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IL-17, IL-21, and IL-22 Cytokines of T Helper 17 Cells in Cancer

Ayten Nalbant

$CD4^+$ T helper (Th) cells are important regulators of cellular immune response. Newly discovered interleukin (IL)-17-producing $CD4^+$ T cells are known as T helper 17 cells (Th17). They are distinct subset from the T helper type 1 (Th1) and 2 (Th2) lineages. The differentiation of Th17 cells has been intensively studied; however, the role of Th17 cells in different diseases including cancer is still under investigation. Besides IL-17 family cytokines, Th17 cells produce IL-22, IL-21, and IL-26. The dysregulated function of Th17 cells and their cytokines could contribute to pathology of diseases, including cancer. The role of cytokines of Th17 cells such as IL-17, IL-21, and IL-22 in cancer will be discussed in this review.

Keywords: Th17 cells, IL-17, cancer, IL-21, IL-22

Introduction

Naive $CD4^+$ $TCR\alpha\beta^+$ T lymphocytes differentiate into different types of effectors when they encounter their antigens. The differentiation of T helper subgroups involves activation of different cytokines, signaling pathways, and transcription factors. These cytokines and transcription factors may contribute to the formation of a subset of cells, while preventing the formation of others. For instance, Th1 cells are produced by T-bet, the main transcription factor, in the presence of IFN-gamma and interleukin (IL)-12. Th2 cells are produced by GATA3 and STAT-6 in the presence of IL-4 cytokine. Foxp3 transcription factor with TGF-β and IL-2 signaling leads to the differentiation of regulatory T cells (Tregs) (Jetten 2009). Recently, a new T helper subset has been discovered and named as T helper 17 (Th17) cells (Harrington and others 2005). This review will focus on Th17 cells and their relevant cytokines in the context of cancer diseases.

Th17 Cells and IL-17 Family

T helper 17 cells are a specific subset of $CD4^+$ T helper lymphocytes and were originally named based on their unique ability to secrete the cytokine IL-17 (Harrington and others 2005). It was shown that proinflammatory cytokines IL-1β, IL-6, and IL-23 as well as TGF-β were essential for human Th17 cell polarization (Volpe and others 2008). Since initial discovery of Th17 cells, it has become clear that in addition to IL-17 family members, Th17 cells express many other effector cytokines, including IL-21, IL-22, and IL-26.

Expression of IL-21 is dependent on STAT3-mediated IL-6 signaling in Th17 cells (Korn and others 2007). The autocrine function of IL-21 via IL-21R in a combined effect with TGF-β promotes Th17 differentiation (Harris and others 2007; Nurieva and others 2007). Th17-secreted IL-22 binds IL-22R on target cells, largely epithelial cells, to induce the expression of antimicrobial peptides β-defensin-2 and β-defensin-3 (Li and others 2015). Recently, it was demonstrated that IL-22 is able to protect hosts against bacterial infections of the lungs and gut (Parks and others 2016).

The RAR-related orphan receptors (RORs) are members of the nuclear receptor family of intracellular transcription factors. There are 3 forms of ROR, ROR-α, -β, and -γ, and each one is encoded by a separate gene. The transcription factor RORγ(t), also known as RORC2, has been identified as the master regulator of Th17 cell differentiation (Ivanov II and others 2006). Signal transducer and activator of transcription 3 (STAT3) acts downstream of IL-6 as well as IL-21 and IL-23, and upregulates RORγt (Nurieva and others 2007). STAT3 is also a key factor in inhibiting TGF-β-induced FOXP3 (Veldhoen and others 2006; Harris and others 2007), which negatively regulates Th17 differentiation (Harris and others 2007; Nurieva and others 2007). The differentiation of Th17 cells has been intensively studied (Nurieva and others 2007), but their contribution to different diseases including cancer is still under investigation.

Th17 cells produce IL-17A and IL-17F cytokines. IL-17A (IL-17) is a member of the IL-17 family, which also includes IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. IL-17F has the highest degree of homology to IL-17A.

Molecular Immunology Laboratory, Department of Molecular Biology and Genetics, İzmir Institute of Technology, İzmir, Turkey.

Structure and signaling of IL-17 and IL-17 receptor family have been reviewed elsewhere (Gu and others 2013; Fabre and others 2016; Alinejad and others 2017). Th17 cell produces IL-17A as a signature cytokine and plays a pathological role in various inflammatory conditions such as autoimmune diseases, metabolic disorders, and cancer (Gu and others 2013). Pathological production of IL-17A leads to excessive inflammation and tissue damage (Song and Qian 2013).

The role of Th17 cells in numerous types of cancers has been mentioned, but their role in cancer disease is still controversial (Zou and Restifo, 2010; Fabre and others 2016; Qian and others 2017). Both tumor-promoting and tumor-suppressing functions of Th17 cells in cancer are being reported. For instance, Tosolini and others found that Th17 (RORC, IL-17A)-related gene expression profile was correlated with poor survival in colorectal cancer. These results were confirmed by *in situ* analysis where patients with high density of IL-17^+ cells had a poor prognosis (Tosolini and others 2011). These data suggested that Th17 or IL-17^+ cells might have a tumor-promoting role. Kryczek and others studied the tissue distribution of Th17 cells in ovarian cancer patients. The proportion of Th17 cells was higher in tumors than blood and tumor-draining lymph nodes of cancer patients. The percentage of Th17 cells in $CD4^+$ T cells in different tissues by gating on IL-$17^+CD4^+CD3^+$ cells were measured. Innate immune cells were also analyzed in the same ovarian cancer ascites. They stated that eosinophils were rarely observed, and moderate levels of mast cells, neutrophils, and natural killer (NK) cells were detected, but Th17 cells had no correlation with eosinophils, mast cells, and neutrophils. They concluded that IL-17 detected in tumor-associated ascites and the levels of IL-17 positively predict patient survival, and Th17 cells are the only source of IL-17 production in the human ovarian tumor microenvironment (Kryczek and others 2009). These data suggest that Th17 cells may contribute to protective tumor immunity in ovarian cancers.

There are numerous reviews in the literature about Th17 cells in cancer (Zou and Restifo 2010; Punt and others 2015a; Fabre and others 2016; Qian and others 2017), but the role of IL-17 cytokine in cancer is much less studied. As mentioned earlier, tumor-promoting as well as tumor-suppressing functions of Th17 cells in cancer have been reported. These findings in the literature have raised confusion about the role of IL-17 cytokine and Th17 cells in cancer. Among the various causes of these results are the study of Th17 cell functions from various angles, looking at these cells in different samples and using different methods (Punt and others 2015b). In addition, there are numerous cell types in the tumor microenvironment. It is also possible that some of these cells can produce IL-17 cytokine, including $CD8^+$ T cells, NK T cells, neutrophils, and eosinophils. Punt and others reported that IL-17 in different types of carcinomas was primarily expressed by granulocytes and mast cells. Neutrophils were primary granulocytes in squamous cervical cancer, and it was associated with poor survival. In addition, IL-17C cells were independently associated with poor survival in early stage disease (Punt and others 2015a). Existing data showed that the different cell types expressing IL-17 can play different roles in the tumor microenvironment (Lee and others 2018). Therefore, adaptive and innate immune cells of tumor microenvironment and their cytokines need to be carefully measured.

IL-21 and IL-22 Cytokines of Th17 Cells

IL-21 is a type 1 cytokine and a member of the common gamma chain family of cytokines with immunoregulatory activity. It is produced by Th17 cells and is a critical regulator of Th17 differentiation (Nurieva and others 2007). IL-21 has pleiotropic effects on both innate and adaptive immune responses (Costanza and others 2010). IL-21 regulates differentiation of B cells into plasma cells, and increases cytotoxicity of CD8 (+) T cells. Besides positive effects of IL-21 on different lineages, it has inhibitory effects on antigen presentation by dendritic cells, and can be proapoptotic for B and NK cells (Spolski and Leonard 2008).

IL-21 has potent antitumor activity (Croce and others 2015). Kim-Schulze and others reported that a stably transfected B16 melanoma cell line secreting functional IL-21 in mice resulted in delayed tumor growth after challenge with the tumor. Analysis of tumor microenvironment showed that local IL-21 secretion prevents accumulation of $CD4^+CD25^+FOXP3^+$ Tregs within the tumor microenvironment. This outcome coincided with the presence of endogenously activated memory T cell responses. These data suggest that local IL-21 expression would enhance antigen-specific T cell responses against an established murine melanoma (Kim-Schulze and others 2009).

In 2 syngeneic mouse tumor models, RenCa renal cell carcinoma and B16 melanoma were used to investigate the effect of subcutaneous and intratumoral (IT) administration of IL-21 protein. The subcutaneous administration compared with IT administration of IL-21 more potently inhibited tumor growth and increased survival by the mechanisms through which IL-21 enhances CD8 T cell-mediated antitumor immunity (Søndergaard and others 2010).

It was shown that IL-21 cytokine can trigger B cells to secrete the serine protease grannzyme B (GrB) (Hagn and others 2009). In a recent study, it was found that GrB-expressing B cells reside within the microenvironment of different tumor types, including breast, ovarian, cervical, colorectal, and prostate carcinomas (Lindner and others 2013). Since IL-21 is a key cytokine for differentiation of B cells into GrB^+ B cells, whether IL-21-expressing cells are also present in the tumor tissue has been investigated. Results showed that IL-21-expressing $CD3^+$ T cells could be identified in the vicinity of B cells in these tumor tissue sections, suggesting the contribution of IL-21 cytokine to the modulation of cellular adaptive immune responses in the tumor microenvironment (Lindner and others 2013).

Tumor-associated macrophages (TAMs) are an important component of the tumor microenvironment. Macrophages are highly plastic and can rapidly change their phenotypes in response to their local signals, including interactions with lymphocyte subsets (Biswas and Mantovani 2010). Study on the therapeutic effects of anti-Her2/neu Ab in a HER2/neu-dependent breast cancer cell TUBO model demonstrated that tumor progression is highly associated with immune-suppressive M2 phenotypes, and deletion of TAMs markedly enhanced the therapeutic outcome. Furthermore, IT delivery of IL-21 skewed TAM polarization away from the immune-suppressive M2 phenotype toward the immune-stimulatory M1 phenotype (Xu and others 2015).

Browning and others (2016) showed that lenalidomide is an immunomodulatory drug, which induced production of

IL-21 in T cells from patients with chronic lymphocytic leukemia (CLL) and enhanced upregulation of functional IL-21 receptor (IL-21R) on the cell surface of CLL cells. In addition, this work showed that lenalidomide enhances the cytotoxic effect of IL-21 on CLL cells. Collectively, published data in the literature show that IL-21 as a pleiotropic cytokine regulates immune responses depending on the context. For instance, biological activities of IL-21 promote the cytotoxic effects of $CD8^+$ T cells and NK cells. IL-21 also induces apoptosis of B cell lymphomas. Furthermore, it promotes the M2 to M1 transition of the TAMs. These studies suggest that IL-21 can affect different types of cells in the tumor microenvironment. Thus, this cytokine might be used alone or in combination with other agents for immunotherapeutic purposes (Leonard and Wan 2016).

IL-22 is a glycoprotein belonging to the IL-10 family. IL-22 is released by several cell types, including $CD4^+$ and $CD8^+$ T lymphocytes as well as NK T cells (Rutz and others 2013). In humans, only a limited number of Th17 cells corelease IL-22 with IL-17 (Duhen and others 2009; Eyerich and others 2009). Several reports suggest that IL-22 favors tumor outgrowth of nonmelanoma skin cancer and metastasis of colon and lung cancers (Nardinocchi and others 2015; Eyerich and others 2017). In humans, increased expression of IL-22 or its receptor was reported to correlate with disease progression and decreased overall survival in pancreatic, gastric, and colorectal cancers (Zhuang and others 2012; Wen and others 2014).

IL-22 is a cytokine with tumor-promoting properties. Unlike other cytokines, IL-22 is produced only by immune cells and binds to IL-22 receptor-1^+ (IL-22-$R1^+$) nonimmune cells. The presence of IL-22-producing cells is linked to a more aggressive phenotype in a variety of cancer entities, such as lung, breast, gastric, and skin cancers, indicating a more universal function of IL-22 in cancer progression (Eyerich and others 2017). Voigt and others showed that cancer cells directly induce IL-22 production *in vitro* and *in vivo* in 2 murine tumor models, which are primarily human breast and lung cancers, respectively. IL-1β induced by inflammasome activation is critical for IL-22 production. IL-1β increased the activity of the IL-22 transcription factors in lineage-committed T cells (Voigt and others 2017). A recent study also showed that Th17, Th22, and $CD4^+$ cells coproducing IL-17/IL-22 were accumulated in colon cancer tissues, and may be involved in the tumor development and progression (Doulabi and others 2018).

Conclusion Remarks

T cells play a highly important role in tumor immune response. Discovery of Th17 cells as a new subset of $CD4^+$ T cells has added a new perspective to cancer studies. The role of Th17 cells in tumor immunity is still not clear, but it has been found to be dependent on a number of factors such as cytokines, chemokines, costimulatory molecules, and cell–cell interactions. The role of Th17 cells either stimulating or inhibiting the tumor is generally dependent on composition of tumor microenvironment. Th17 cells produce IL-17, IL-17F, IL-21, IL-22, IL-26, and TNF. These cytokines can modulate fibroblasts, endothelial cells, epithelial cells, macrophages, and tumor cells within the tumor microenvironment. Tumor-promoting function of IL-17 can be accomplished by preventing tumor cell apoptosis, diminishing antitumor responses, increasing tumor angiogenesis, and stimulating tumor metastasis and invasion (Qian and others 2017). Opposing to tumor-stimulating function, IL-17 can also act as a tumor suppressor during the process of tumorigenesis. IL-17 exerts antitumor functions by enhancing NK cell and CTL cell activation, and by recruiting neutrophil, NK cell, $CD4^+$ and $CD8^+$ T cell infiltration into tumor tissue (Qian and others 2017). Recent data on the behavior of T cell subsets including Th17 cells in tumor microenvironment highlighted the need for a more detailed examination of immune cells in the tumor microenvironments.

As mentioned earlier, Th17 cells produce IL-17A, IL-17F, IL-21, and IL-22. Th17 cells were studied in different types of cancers, but the results of the studies are controversial due to various reasons. Besides Th17 cells, IL-17 family cytokines in cancer are not deeply studied yet. One of the cytokines of Th17 cells is IL-21. It is involved in the proliferation and expansion of tumor-infiltrating lymphocytes and $CD8^+$ memory T cells. IL-21 stimulates IFN-gamma production and increased granularity in NK cells (Davis and others 2015). Therefore, IL-21 regulates strong antitumor activity. IL-22 is also the other cytokine of Th17 cells. It has been identified as a cancer-promoting cytokine. It was recently shown that breast and lung cancer cells induce IL-22 production from memory $CD4^+$ T cells by IL-1 to promote tumor growth (Voigt and others 2017). Overall, Th17 cytokines have different functions in the tumor microenvironments. A better understanding of the mechanisms of producing antitumor responses in Th17 cells will lead to the development of more effective vaccines and T cell-dependent therapies for cancer patients.

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References

Alinejad V, Dolati S, Motallebnezhad M, Yousefi M. 2017. The role of IL17B-IL17RB signaling pathway in breast cancer. Biomed Pharmacother 88:795–803.

Biswas SK, Mantovani A. 2010. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 11(10):889–896.

Browning RL, Byrd WH, Gupta N, Jones J, Mo X, Hertlein E, Yu L, Muthusamy N, Byrd JC. 2016. Lenalidomide induces interleukin-21 production by T cells and enhances IL21-mediated cytotoxicity in chronic lymphocytic leukemia B cells. Cancer Immunol Res 4(8):698–707.

Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. 2010. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci 60(2):61–66.

Croce M, Rigo V, Ferrini S. 2015. IL-21: a pleiotropic cytokine with potential applications in oncology. J Immunol Res 2015: 696578.

Davis MR, Zhu Z, Hansen DM, Bai Q, Fang Y. 2015. The role of IL-21 in immunity and cancer. Cancer Lett 358(2):107–114.

Doulabi H, Rastin M, Shabahangh H, Maddah G, Abdollahi A, Nosratabadi R, Esmaeili SA, Mahmoudi M. 2018. Analysis of Th22, Th17 and $CD4^+$ cells co-producing IL-17/IL-22 at different stages of human colon cancer. Biomed Pharmacother 103:1101–1106.

Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. 2009. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat Immunol 10:857–863.

Eyerich K, Dimartino V, Cavani A. 2017. IL-17 and IL-22 in immunity: driving protection and pathology. Eur J Immunol 47(4):607–614.

Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, Cianfarani F, Odorisio T, Traidl-Hoffmann C, Behrendt H, Durham SR, Schmidt-Weber CB, Cavani A. 2009. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 119:3573–3585.

Fabre J, Giustiniani J, Garbar C, Antonicelli F, Merrouche Y, Bensussan A, Bagot M, Al-Dacak R. 2016. Targeting the tumor microenvironment: the protumor effects of IL-17 related to cancer type. Int J Mol Sci 17(9). pii: e1433. DOI: 10.3390/ijms17091433.

Gu C, Wu L, Li X. 2013. IL-17 family: cytokines, receptors and signaling. Cytokine 64(2):477–485.

Hagn M, Schwesinger E, Ebel V, Sontheimer K, Maier J, Beyer T, Syrovets T, Laumonnier Y, Fabricius D, Simmet T, Jahrsdöfer B. 2009. Human B cells secrete granzyme B when recognizing viral antigens in the context of the acute phase cytokine IL-21. J Immunol 183:1838–1845.

Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. 2005. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 6(11):1123–1132.

Harris TJ, Grosso JF, Yen HR, Xin H, Kortylewski M, Albesiano E, Hipkiss EL, Getnet D, Goldberg MV, Maris CH, Housseau F, Yu H, Pardoll DM, Drake CG. 2007. Cutting edge: an in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. J Immunol 179:4313–4317.

Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR. 2006. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126(6):1121–1133.

Jetten AM. 2009. Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. Nucl Recept Signal 7:e003.

Kim-Schulze S, Kim HS, Fan Q, Kim DW, Kaufman HL. 2009. Local IL-21 promotes the therapeutic activity of effector T cells by decreasing regulatory T cells within the tumor microenvironment. Mol Ther 17(2):380–388.

Korn T, Bettelli E, Gao W, Awasthi A, Jäger A, Strom TB, Oukka M, Kuchroo VK. 2007. IL-21 initiates an alternative pathway to induce pro-inflammatory T(H)17 cells. Nature 448:484–487.

Kryczek I, Banerjee M, Cheng P, Vatan L, Szeliga W, Wei S, Huang E, Finlayson E, Simeone D, Welling TH, Chang A, Coukos G, Liu R, Zou W. 2009. Phenotype, distribution, generation, and functional and clinical relevance of Th17 cells in the human tumor environments. Blood 114:1141–1149.

Lee MH, Tung-Chieh Chang J, Liao CT, Chen YS, Kuo ML, Shen CR. 2018. Interleukin 17 and peripheral IL-17-expressing T cells are negatively correlated with the overall survival of head and neck cancer patients. Oncotarget 9(11): 9825–9837.

Leonard WJ, Wan CK. 2016. IL-21 signaling in immunity. F1000Res 26;5. pii: F1000 Faculty Rev-224. DOI: 10.12688/f1000research.7634.1.

Li A, Gan Y, Wang R, Liu Y, Ma T, Huang M, Cui X. 2015. IL-22 up-regulates β-defensin-2 expression in human alveolar epithelium via STAT3 but not NF-κB signaling pathway. Inflammation 38(3):1191–1200.

Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, Beyer T, Reister F, Fabricius D, Lotfi R, Lunov O, Nienhaus GU, Simmet T, Kreienberg R, Möller P, Schrezenmeier H, Jahrsdörfer B. 2013. Interleukin 21-induced granzyme B-expressing B cells infiltrate tumors and regulate T cells. Cancer Res 73(8):2468–2479.

Nardinocchi L, Sonego G, Passarelli F, Avitabile S, Scarponi C, Failla CM, Simoni S, Albanesi C, Cavani A. 2015. Interleukin-17 and interleukin-22 promote tumor progression in human nonmelanoma skin cancer. Eur J Immunol 45:922–931.

Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C. 2007. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature 448:480–483.

Parks OB, Pociask DA, Hodzic Z, Kolls JK, Good M. 2016. Interleukin-22 signaling in the regulation of intestinal health and disease. Front Cell Dev Biol 3:85.

Punt S, Fleuren GJ, Kritikou E, Lubberts E, Trimbos JB, Jordanova ES, Gorter A. 2015a. Angels and demons: Th17 cells represent a beneficial response, while neutrophil IL-17 is associated with poor prognosis in squamous cervical cancer. Oncoimmunology 4(1):e984539.

Punt S, Langenhoff JM, Putter H, Fleuren GJ, Gorter A, Jordanova ES. 2015b. The correlations between IL-17 vs. Th17 cells and cancer patient survival: a systematic review. Oncoimmunology 4:e984547.

Qian X, Chen H, Wu X, Hu L, Huang Q, Jin Y. 2017. Interleukin-17 acts as double-edged sword in anti-tumor immunity and tumorigenesis. Cytokine 89:34–44.

Rutz S, Eidenschenk C, Ouyang W. 2013. IL-22, not simply a Th17 cytokine. Immunol Rev 252:116–132.

Søndergaard H, Galsgaard ED, Bartholomaeussen M, Straten PT, Odum N, Skak K. 2010. Intratumoral interleukin-21 increases antitumor immunity, tumor-infiltrating CD8+ T-cell density and activity, and enlarges draining lymph nodes. J Immunother 33(3):236–249.

Song X, Qian Y. 2013. IL-17 family cytokines mediated signaling in the pathogenesis of inflammatory diseases. Cell Signal 25(12):2335–2347.

Spolski R, Leonard WJ. 2008. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol 26:57–79.

Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, Mauger S, Bindea G, Berger A, Bruneval P, Fridman WH, Pagès F, Galon J. 2011. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, Th2, Treg, Th17) in patients with colorectal cancer. Cancer Res 71:1263–1271.

Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. 2006. TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 24:179–189.

Voigt C, May P, Gottschlich A, Markota A, Wenk D, Gerlach I, Voigt S, Stathopoulos GT, Arendt KAM, Heise C, Rataj F, Janssen KP, Königshoff M, Winter H, Himsl I, Thasler WE, Schnurr M, Rothenfußer S, Endres S, Kobold S. 2017. Cancer cells induce interleukin 22 production from memory $CD4_+$ T cells via interleukin-1 to promote tumor growth. Proc Natl Acad Sci U S A 114(49):12994–12999.

Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupé P, Barillot E, Soumelis V. 2008. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol 9(6):650–657.

Wen Z, Liao Q, Zhao J, Hu Y, You L, Lu Z, Jia C, Wei Y, Zhao Y. 2014. High expression of interleukin-22 and its receptor predicts poor prognosis in pancreatic ductal adenocarcinoma. Ann Surg Oncol 21:125–132.

Xu M, Liu M, Du X, Li S, Li H, Li X, Li Y, Wang Y, Qin Z, Fu YX, Wang S. 2015. Intratumoral delivery of IL-21 overcomes anti-Her2/Neu resistance through shifting tumor-associated macrophages from M2 to M1 phenotype. J Immunol 194(10): 4997–5006.

Zhuang Y, Peng LS, Zhao YL, Shi Y, Mao XH, Guo G, Chen W, Liu XF, Zhang JY, Liu T, Luo P, Yu PW, Zou QM. 2012. Increased intratumoral IL-22-producing CD4(+) T cells and Th22 cells correlate with gastric cancer progression and predict poor patient survival. Cancer Immunol Immunother 61:1965–1975.

Zou W, Restifo NP. 2010. T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol 10:248–256.

Address correspondence to:
Dr. Ayten Nalbant
Molecular Immunology Laboratory
Department of Molecular Biology and Genetics
İzmir Institute of Technology
İzmir 35430
Turkey

E-mail: aytennalbant@iyte.edu.tr

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