Tumor Necrosis Factor and Regulatory T Cells

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CD4+CD25+FoxP3+ regulatory T (Treg) cells play major roles in the maintenance of immune homeostasis. In this review, we comprehensively describe the relationship between tumor necrosis factor (TNF) and Treg cells, focusing on the effects of TNF on Treg cells and on TNF-producing Treg cells. Contradictory results have been reported for the effect of TNF on the suppressive activity of Treg cells. In patients with rheumatoid arthritis, TNF has been shown to reduce the suppressive activity of Treg cells. Meanwhile, however, TNF has also been reported to maintain the suppressive activity of Treg cells via a TNFR2-mediated mechanism. In addition, Treg cells have been found to acquire the ability to produce TNF under inflammatory conditions, such as acute viral hepatitis. These TNF-producing Treg cells exhibit T helper 17-like features and hold significance in various human diseases.

Key Words: Tumor necrosis factor, regulatory T cell, inflammation, TNFR2

INTRODUCTION

CD4+CD25+FoxP3+ regulatory T (Treg) cells are specialized T cells involved in the maintenance of immune homeostasis, and their dysregulation is involved in various autoimmune and inflammatory diseases. In many inflammatory diseases, tumor necrosis factor (TNF) is produced by various immune cells, including activated macrophages, monocytes, and T cells. However, the interactions between TNF and Treg cells have not been clearly elucidated.[1] Though some studies have suggested that TNF enhances the suppressive function of Treg cells,[2-4] others have shown that TNF reduces the suppressive function of Treg cells.[5-7]

Under inflammatory conditions, Treg cells that stably express FoxP3 acquire the ability to produce pro-inflammatory cytokines. Treg cells that produce pro-inflammatory cytokines are referred to as T helper (Th)-like Treg cells. These cells express lineage-specific transcription factors and chemokine receptors.[8,9] Th1-like Treg cells produce IFN-γ and express T-bet and CXCR3, which are Th1-specific molecules.[8,10] Th17-like Treg cells produce IL-17A and express STAT3, RORγt, and CCR6, which are Th17-specific molecules.[9,11] Th1- and Th17-like Treg cells have been proposed to suppress Th1 and Th17 effector T cell responses, respectively, via tissue migration mediated by specific chemokine receptors, such as CXCR3 and CCR6.[8-11] Meanwhile, however, Th1- or Th17-like Treg cells have also been suggested to be involved in the pathogenesis of autoimmune and inflammatory diseases.[12] We recently reported that Treg cells can produce TNF in patients with acute viral hepatitis and that TNF-producing Treg cells exhibited Th17-like features.[13]

In this review, we describe the effects of TNF on Treg cells and TNF-producing Treg cells and the possible implications of this interaction in various human diseases.

TUMOR NECROSIS FACTOR

TNF is a pro-inflammatory cytokine first discovered as an endotoxin-induced factor in 1975.[14] TNF plays a role in septic shock, cachexia, and the pathogenesis of various autoimmune and inflammatory diseases. TNF is produced by monocytes and macrophages, as well as other immune cells, in-

cluding dendritic cells, B cells, activated natural killer cells, and activated T cells.[15,16] When exogenous or endogenous stimuli induce the production of TNF, it is initially expressed on the cell surface in membrane-bound form (mTNF, 26 kDa), which is then cleaved by a metalloproteinase, TNFα converting enzyme (TACE), and released as soluble TNF (sTNF, 17 kDa).[17,18]

TNF has two cell membrane receptors, TNFR1 (p55) and TNFR2 (p75). TNFR1 is a major TNF receptor ubiquitously expressed on most cell types. TNFR1 binding to either mTNF or sTNF leads to recruitment and clustering of TNF receptor-associated factor (TRAF), TNFR-associated death domain (TRADD), and receptor-interacting protein-1 (RIP1).[19-21] This complex activates activator protein-1 (AP-1), mitogen-activated protein kinases (MAPKs), and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), which are important factors in the expression of multiple inflammatory cytokines. TNFR1 can also activate another signaling pathway: the TNFR1 signaling complex can recruit FAS-associated death domain protein (FADD), which activates apoptotic caspase cascades and the pro-apoptotic protein BH3 interacting domain death agonist (BID).[22,23]

The expression of TNFR2 is restricted to immune cells[24] and binds with higher affinity to mTNF than sTNF.[25] Binding of TNF to TNFR2 recruits TRAF1, 2, and 3, as well as cellular inhibitor of apoptosis proteins 1/2 (cIAP1/2). TNFR2 does not possess a death domain and its activation results in different signaling than TNFR1. The downstream signals of TNFR2 activate both the canonical and non-canonical NF-kB pathways,[26,27] as well as the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway directly related to survival and cell proliferation. Interestingly, TNFR2 is more highly expressed on Treg cells, compared to non-Treg effector T cells,[28] whereas TNFR1 expression is not different between Treg and non-Treg CD4^{+} T cells.[29] TNFR2 is upregulated in a suppressive subset of Treg cells[2] and is required for the stabilization of Treg cells in the murine system.[24] In humans, TNFR2^{+} Treg cells express higher levels of CTLA-4, which is involved in the suppressive activity of Treg cells, compared to TNFR2^{-} Treg cells and non-Treg CD4^{+} T cells.[28] Furthermore, TNFR2 may play a role in the suppressive activity of Treg cells, although the underlying mechanisms have only recently begun to be clarified.

EFFECTS OF TNF ON REGULATORY T CELLS

Successful treatment of several inflammatory disorders, such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, and vasculitis, with anti-TNF agents suggests the importance of TNF in inflammatory processes in the human immune system. As a bridging cytokine between innate and adaptive immune responses in inflammation, TNF exerts pleiotropic ef-

fects on Treg cells.

Treg cells in patients with autoimmune diseases are exposed to the inflammatory milieu, including TNF, which is provided by various immune cells. At a highly pro-inflammatory site, such as the synovial fluid of RA patients, TNF produced by activated monocytes diminishes the suppressive activity of Treg cells and contributes to chronic inflammation:[7] the direct effect of TNF on Treg cells has been investigated primarily in RA patients. TNF appears to suppress the function of Treg cells in RA patients by reducing FoxP3 expression.[6] Interestingly, the anti-TNF antibody infliximab was found to restore the reduced FoxP3 expression in RA patients.[6] Another study demonstrated that TNF activates the canonical NF-κB pathway and disturbs the suppressive function in human Treg cells, particularly for the CD45RA^{-} population, though FoxP3 levels remain stable.[5] Restoration of the compromised function of Treg cells in RA patients by anti-TNF treatment also suggests that TNF down-regulates the suppressive function of Treg cells.[1]

While the negative effects of TNF on Treg cell function and proliferation were reported first, recent studies have shown contrasting effects for TNF on the function of Treg cells. In healthy human subjects, the suppressive activity of Treg cells was maintained after exposure to TNF *in vitro*.[30] A murine model of graft versus host disease also showed that TNF enhances the suppressive function of Treg cells but does not change the function of non-Treg CD4^{+} T cells.[4] The positive effect of TNF on Treg cell function was further supported by TNF-deficient mice developing prolonged and exacerbated experimental autoimmune encephalomyelitis.[31] TNFR2-mediated signaling was also recently reported to be important in the effect of TNF on Treg cells:[32] TNFR2 is expressed in the subpopulation of Treg cells with superior suppressive ability. In addition, TNFR2 has been shown to stabilize the phenotype and function of Treg cells in a murine model,[24] even in a highly inflammatory environment, which destabilizes FoxP3 expression in Treg cells.

TNFR2 is expressed on suppressive Treg cells, and it has been used to isolate suppressive Treg cells for therapeutic application.[2,33,34] In addition, as mTNF effectively stimulates TNFR2,[35] a method was developed for mTNF-induced stimulation of isolated Treg cells for immunosuppressive therapy.[36] Chemical agonists of TNFR2 have also been used for the selective expansion of suppressive Treg cells.[37]

The effect of TNF on Treg cells in tumor tissues was reported recently. TNF induced proliferation of Treg cells at tumor sites via TNFR2, and TNFR2^{+} Treg cells enhanced the escape of tumor cells from immune surveillance.[38] In the B16F10 murine model of metastatic melanoma, TNF was shown to activate Treg cells and expand the suppressive subpopulation. Silencing of TNF or TNFR2 expression reversed the immunotolerant tumor microenvironment to prevent metastasis.[39] Meanwhile, increased expression of TNFR2 among Treg cells

was observed in malignant ascites from ovarian cancer patients.[40] Thus, TNFR2+ Treg cells can be targeted to enhance anti-tumor immune responses.

Analysis of Treg cells in patients undergoing anti-TNF treatment has provided understanding of the effect of TNF on Treg cells. Decreased function of Treg cells has been reported in RA patients, as well as its reversal by anti-TNF agents.[31,41] More than a decade after the first clinical use of anti-TNF agents in humans, the mechanism underlying the restorative effect of anti-TNF agents on Treg cells was discovered.[42] Anti-TNF antibody adalimumab was found to promote the interaction of monocytes and Treg cells and to expand Treg cells, particularly via TNFR2.[42] Considering the positive role of TNF signaling via TNFR2 on Treg cells with respect to immunomodulation, selective blocking antibodies against TNFR1 have been tested in a murine collagen-induced arthritis model and primary cell culture obtained from the synovial tissues of RA patients with positive results.[43,44] Anti-TNF agents rarely induce unexpected, so-called 'paradoxical' exacerbation of autoimmune diseases, such as psoriasis.[31] A study in the murine psoriasis model has shown that the disturbance of Treg cells and relative expansion of the Th17 population contribute to the paradoxical exacerbation.[45]

TNF-PRODUCING REGULATORY T CELLS

Treg cells typically produce anti-inflammatory cytokines, such as IL-10, TGF-β, and IL-35, which are involved in the suppressive function of Treg cells; however, they can also produce pro-inflammatory cytokines under certain inflammatory conditions.[46-48] Treg cells have been found to produce IFN-γ

in patients with multiple sclerosis and type I diabetes,[49,50] and IL-17A in patients with Crohn's disease and RA.[9,51-57] These inflammatory Treg cells may be involved in the pathogenesis of autoimmune and inflammatory diseases.[12] During microbial infection, inflammatory Treg cells may contribute to the elimination of microbial pathogens by secreting pro-inflammatory cytokines. However, they may also enhance inflammation and exacerbate host injury during infection.

A study investigating RA suggested that memory Treg cells (CD4+CD45RO+CD25+CD127low) acquire the ability to produce pro-inflammatory cytokines, including not only IFN-γ and IL-17, but also TNF, in response to inflammatory stimuli.[58] These Treg cells maintain their suppressive capacity. In addition, Treg cells from healthy donors appeared to acquire the ability to produce pro-inflammatory cytokines, including TNF, in co-culture with autologous monocytes activated by lipopolysaccharide. These data suggest that activated monocytes potently induce the production of pro-inflammatory cytokines by Treg cells.

Another recent study reported that Treg cells from patients with acute hepatitis A (AHA) produce pro-inflammatory cytokines in direct *ex vivo* assays.[13] A high proportion of Treg cells in the peripheral blood of patients with AHA produced TNF, and TNF-producing Treg cells were associated with severe liver injury, indicating that TNF-producing Treg cells are involved in the process of immune-mediated liver injury during AHA (Fig. 1). TNF-producing Treg cells from AHA patients were confirmed to be *bona fide* Treg cells, not activated T cells transiently expressing Foxp3, based on hypo-methylation at the Treg-specific demethylated region.[4] TNF-producing Treg cells from patients with AHA exhibited features of Th17-like cells, as characterized by up-regulation of RORγt, CCR6, and
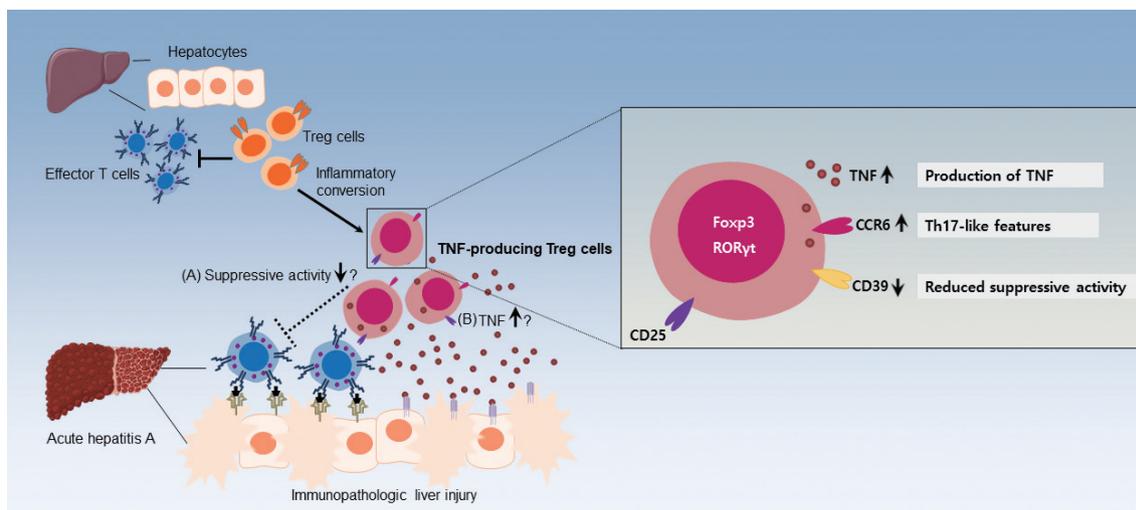

Fig. 1. TNF-producing Treg cells in AHA patients. Treg cells from AHA patients produce TNF and exhibit reduced suppressive activity due to inflammatory conversion. In AHA patients, TNF-producing Treg cells are associated with severe liver injury mediated by immunopathologic mechanisms. Two possible mechanisms have been proposed to explain how TNF-producing Treg cells are involved in liver injury. (A) First, the reduced suppressive activity of TNF-producing Treg cells may lead to unchecked activation of effector T cells, which contributes to liver injury. (B) Second, TNF produced by Treg cells may directly contribute to liver injury. The magnified figure on the right shows the phenotypic characteristics of TNF-producing Treg cells. TNF, tumor necrosis factor; AHA, acute hepatitis A; Treg, regulatory T.

IL-17A. Importantly, RORγt inhibition decreased the production of TNF by Treg cells, indicating that TNF is produced by Treg cells from AHA patients in a RORγt-dependent manner.

TNF-producing Treg cells from AHA patients have been shown to express low levels of CD39 (ectonucleoside triphosphate diphosphohydrolase-1), which contributes to the suppressive activity of Treg cells. Treg cells from AHA patients have reduced suppressive functions, compared to Treg cells from healthy individuals. However, blockade of TNF does not restore the suppressive activity of Treg cells, indicating that TNF itself is not responsible for the reduced suppressive functions of Treg cells from AHA patients.[13] Interestingly, the relative frequency of TNF-producing Treg cells in peripheral blood is also increased in patients with other inflammatory liver diseases, including chronic hepatitis B and C and toxic/drug-induced hepatitis.[13]

CONCLUSIONS

Here, we reviewed the relationship between TNF and Treg cells in regards to the effects of TNF on Treg cells and TNF-producing Treg cells. TNF is a pleiotropic cytokine reported to exert a variety of effects on Treg cells. TNF downregulates the suppressive function of Treg cells in co-culture,[6] but inconsistently increases the suppressive function of Treg cells and promotes their proliferation under certain circumstances.[2,59,60] Whether these discrepancies can be attributed to the microenvironment in which Treg cells meet TNF remains unclear.

Treg cells produce TNF under specific disease-related inflammatory conditions. The functions of TNF-producing Treg cells depend on environmental cues, and further investigation is needed to determine the specific characteristics of TNF-producing Treg cells and related mechanisms. Understanding the detailed mechanism underlying how Treg cells produce TNF and the pathological role of these cells in human disease is important, as these cells may serve as therapeutic targets for the treatment of various inflammatory diseases.

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AUTHOR CONTRIBUTIONS

Wrote the first draft of the manuscript: Min Kyung Jung, Jeong Seok Lee, and Jeong-Eun Kwak. Approved the final version: Min Kyung Jung and Eui-Cheol Shin. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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