-1β and IL-21 [7, 8]. IL-23 is produced by activated monocytes, macrophages, dendritic cells and endothelial cells. Binding to its specific receptor activates JAK/STAT T cell pathway. IL-23 might be involved in the upregulation of IL-17 production. It also stabilizes the Th17 cell phenotype and helps Th17 cells acquire effector functions [8, 9]. The role of TGF-β in the development of Th17 cells from naïve human T cells has been somewhat controversial. What is more, TGF-β appears to determine Th17 cells differentiation in a dose-dependent manner. Lower concentrations of TGF-β in the presence of IL-6 induce Th17 differentiation, the production of IL-21 and the upregulation of IL-23R, while higher doses of this cytokine inhibit IL-23R expression and promote the Treg phenotype by activation of the transcription factor FOXP3 [8, 10] (Fig. 1). In addition the lectin receptor CD161, the human homologue of murine NK1.1, has been reported to be expressed in all human Th17 cells in the peripheral blood and inflamed tissues. Moreover, in humans the chemokine receptor CCR6 is involved in the process of differentiation of Th17 cell phenotype [11, 12].

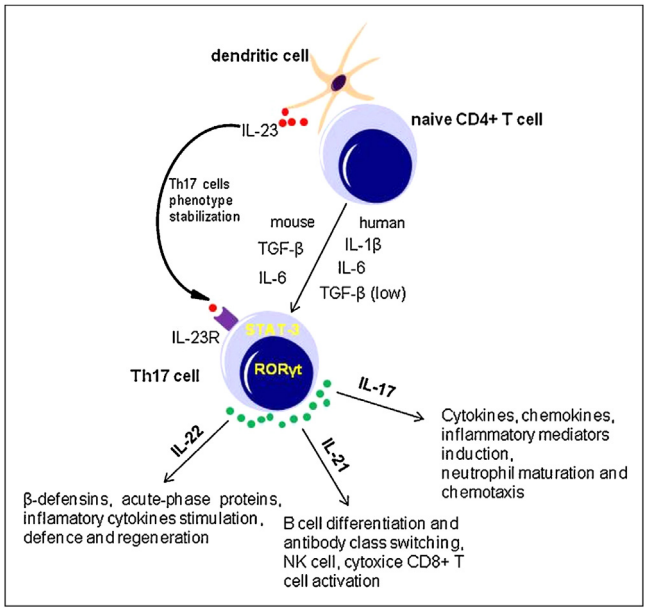

Fig. 1 – Differentiation and function of Th17 cells in mice and human

Ryc. 1 – Różnicowanie i funkcje komórek Th17 u myszy i ludzi

The differentiation of Th17 cells requires the expression of the retinoic acid receptor-related orphan receptor-γt (RORγt), which belongs to the retinoic acid-related nuclear hormone receptor family. The induction of RORγt depends on signal transducer and an activator of transcription 3 (STAT-3), and the overexpression of RORγt regulates IL-17 production and Th17 cells differentiation. In human, the overexpression of RORC2 (the human ortholog of RORγt) in native T cells induces the expression of IL-17A, IL-17F, IL-26 and CCR6 [7, 13]. STAT-3 regulates Th17 cell lineage development in cooperation with IL-6, IL-21 and IL-23. STAT-3 affects RORγt expression and binds to IL-17A, IL-17F and IL-21 promoters [14]. The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor, which can induce Th17 differentiation, presumably through the inhibition of STAT1 and STAT5, which negatively regulates Th17 development [15, 16]. Recent data have shown that interferon regulatory factor 4 (IRF4) is also important in the differentiation of Th17 cells through the IL-6 and TGF-β pathway or through the IL-21-mediated pathway [17].

Function of Th17 cells

Th17 cells secrete a number of cytokines among which the most important is IL-17. IL-17 is the member of the IL-17 family, which consists of six cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. Th17 cells secrete large quantities of IL-17A in humans, the gene encoding IL-17 is localized on chromosome 6. IL-17 has pleiotropic effect on the tissue cells and several immune cells. IL-17 stimulates the production of inflammatory cytokines, such as IL-6, TNF-α, IL-1β, chemokines (CXCL1, CXCL3, CXCL5, CXCL6), and several growth factors including granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) from epithelial cells and fibroblast. This cytokine plays an important role in combating extracellular pathogens (bacteria and fungi) by inducing neutrophil maturation and chemotaxis. Furthermore, IL-17 increases the expression of intracellular adhesion molecule 1 (ICAM1) on epithelial cells and induces the secretion of matrix metalloproteinases (MMPs) that are involved in tissue remodeling and damage. IL17A signaling occurs through a receptor IL17RA, which is expressed in multiple tissues, such as hematopoietic tissue, skin, and lung [18, 19]. Th17 cell also produces other effector molecules, such as IL-21, IL-22, IL-26, IL-6 and CCL20.

IL-22 belongs to IL-10 family of cytokines and is produced by terminally differentiated Th17 cells and activated by T cells. IL-22 has a protective effect on epithelial cells. This cytokine stimulates defence, regeneration and healing in tissue through the induction of antimicrobial agents and proteins involved in epithelial cell differentiation and cell

mobility. IL-22 induces antimicrobial proteins (S100 proteins), β-defensins, acute-phase proteins, inflammatory cytokines and chemokines in keratinocytes [20, 21].

Il-21 is a member of the IL-2 family and mediates its functions via the IL-21 receptor (IL-21R), which is expressed on B cells, T cells and natural killer (NK) cells and non-immune cells such as epithelial cells and fibroblasts. IL-21 stimulates the proliferation and activation of CD4+ and CD8+ cells and the expansion and activation of NK cells [22, 23]. In addition, IL-21 regulates the maturation and differentiation of B lymphocytes. It can also promote antibody production and antibody class switching by the induction of involved transcription factor (Blip-1, Bcl-6) [24, 25]. This cytokine can also induce the secretion of chemokines and the production of MMP in non-immune cells, such as epithelial cells and fibroblasts [26]. IL-21 also induces the expression of the IL-23R [27].

IL-26 is a member of the IL-10 family, which is produced by the activated memory T cells and induces the expression of proinflammatory cytokines, such as TNF-α and IL-8, and inhibits cell proliferation [28]. CCL20 is a ligand for CCR6 and it have an antimicrobial and chemoattractive activities [19].

The role of Th17 in tumor immunity

Th17 cell subpopulation has been described in many types of cancers, including gastric cancer, melanoma, breast cancer, and ovarian cancer, but it is not clear whether Th17 cells promote or inhibit tumor progression and the mechanism of their involvement in tumor immunity is unknown. The development of cancer is affected by many factors. It depends on the production of profile of pro-inflammatory and angiogenic cytokines, antitumor immunity and immunogenicity of the tumor [29–31].

Tumor promotion by Th17 cells and IL-17

Potential mechanisms responsible for the promotion of tumor growth activity by IL-17 and Th17 cells involve angiogenesis. IL-17 influences the proliferation of tumor cells by stimulation of new vessels formation due to its pro-inflammatory as well as angiogenic activity. This induces VEGF, which markedly promotes inflammatory and tumor angiogenesis [32]. Moreover, VEGF stimulates the production of TGF-β, which seems to enhance cancer growth and metastasis by stimulating angiogenesis [33]. IL-17 also induces IL-6 and enhances the expression of ICAM-1 in fibroblasts. These molecules play an important role in angiogenesis and tumor invasion. IL-6 induces activation of the oncogenic signal STAT3, resulting in prosurvival and proangiogenetic genes upregulation [34, 35]. IL-17 seems to induce the production of IL-8. It promotes angiogenic response in endothelial cells, increases proliferation and survival of endothelial and tumor cells, and infiltration of neutrophils on the site of the tumor. Expression of IL-8 correlates with angiogenesis and metastasis [35, 36]. IL-17 stimulates the secretion of IL-1β and TNF-α by macrophages. These cytokines activate neutrophils to secrete specific chemokines that recruit them to the site of inflammation. In addition, IL-17 increases the production of angiogenic chemokines such as CXCL1, CXCL5, CXCL6, and CXCL8 in endothelial cells and cancer cells. These chemokines can induce proliferation and chemotaxis of vascular endothelial cells, which promote tumor growth [37, 38]. IL-23 may upregulate IL-17 and matrix metalloprotease 9 (MMP-9) to stimulate angiogenesis and reduce the number of CD8+ T cells in the tumor microenvironment. It has also been demonstrated that tumor cells and tumor-derived fibroblasts secrete monocyte chemotactic protein 1 (MCP-1) mediating the recruitment of Th17 cells [30]. Protumor activity mediated by Th17 and IL-17 has been observed both in mouse tumor models and in human cancer patients.

Tartour et al. [39] injected nude mice with human cervical tumor cells transfected with human cDNA encoding IL-17 and found that they grew more quickly than parental tumors. Numasaki et al. [38] demonstrated that human non-small cell lung cancer transfected with human IL-17 grew faster in severe combined immunodeficiency (SCID) mice than did control non-small cell lung cancer cells.

In the study of hepatocellular carcinoma significantly higher levels of Th17 cells in tumor in comparison to non-tumor tissue have been described. The levels of Th17 cells are positively correlated with microvessel density in the tumor [40]. Alexandrakis et al. [41] in patients with multiple myeloma found correlation between high levels of IL-17 in serum and concentration of proangiogenic cytokines, density of blood vessels and clinical stage of the disease. In the study of gastric cancer the frequency of Th17 cells was significantly increased when compared to healthy donors. The percentage of Th17 cells in stage III–IV was higher than that in stage I–II patients [29]. Tosolini and coworkers [42] reported that high expression of Th17 gene in colorectal tumor was associated with poor prognosis. In the study by Sfanos et al. [43] it was demonstrated that Th17 cells infiltrating the tumor correlated inversely with the Gleason score in prostate cancer.

Wang et al. [44] showed significantly higher percentage of Th17 cells in both colorectal adenoma (CRA) and colorectal carcinoma (CRC) compared to that in healthy controls. They observed that the percentage of Th17 cells was decreased in advanced stages of CRAs and CRCs in comparison with early stage of the diseases. Also, the concentrations of IL-17A and IL-23 were higher in CRA and CRC patients when compared to that in healthy controls.

Wu et al. [45] reported significantly higher frequency of Th17 cells in untreated acute myeloid leukemia (AML) patients compared to that in healthy controls. They also found increased concentrations of IL-6 and TGF-β1 in AML patients than in controls; the IL-6 concentrations showed a positive correlation with frequencies of Th17 cells. Furthermore, the frequencies of Th17 cells were significantly reduced in patients with complete remission (CR) compared to that in the same patients before treatment, and in comparison to non-CR patients who did not present reduced frequencies after therapy.

In the study of chronic lymphocytic leukemia Jadidi-Niaraghet al. [46] showed lower number of Th17 cells in progressive compared to indolent patients and healthy controls. Additionally, Th17 cells were decreased in patients in II-IV Rai stages when compared to that in those in early

Table I – The role of Th17 cells and IL-17 in tumor immunity
Tabela I – Znaczenie komórek Th17 i IL-17 w odporności przeciwnowotworowej

Malignancy type	Number of patients	Expression of Th17 or IL-17 level	Biological significance	Clinical significance	References
Hepatocellular carcinoma	178	↑	Higher Th17 numbers correlated with higher microvessel density	Higher Th17 numbers correlated with shorter overall survival	40
Multiple myeloma	40	↑	Increasing serum levels of IL-17 positively correlated with angiogenetic factor such as TNF, VEGF	Increasing serum levels of IL-17 correlated with advancing disease stage	41
Acute myeloid leukemia	42	↑	Increasing TGF-β, IL-6, IL-17 concentrations in plasma, IL-6 and IL-17 concentrations showed a positive correlation with the frequencies of Th17 cells	Not assessed	45
Colorectal cancer	231	↑Th17 gene	Not assessed	High expression of the Th17 cluster genes correlated with shorter overall survival	42
Ovarian cancer	201	↑	Higher Th17 numbers positively correlated with the percentage of effector CD8+ lymphocytes	Higher levels of IL-17 correlated with longer overall survival	55
Chronic lymphocytic leukemia	66	↑	Not assessed	Higher circulating Th17 levels correlated with longer overall survival	46
Breast cancer	27	↓	Lower number of Th17 cells correlated with higher numbers of Treg	Not assessed	54

stages 0–I. They observed a significant decrease of Th17 cells in unmutated *IGHV* compared to mutated samples. The mean fluorescence intensity (MFI) of IL-17 was lower in progressive as compared to indolent patients and normal subjects. Earlier we found higher frequency of Th17 cells in patients with CLL, even in patients in early stage of the disease. We reported that the expression of Th17 did not correlate with disease stage and prognostic factors [54]. Hus et al. [55] observed higher percentages of Th17 cells and IL-17A plasma levels in patients in early clinical stages of CLL compared to those in advanced Rai stages and healthy controls. The frequencies of Th17 cells and IL-17A were lower in patients with adverse prognostic factors. Furthermore, they found that IL-17A plasma levels were lower in patients who required therapy compared to that in patients who were not treated. Biological and clinical effects of Th17 cells and IL-17 in cancer patients are summarized in Table I.

The anti-tumor function of Th17 cells and IL-17

The antitumor function of Th17 cells reflects the influence of IL-17 on many cell types. IL-17 stimulates the maturation of dendritic cells by increasing the surface expression of MHC class II molecules. The presentation of tumor antigens to CD8+cells leads to their differentiation in cytotoxic T lymphocytes. IL-17 stimulates the production of IL-12 in macrophages, leading to the activation of cytotoxic lymphocytes. It is believed that Th17 cells indirectly affect the anti-tumor immunity by recruiting cytotoxic lymphocytes, NK cells, macrophages, neutrophils and dendritic cells [47, 48].

Hirahara et al. [49] have transfected human IL-17 gene into hamster ovarian cancer cells and shown a significantly lower metastatic potential of tumor cells by direct modulation of invasiveness and metastasis as well as by increasing the activity of NK cells. In a murine model Muranski et al. [50] have obtained eradication of advanced melanoma using tumor-specific Th17 lymphocytes generated in vitro.

Kryczek et al. [51] have shown a positive correlation between the percentage of Th17 tumor infiltrating cells and the percentage of effector CD8+ lymphocytes as well as negative correlation between the percentage of Th17 cells and regulatory T cells in patients with advanced ovarian carcinoma.

Horlock et al. [52] in their study have demonstrated significantly lower number of Th17 cells in peripheral blood in HER-positive breast cancer patients when compared to HER-negative patients and healthy controls. Furthermore, the percentage of regulatory T cells was significantly higher in breast cancer patients compared to healthy volunteers. In addition, Jain et al. [53] have reported significantly higher absolute number of blood Th17 cells in patients with chronic lymphocytic leukemia compared to healthy controls. They have also demonstrated positive correlation between circulating Th17 cells number and survival of CLL patients. Patients with high Th17 cells number had longer median overall survival than patients with low Th17 cells number.

In summary, the presented data suggest the importance of Th17 cells in tumor immunity, but their impact on the development of cancer remains undefined. Characterization of the functional roles of Th17 cells, as well as identification of the mechanisms underlying Th17 cell heterogeneity in individual tumors or during tumor development, is urgently

required for the development of effective and specific antitumor immunotherapies.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; and Uniform Requirements for manuscripts submitted to Biomedical journals.

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