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Review

Contrasting effects of TNF and anti-TNF on the activation of effector T cells and regulatory T cells in autoimmunity

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ABSTRACT

Anti-TNF treatment is effective in a majority of rheumatoid arthritis (RA), however, this treatment can unexpectedly trigger the onset or exacerbate multiple sclerosis (MS). Recent progress in cellular immunology research provides a new framework to analyze the possible mechanism underlying these puzzling contradictory effects. The delicate balance of protective $CD4^+FoxP3^+$ regulatory T cells (Tregs) and pathogenic $CD4^+FoxP3^-$ effector T cells (Teffs) is crucial for the outcome of anti-TNF treatment of autoimmune disease. There is convincing evidence that TNF, in addition to stimulating Teffs, is able to activate and expand Tregs through TNFR2, which is preferentially expressed by Tregs. Therefore, the contrasting effects of TNF on Tregs and Teffs are likely to determine the therapeutic effect of anti-TNF treatment. In this review, we discuss the current understanding of the general effect of TNF on the activation of T cells, and the impact of TNF on the function of Teffs and Tregs. Understanding the differential effects of TNF on Teffs and Tregs is fundamentally required for the design of more effective and safer anti-TNF or anti-TNF receptor(s) therapeutic strategy for autoimmune diseases.

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1. Introduction

1.1. Contrasting immunopathogenic and immunoprotective effects of TNF

The pleiotropic cytokine tumor necrosis factor-alpha (TNF) is a major participant in the initiation and orchestration of complex events in inflammation and immunity [1]. Upon stimulation by pathogens and inflammatory signaling, TNF is produced primarily by immune cells, such as macrophages and T and B lymphocytes, as well as by other somatic cell types, including endothelial cells, mast cells, neuronal tissues and tumor cells [2,3]. Initially, transmembrane TNF is synthesized [4], and it can be subsequently released as soluble TNF (sTNF) upon cleavage by the metalloprotease TNF-α-converting enzyme (TACE or ADAM17) [5]. Both the soluble and transmembrane forms of TNF are biologically active in their trimeric forms [5].

The effects of TNF are mediated by two structurally related, but functionally distinct receptors, TNFR1 (or p55) and TNFR2 (or p75) [6]. These receptors also can be released from the cell surface as soluble forms by proteolysis and have the capacity to neutralize the action of TNF [7,8]. In contrast to the ubiquitous expression of TNFR1, TNFR2 is more restricted to lymphocytes and is more efficiently activated by transmembrane as opposed to sTNF [9]. TNFR1 with its death domain (DD) is the primary signaling receptor on most cell types and accounts for the majority of the proinflammatory, cytotoxic and apoptotic effects classically attributed to TNF [10,11]. In contrast, TNFR2 lacks an intracellular death domain and predominantly mediates signals promoting lymphocyte activation and proliferation [12,13].

TNF has well-documented proinflammatory effects. Nevertheless, increasing evidence reveals that TNF also has unexpected anti-inflammatory and immunosuppressive effect, especially after prolonged exposure (reviewed in Refs. [14–16]). Several transgenic mouse strains overproducing TNF consistently develop autoimmune disorders (reviewed in Ref. [17]). However, transgenic non-obese diabetic (NOD) mice over-expressing TNF in their pancreatic islets failed to develop autoimmune diabetes [18] and repeated injection of TNF paradoxically suppressed both type I diabetes in NOD mice and lupus nephritis in susceptible mouse strains [19]. Furthermore, NZB mice deficient in TNF unexpectedly exhibited acceleration of autoimmunity and lupus nephritis [20]. C57BL/

Abbreviations: DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; LLC, Lewis lung carcinoma; MS, multiple sclerosis; mTNF, membrane-bound TNF; NOD, non-obese diabetic; PB, peripheral blood; RA, rheumatoid arthritis; sTNF, soluble TNF; Teffs, effector T cells; Tregs, regulatory T cells; Trx-1, thioredoxin-1; VD3, vitamin D3

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6.129 mice deficient in TNF developed mild autoimmunity resembling the initial stages of lupus nephritis [21]. TNF knockout (KO) mice developed prolonged and exacerbated experimental autoimmune encephalomyelitis (EAE), although with a delayed onset, after EAE induction [22]. Thus, in mouse models of autoimmunity, TNF can either promote or inhibit inflammatory responses depending on complex factors which may include disease stage, background genetic susceptibility, length and timing of TNF expression.

Anti-TNF therapy is clearly beneficial for most of rheumatoid arthritis (RA) patients. Perhaps reflecting the strikingly contrasting activities of TNF, anti-TNF therapy in patients with RA and inflammatory bowel disease (IBD), however, a minority of patients develop lupus and neuroinflammatory diseases [21]. Furthermore, multiple sclerosis (MS) patients treated with anti-TNF agents resulted almost uniformly in immune activation and exacerbation of disease [21]. To date, the cellular and molecular mechanism underlying the contrasting proinflammatory and immunosuppressive effect of TNF, as well as anti-TNF agents, in autoimmunity remain to be clarified.

1.2. Immune equilibrium between regulatory T cells and effector T cells determines the outcome of autoimmune responses

Extensive studies provide compelling evidence that $CD4^+FoxP3^+$ regulatory T cells (Tregs) play an indispensable role in maintaining immune homeostasis and in suppressing deleterious excessive immune responses [23]. The induction of Treg suppressive activity is antigen specific and requires stimulation through the TCR, however, the suppressive function of Tregs is not antigen specific [24]. Therefore, a wide range of immune responses can be inhibited by Tregs through "bystander" suppression [25]. It is known that the cellular targets of Tregs include CD4 cells [26], CD8 cells [27], NK cells [28], NKT cells [29], dendritic cells (DCs) [30], macrophages [31] and B cells [32]. The in vitro suppressive activity of Tregs depends on cell-to-cell contact [26]. Several molecules, such as IL-10, TGFβ, CTLA-4, IDO and granzyme/perforin are reported to contribute to the suppressive activity of Tregs (reviewed in Ref. [33]). However, the exact molecular mechanisms responsible for the cell contact dependent suppression by Tregs remain elusive.

Autoreactive effector T cells (Teffs) exist even in the healthy individual and their activation is persistently suppressed by Tregs, since removal of Tregs can result in the expansion and activation of these autoreactive Teffs [34]. Breakdown of tolerance by favoring the activities of Teffs over Tregs is a hallmark of autoimmune diseases [23]. The outcome of the autoimmune process is therefore largely determined by factors which tip the balance between the activation of Teffs and Tregs. The immune equilibrium between Teffs and Tregs, therefore, determines the cellular and molecular basis of immunopathological and immunoprotective effects of TNF. The capacity of TNF to expand the pool of functional Tregs represents the major negative feedback loop by which TNF counters its potent pro-inflammatory effects.

1.3. The complex relationship between protective Tregs and pathogenic Th17 cells

Upon activation by antigenic and cytokine stimulation, naïve CD4 cells can differentiate into different lineages of T helper subsets with an unique cytokine profile and effector functions [35]. Recent compelling evidence shows that IL-17-producing T lymphocytes comprise a distinct lineage of proinflammatory T helper cells, termed Th17 cells, that are major contributors to autoimmune disease [36,37]. Intriguingly, both Th17 cells and immunosuppressive Tregs derived from naïve CD4 cells can be reciprocally induced, contingent upon the presence of either IL-6 or IL-2, respectively, in the presence of TGFβ [37–39]. However, during the process of differentiation, both FoxP3 and RORγt, the transcription factors specific for Tregs and Th17 cells respectively, can occasionally be expressed by one cell at the same time [40]. Furthermore, it has been shown that Tregs exhibit "plasticity" and can become IL-17-producing cells after treatment with IL-6 both in vitro [41] and in vivo [42,43]. The functional relationship of Th17 and Tregs is also complicated. It has been clearly shown that both Th1 and Th2 responses can be potently suppressed by Tregs, however, Th17 responses are not always susceptible to Treg-mediated inhibition [44–46]. Actually, Tregs can promote in vitro generation of Th17 cells [39], as confirmed by our own experiments. This paradoxical effect of Tregs has pathophysiological relevance, since in a model of a T cell-mediated systemic autoimmune disorder resembling graft-versus-host disease, adoptive transfer of Tregs promoted the generation of Th17 cells [47]. Thus, the complex conversion to and support by Tregs of Th17 cells may also contribute to the puzzling effect of TNF and anti-TNF on the outcome of an autoimmune inflammation.

T cells play a critical role in the initiation and sustain an inflammatory response, nevertheless, many other types of cells are also involved in the pathogenesis of autoimmune disorders [48]. The direct and indirect responses of these non-T cells to anti-TNF, although representing major aspect of therapeutic effect, are beyond the scope of this review.

2. TNF activates Tregs through TNFR2

2.1. Human and mouse Tregs preferentially express high levels of TNFR2

We found that the majority (>80%) of thymic Tregs in normal mice express TNFR2 [49]. In normal mouse peripheral lymphoid tissues, TNFR2 is expressed primarily by CD4 T cells, in contrast, CD8 T cells express markedly lower levels of TNFR2 [49]. Compared with thymic Tregs, TNFR2-expressing Tregs are reduced to 30–40% in the peripheral lymphoid organs and further reduced to 10% in the circulation. Nevertheless, TNFR2 is still preferentially expressed by Tregs, since fewer than 10% of Teffs in the LNs and spleen of normal mice express lower levels of TNFR2 on a per cell basis [49,50].

TNF is expressed in human and mouse thymus and participates the development of thymocytes [51–53]. It is possible that either TNF or LTα, which also uses TNFR2, actually contribute to the thymic differentiation and generation of Tregs. Similar to their mouse counterparts, all human thymic Tregs, but not conventional thymocytes, express TNFR2 [54]. Recently it has been shown that TNF-TNFR2 interaction plays a critical role in the expansion of human $CD4^+$ and $CD8^+$ Tregs [55,56]. Although TNF does not convert, but proliferatively expands $FoxP3^+$ Tregs in the periphery. Human circulating $FoxP3^+$ cells present in $CD25^{hi}$, $CD25^{low}$ and even $CD25^-$ subsets of $CD4^+$ cells expressed markedly higher levels of TNFR2 (~70%), as compared with $CD4^+FoxP3^-$ Teffs (~20%) [50,57,58]. TNFR2 is also expressed on antigen-specific CD4 Tregs induced by tolerogeneic DCs [55] and $CD8^+$ Tregs generated by anti-CD3 treatment [56]. The functional implications of TNFR2 in human Treg activity also are becoming evident. For example, both activated human and mouse Tregs produce high levels of sTNFR2 which contribute to their immunosuppressive activity [57]. TNF–TNFR2 interaction promotes the survival of Tregs in cancer and at inflammatory sites by inducing thioredoxin-1, a major antioxidative molecule, of Tregs in a NFκB-dependent manner [59]. Furthermore, as in mice, TNF-TNFR2 interaction increases FoxP3 expression by human Tregs (our unpublished data).