Published in final edited form as:

Cytokine. 2018 January ; 101: 14–18. doi:10.1016/j.cyto.2016.08.003.

TNF Activity and T cells

Amit K. Mehta, Donald T. Gracias, and Michael Croft

La Jolla Institute for Allergy and Immunology, Division of Immune Regulation, 9420 Athena Circle, La Jolla, CA 92037, United States

Abstract

TNF (tumor necrosis factor) is both a pro-inflammatory and anti-inflammatory cytokine that is central to the development of autoimmune disease, cancer, and protection against infectious pathogens. As well as a myriad other activities, TNF can be a product of T cells and can act on T cells. Here we review old and new data on the importance of TNF produced by T cells and how TNF signaling via TNFR2 may directly impact alternate aspects of T cell biology. TNF can promote the activation and proliferation of naïve and effector T cells, but also can induce apoptosis of highly activated effector T cells, further determining the size of the pathogenic or protective conventional T cell pool. Moreover, TNF can have divergent effects on regulatory T cells. It can both downregulate their suppressive capacity, but also contribute in other instances to their development or accumulation. Biologics that block TNF or stimulate TNFR2 therefore have the potential to strongly modulate the balance between effector T cells and Treg cells which could impact disease in both positive and negative manners.

Keywords

TNF; TNFR1; TNFR2; T cells; Treg

1. Introduction

Tumor necrosis factor (TNF, previously referred to as TNF- α) is a pleiotropic cytokine involved in the pathogenesis of a range of physiological processes that control inflammation, anti-tumor responses, and immune system homeostasis [1, 2]. TNF is best known for its protective activity against pathogens, being a product of effector CD4 and CD8 T cells or innate cells, that can lead to killing of infected cells. It is also known for its activity in tissues, highlighted by the successes of the TNF inhibitors in patients with RA, psoriatic arthritis, crohn's disease and other indications, where it mediates inflammatory activity, at least in part via effects in structural cells such as fibroblasts, endothelial cells, and epithelial cells. These actions are largely mediated by TNF receptor 1 (TNFR1, p55) [3–6] that is

Corresponding author: M. Croft (mick@lji.org).

Disclosure

M.C. has licensed patents on several TNF superfamily molecules.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ubiquitously expressed by almost all cell types and has been suggested to be the primary receptor for soluble TNF. What has received less attention are the effects of TNF on T cells, even though the initial observations of a TNF receptor being induced in T cells or thymocytes after activation, and TNF controlling some functional responses, were reported many years ago [7–10]. In this article, we review both older and recent literature on the importance of TNF made by T cells, and the role of TNF in modulating T cell activity, which may primarily reflect the activity of TNFR2 (p75/p80) that can respond strongly to membrane-bound TNF as well as soluble TNF [11].

2. Role of TNF during T cell-mediated immunity or autoimmunity

Early studies in TNF^{−/−} or TNFR^{−/−} mice suggested both beneficial and harmful effects of TNF in immune responses [12–14], although the source of TNF for these activities was not clear. More recent studies with conditional ablation of TNF in T cells versus myeloid cells have clarified the role of T cell-derived TNF to a certain extent [15]. For example, TNF^{−/−} or TNFR1^{−/−} mice are resistant to lethal doses of lipopolysaccharide (LPS) or *S. aureus* enterotoxin B (SEB) but are severely impaired in clearing *Listeria monocytogenes*. Specific TNF ablation in T lymphocytes in mice mimicked the increased susceptibility to high doses of *Listeria*, but these mice remained resistant to low dose infection [16]. In contrast, TNF deletion in T cells did not protect mice against LPS-induced septic shock, but reduced lethality from shock induced by SEB [16], illustrating the complexity of the role of TNF produced by T cells. Similarly, TNF produced by myeloid cells has been shown to control early stages of *Mycobacterium tuberculosis* infection with little role for T cell-derived TNF, whereas the latter was crucial for protection at later stages of infection [17].

Further underscoring the intricacies of TNF action, TNF can be expressed by T cells in a transmembrane form and produced as a soluble molecule after membrane cleavage by an ADAM family metalloprotease. Several groups utilized mice that express only transmembrane TNF, and found roles for both forms of TNF but under alternate scenarios [18–20]. Mice with only membrane TNF showed increased sensitivity to high doses of *Listeria* similar to TNF^{−/−} mice and T cell TNF-conditional knockout mice, indicating that soluble TNF made by T cells was critical. However, transmembrane TNF expressed on memory T cells was sufficient for control of a secondary *Listeria* infection. Similar to the latter observation, TNF was found indispensable for control of *Francisella tularensis* live vaccine strain (LVS) that is mediated by memory CD8 T cells, and the transmembrane form was shown to be critical for this activity [21].

It is well established that TNF is pathogenic in many scenarios given the results from inhibiting TNF in patients with RA, Crohn's disease, psoriatic arthritis, and ankylosing spondylitis. However, TNF may be protective in other inflammatory diseases typified by reports of exacerbated symptoms in MS patients. How much T cell-derived TNF, and the soluble or membrane version, contributes to autoimmunity, or protection against autoimmunity, is not clear. In the case of the protective effect of TNF in neuroinflammation, the transmembrane form acting through TNFR2 has been suggested to be most important as shown by studies of mice capable of making transmembrane TNF but not soluble TNF, that were protected from developing MS-like disease in the murine model of EAE [18]. In other

cases, variable effects of T cell-derived membrane vs. soluble TNF have been seen in GVHD models. Mice receiving T cells expressing only membrane TNF exhibited less severe GVHD compared to those receiving T cells that could produce soluble TNF. In contrast, the graft-versus-tumor activity of the T cells remained intact when only membrane TNF could be produced [22], again illustrating different roles for the two versions. In type I diabetes, T cells have been suggested to have a prominent role in pathogenesis, and elimination of CD8 T cells fully protects mice from the experimental disease. Indirect data has suggested that membrane TNF interacting with TNFR2 is required for islet destruction [23]. Furthermore, pathogenic Th1 clones that make soluble TNF when transferred into NOD/SCID recipients can drive autoimmune attack in the pancreas [24]. T cells are also one of the most abundant cell types in the RA synovium, comprising 30–50% of synovial tissue cells [25], but there is little understanding about how T cell derived TNF contributes to disease. Initial studies with an overexpression system of TNF in T cells showed this was sufficient to promote arthritis, wasting syndrome, and organ necrosis [26]. Experiments using knock-in mice with a deletion of the AU-rich elements in the TNF gene 3' UTR, that results in overproduction of TNF, showed the development of chronic inflammatory arthritis and inflammatory bowel disease. Interestingly, when crossed with RAG 1^{-/-} mice, these animals still displayed full signs of destructive arthritis, but were protected from Crohn's-like intestinal phenotype, implying a role for TNF derived from T cells in the later but not former phenotype [27].

Another variable in terms of the activity of T cell derived TNF is that the transmembrane form can be a receptor as well as a ligand for TNFR1/2, and similar to other TNF family proteins membrane TNF can “reverse” signal into the cell that bears this molecule [28]. It is not clear what is the physiological role of any signal generated by cross-linking membrane TNF, and reported activities from in vitro studies describe both anti-inflammatory and pro-inflammatory effects in T cells depending on the subset (CD4 or CD8) and depending on the aspect of response analyzed [29, 30]. Anti-inflammatory effects of reverse signaling through membrane TNF have been discussed as contributing to the therapeutic effects of the approved anti-TNF biologics, such as infliximab, in particular the idea that this can induce apoptosis in cells such as monocytes/macrophages [31]. Although antibodies cross-linking membrane TNF have been reported to also promote apoptosis in T cell lines or upregulation of suppressive molecules like IL-10 [32], there is a paucity of information in this regard in primary T cells and from in vivo studies.

In summary, although we have not reviewed all of the literature that relates to T cell production of TNF, it is clear that both the membrane bound form and the soluble form can be active, but when and where they are active, in driving or protecting against autoimmune disease, or protecting against pathogens, is highly variable and not necessarily predictable.

3. Activity of TNF on naïve and effector T cell proliferation and survival

As opposed to the role of TNF made by T cells, a substantial amount of data has now shown that T cells can be the recipients of TNF activity. During the early phase of T cell receptor (TCR) triggering, TNF has been shown to be capable of enhancing TCR-dependent activation of both CD4 and CD8 T cells, including augmenting levels of IL-2R, enhancing T cell proliferation, and increasing cytokine production [7, 10]. This is potentially by

increasing the activation of NF- κ B signaling pathways that can impact all of these functional responses [33]. As such TNF can act as a co-stimulatory molecule for T cells given that antigen recognition only weakly activates NF- κ B. Importantly, it is TNF signaling through the TNFR2, and not TNFR1, that has been shown to be directly co-stimulatory to TCR-mediated T cell activation [34–37]. TNFR2-deficient T cells are less responsiveness when activated via cross-linking the TCR, and interestingly, provision of CD28 signals did not restore the response of these cells, thus suggesting a non-redundant role for TNF in promoting early T cell activity [38]. Importantly, TNFR2 signals were found to lower the threshold level of TCR signaling required for T cell activation, again consistent with the idea of supplementing NF- κ B activity, that can be limiting when the TCR is engaged in isolation [38]. In line with this, a TNFR2-deficiency in mice resulted in both decreased proliferation and cytokine production in CD4 and CD8 T cells [38, 39]. Similarly, TNF/TNFR2 signals in T cells were found to be critically required for effective priming, proliferation and recruitment of CD8 T cells to the sites of tumor growth in vivo, although were not required for the stronger CD8 T cell response to LCMV [40]. These are the types of observations that have also been reported for many other co-stimulatory molecules in varying scenarios, including CD28, and TNFR family members such as OX40 and CD27, where the level of antigenic stimulation and the presence of other inflammatory molecules can modulate how critical certain molecules are to the T cell response. However, it again supports the notion that TNF can be viewed as a bona fide co-stimulatory ligand for T cells. In addition, as reported with other co-stimulatory molecules [1], TNFR2 signaling in CD4 effector T cells was recently shown to increase resistance to regulatory T cell (Treg)-mediated suppression [41], and signaling into responding naïve CD4 T cells antagonized the action of TGF- β in promoting the differentiation of Foxp3⁺ Treg cells [42]. This furthers the conclusion that TNF can play a strong role in promoting the effector arm of the T cell response.

In addition to TNF's action in driving T cell proliferation, it can also contribute to sustaining T cell survival during initiation of immune responses. Some studies have revealed TNF signaling through TNFR2 can increase expression of anti-apoptotic molecules such as Bcl-2, Bcl-xL and survivin during the early phase of T cell activation [39, 43]. These observations were strengthened by finding that TNFR2-deficient mice can possess significantly reduced pools of memory T cells that is likely a consequence of poor effector T cell accumulation in the primary response [39]. Additionally, it was reported that the clinically approved TNF neutralizing antibodies led to T cell apoptosis, when CD4 T cells from the lamina propria and membrane TNF⁺ intestinal macrophages from IBD patients were cultured together [44], likely indicative of removing an NF- κ B driven survival signal. Similarly, signaling through both TNFR2 and α 1 β 1 integrin were suggested to protect airway CD8 effector T cells from apoptotic death during influenza virus infections [45]. Lastly, a potential cross-play between TNFR2 and TNFR1 on CD8 T cells was reported. The absence of TNFR2 signaling during early T cell activation led to resistance to undergo activation-induced cell death (AICD) upon restimulation with anti-CD3, and this was resistance was mediated by TNF signaling through TNFR1 [46]. Therefore, it is possible that TNFR1 might also provide survival signals to T cells in some scenarios.

4. Role of TNF in apoptosis and clonal contraction of effector T cells

In contrast to a role in supporting pro-inflammatory activity, TNF may also have an anti-inflammatory effect through an action on T cells in some scenarios. TNF can be a primary pathway leading to apoptosis of various cells [47], and this may also be true for T cells, particularly for CD8 T cells that can undergo strong clonal contraction after the peak of the effector response or those that might be susceptible to undergoing apoptosis while in an effector state in tissues. Thus, prolonged exposure to TNF, or TNF signaling at the later stages of the effector response, may support increased T cell death. This could either limit pathology associated with exaggerated pathogen responses or limit inflammation in some chronic autoimmune responses.

The apoptotic activity of TNF in many cell types has been primarily attributed to TNFR1, but TNFR2 can enhance apoptotic death driven by TNFR1 [48], and data supports a role for TNFR2 in controlling this activity in T cells. In mice lacking both receptors, but not those deficient in either one, clonal contraction of CD8 T cells responding to LCMV was impaired [49]. In other studies, while TNF/TNFR2 signaling was found to enhance effector T cell functions during a response to influenza virus, at the same time it was found that a selective deficiency in TNFR2 in CD8 T cells led to enhanced numbers of these cells persisting after clearance of the virus [50]. Whether this was due to impaired TNFR1-driven apoptosis, or some compensation mechanism whereby the loss of TNFR2 signaling potentiated the activity of pro-survival signals, as suggested from some in vitro studies [46], is not clear. However, TNF and agonists to TNFR2 have been shown to cause the death of auto-reactive CD8 T cells from patients with diabetes [51], hinting towards an apoptotic role for TNFR2 in modulating T cell responses to self-antigen. Similar to studies done with CD8 T cells, various reports have also indicated a role for TNF signaling, through either TNFR1 or TNFR2, in inducing apoptosis of CD4 T cells, particularly in aged or HIV-infected patients [52–54]. It is likely that alternate T cell subsets, or stages of activation, will exhibit differential sensitivities to TNF-driven apoptosis, as suggested in some studies [55], which will be further controlled by any additional environmental signals that a T cell is receiving when it encounters TNF.

Other anti-inflammatory activities of TNF have been described related to T cells. Chronic exposure of diabetogenic T cell clones to TNF led to T cell unresponsiveness in one study [56]. Furthermore, as described above, mice expressing only the transmembrane form of TNF were protected from developing MS-like disease in the murine model of EAE, an action independent of TNFR1 [18]. While the explanation for these effects are not clear, they may be related to TNF/TNFR2 activity promoting apoptosis in T cells or as detailed below an activity in promoting expansion or maintenance of regulatory T cells.

5. TNF control of regulatory T cells

As well as effects on conventional T cells, it has recently become apparent that TNF can exert strong activity on regulatory T (Treg) cells. TNFR2 but not TNFR1 is expressed by human and mouse CD4 Foxp3⁺ Treg cells [57], and co-expression of CD25 with TNFR2 has been suggested to mark the cells with the most suppressive capacity [58]. Similar to other

co-stimulatory molecules in the TNFR family, like OX40L and GITRL, TNF can exert two divergent effects on Treg cells, one to downregulate their suppressive capacity, and two to promote their proliferation. Therefore, depending on which effect prevails, this would be another example where TNF could exert either protective (anti-inflammatory) or pathogenic (pro-inflammatory) activity.

In the joints of patients with rheumatoid arthritis, Treg cells are poor at inhibiting effector cytokine production by conventional T cells, and several studies have suggested that this defect in suppressive capacity is due to TNF as it can be reversed by the approved TNF inhibitors [59–61]. Although indirect, the Treg cell defect in RA joints has been associated with a lack of CTLA-4 accumulation on their surface, suggesting that TNF signaling could downregulate this molecule that has been implicated in mediating suppression [62]. Other mechanisms by which TNF might control the suppressive action of Treg cells have also been proposed. Foxp3 is the master transcription factor for many Treg cells and dictates inhibitory function. TNF was found to strongly downregulate Foxp3 expression in studies of human Treg cells [60], and TNF also antagonized the upregulation of Foxp3 in naïve T cells differentiating into Treg cells under the influence of TGF- β [42]. Foxp3 also needs to be phosphorylated to impart suppressive capacity. TNF signaling to Treg cells in another study increased the levels and activity of protein phosphatase 1. This was in turn described to dephosphorylate Foxp3, leading to impaired suppressive function [61]. The exact signaling pathways required for these effects of TNFR2 are not known, but canonical NF- κ B signaling may be key as well as the PI3K/Akt pathway [42, 63].

In a diametrically opposite activity, a number of reports have shown that TNF can promote the proliferation and expansion of Treg cells, and thus drive the accumulation of this suppressive population. In co-cultures of murine Treg cells and effector T cells, exposure to TNF transiently abrogated suppression, but longer exposure to TNF restored the suppressive effects, and in synergy with IL-2, TNF resulted in an expanded population of Treg cells that up-regulated expression of CD25 and Foxp3 [57]. Furthermore, TNF was found to maintain Foxp3 expression in thymic-derived Treg cells in vitro through an action of TNFR2, and Treg cells lacking TNFR2 were unable to suppress colitis when transferred into RAG-/- mice, which could have been related to a lack of survival of the Treg cells or specific loss of Foxp3 [64, 65]. As described above, this action may also explain why mice only expressing transmembrane TNF were protected from developing EAE, as it may have focused TNFs action on promoting Treg cell accumulation via selectively activating TNFR2 signaling [18]. In accordance, another study in a murine model of type I diabetes showed that pathogenic effector T cells stimulated the expansion and suppression of islet-specific Treg cells when co-transferred in vivo, at least partially through TNF/TNFR2 interaction [66]. Lastly, it was recently suggested that the development of Foxp3⁺ Treg cells in the thymus was also dependent on TNFR2 activity, in concert with two other TNFR family molecules [67]. This illustrates that TNF signaling has the capability to augment the accumulation of Treg cells just as it can in some instances augment the accumulation of effector T cells. These data suggest that manipulating TNF activity has the possibility of tipping the balance between pathogenic effector T cells and Treg cells in either direction, perhaps dictated by what other inflammatory factors are present at the time. Whether this can in part explain why blocking

TNF is effective in some diseases, but contraindicated in others such as MS, is not known, but this is undoubtedly a possibility.

Concluding Remarks

At the present time, it is obvious that TNF can have several actions related to T cell biology. It is an important effector molecule made by T cells, either in transmembrane or soluble form, but also is an important effector molecule for controlling the activity of both conventional T cells and Treg cells. While the potential effects of TNF on T cells have been well documented, major questions that remain unanswered are how much of the beneficial or detrimental effects of therapeutically targeting TNF in vivo are related to modulating T cell activity. Moreover, would specific reagents that only block TNF binding to TNFR1, or to TNFR2, display similar, better, or worse activity compared to the pan-TNF inhibitors, especially given the notion that most of the T cell related activity of TNF is via TNFR2.

It could certainly be suggested that part of the therapeutic activity of the approved TNF biologics in diseases such as RA or Crohn's might be related to inhibiting the accumulation of pathogenic T cells and/or relieving the negative effect TNF can have on Treg cell suppressive activity. However, there is still the primary issue of whether blocking all TNF activity in vivo, or selectively blocking TNFR2, is going to positively or negatively affect Treg cells given the mounting data that TNF can also promote the survival of these cells or help maintain the Treg cell phenotype. As discussed above, some of the therapeutic activity of the anti-TNF antibodies has also been suggested to depend on suppressive signaling through the transmembrane form of TNF, rather than simple blockade of TNF activity. This has been proposed to in part explain why etanercept, that cannot induce this type of reverse signaling well, does not have the same activity in inflammatory bowel disease as antibodies like infliximab and adalimumab. If reverse signaling in T cells is activated by the therapeutic antibodies, another question here is whether the capacity of membrane TNF to signal is the same in Treg cells versus pathogenic T cells and if so whether this enhances or suppresses Treg cell activity.

As opposed to reagents that target TNF, there have been proposals that agonists of TNFR2 might also be therapeutically useful for autoimmunity and inflammatory disease, with the idea that they will preferentially promote Treg cell expansion and/or induce apoptosis in highly active autoreactive T cells, or simply have beneficial effects not related to T cells [68]. But, again, whether agonists would similarly enhance the accumulation of pathogenic T cells is not clear, although this is also a distinct possibility.

In an alternative disease scenario, blocking TNFR2 in cancer patients might have the ability to suppress the survival or accumulation of tumor-resident Treg cells, as implied by recent studies that found increased control of tumor cell growth in TNFR2-deficient animals [69] that may be related to defective activity of myeloid suppressor cells and Treg cells [70–72]. Conversely, one could argue that accumulation of tumor-infiltrating conventional T cells might equally rely on TNFR2 activity, and agonist targeting of TNFR2 would be a better strategy to promote the protective effector T cell arm of the anti-tumor response.

Ultimately, even though the literature on TNF that is related to T cells dates back almost 30 years, as with other members of the TNF family [73], we can still benefit from more pre-clinical data to inform future strategies for therapeutically manipulating TNF and T cell activity.

Acknowledgments

M.C is supported by NIH grants AI070535, AI103021, AI110929, AI123134.

References

1. Croft M. The role of TNF superfamily members in T-cell function and diseases. *Nature reviews Immunology*. 2009; 9(4):271–85.
2. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nature reviews Immunology*. 2003; 3(9):745–56.
3. Clark J, Vagenas P, Panesar M, Cope AP. What does tumour necrosis factor excess do to the immune system long term? *Annals of the rheumatic diseases*. 2005; 64(Suppl 4):iv70–6. [PubMed: 16239393]
4. Cope AP. Regulation of autoimmunity by proinflammatory cytokines. *Current opinion in immunology*. 1998; 10(6):669–76. [PubMed: 9914219]
5. Kollias G, Kontoyiannis D. Role of TNF/TNFR in autoimmunity: specific TNF receptor blockade may be advantageous to anti-TNF treatments. *Cytokine & growth factor reviews*. 2002; 13(4–5): 315–21. [PubMed: 12220546]
6. Sfrikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Current directions in autoimmunity*. 2010; 11:180–210. [PubMed: 20173395]
7. Scheurich P, Thoma B, Ucer U, Pfizenmaier K. Immunoregulatory activity of recombinant human tumor necrosis factor (TNF)-alpha: induction of TNF receptors on human T cells and TNF-alpha-mediated enhancement of T cell responses. *Journal of immunology*. 1987; 138(6):1786–90.
8. Hurme M. Both interleukin 1 and tumor necrosis factor enhance thymocyte proliferation. *European journal of immunology*. 1988; 18(8):1303–6. [PubMed: 3262066]
9. Ranges GE, Zlotnik A, Espevik T, Dinarello CA, Cerami A, Palladino MA Jr. Tumor necrosis factor alpha/cachectin is a growth factor for thymocytes. Synergistic interactions with other cytokines. *The Journal of experimental medicine*. 1988; 167(4):1472–8. [PubMed: 3282023]
10. Yokota S, Geppert TD, Lipsky PE. Enhancement of antigen- and mitogen-induced human T lymphocyte proliferation by tumor necrosis factor-alpha. *Journal of immunology*. 1988; 140(2): 531–6.
11. Grell M, Douni E, Wajant H, Lohden M, Clauss M, Maxeiner B, Georgopoulos S, Lesslauer W, Kollias G, Pfizenmaier K, Scheurich P. The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor. *Cell*. 1995; 83(5):793–802. [PubMed: 8521496]
12. Marino MW, Dunn A, Grail D, Inglese M, Noguchi Y, Richards E, Jungbluth A, Wada H, Moore M, Williamson B, Basu S, Old LJ. Characterization of tumor necrosis factor-deficient mice. *Proceedings of the National Academy of Sciences of the United States of America*. 1997; 94(15): 8093–8. [PubMed: 9223320]
13. Pfeffer K, Matsuyama T, Kundig TM, Wakeham A, Kishihara K, Shahinian A, Wiegmann K, Ohashi PS, Kronke M, Mak TW. Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to *L. monocytogenes* infection. *Cell*. 1993; 73(3):457–67. [PubMed: 8387893]
14. Rothe J, Lesslauer W, Lotscher H, Lang Y, Koebel P, Kontgen F, Althage A, Zinkernagel R, Steinmetz M, Bluethmann H. Mice lacking the tumour necrosis factor receptor 1 are resistant to TNF-mediated toxicity but highly susceptible to infection by *Listeria monocytogenes*. *Nature*. 1993; 364(6440):798–802. [PubMed: 8395024]

15. Winsauer C, Kruglov AA, Chashchina AA, Drutskaya MS, Nedospasov SA. Cellular sources of pathogenic and protective TNF and experimental strategies based on utilization of TNF humanized mice. *Cytokine & growth factor reviews*. 2014; 25(2):115–23. [PubMed: 24405806]
16. Grivennikov SI, Tumanov AV, Liepinsh DJ, Kruglov AA, Marakusha BI, Shakhov AN, Murakami T, Drutskaya LN, Forster I, Clausen BE, Tessarollo L, Ryffel B, Kuprash DV, Nedospasov SA. Distinct and nonredundant in vivo functions of TNF produced by T cells and macrophages/neutrophils: protective and deleterious effects. *Immunity*. 2005; 22(1):93–104. [PubMed: 15664162]
17. Allie N, Grivennikov SI, Keeton R, Hsu NJ, Bourigault ML, Court N, Fremont C, Yermeev V, Shebzukhov Y, Ryffel B, Nedospasov SA, Quesniaux VF, Jacobs M. Prominent role for T cell-derived tumour necrosis factor for sustained control of Mycobacterium tuberculosis infection. *Scientific reports*. 2013; 3:1809. [PubMed: 23657146]
18. Alexopoulou L, Kranidioti K, Xanthouleas S, Denis M, Kotanidou A, Douni E, Blackshear PJ, Kontoyiannis DL, Kollias G. Transmembrane TNF protects mutant mice against intracellular bacterial infections, chronic inflammation and autoimmunity. *European journal of immunology*. 2006; 36(10):2768–80. [PubMed: 16983719]
19. Musicki K, Briscoe H, Tran S, Britton WJ, Saunders BM. Differential requirements for soluble and transmembrane tumor necrosis factor in the immunological control of primary and secondary *Listeria monocytogenes* infection. *Infection and immunity*. 2006; 74(6):3180–9. [PubMed: 16714545]
20. Torres D, Janot L, Quesniaux VF, Grivennikov SI, Maillet I, Sedgwick JD, Ryffel B, Erard F. Membrane tumor necrosis factor confers partial protection to *Listeria* infection. *The American journal of pathology*. 2005; 167(6):1677–87. [PubMed: 16314479]
21. Cowley SC, Sedgwick JD, Elkins KL. Differential requirements by CD4+ and CD8+ T cells for soluble and membrane TNF in control of *Francisella tularensis* live vaccine strain intramacrophage growth. *Journal of immunology*. 2007; 179(11):7709–19.
22. Borsotti C, Franklin AR, Lu SX, Kim TD, Smith OM, Suh D, King CG, Chow A, Liu C, Alpdogan O, van den Brink MR. Absence of donor T-cell-derived soluble TNF decreases graft-versus-host disease without impairing graft-versus-tumor activity. *Blood*. 2007; 110(2):783–6. [PubMed: 17395784]
23. Herrera PL, Harlan DM, Vassalli P. A mouse CD8 T cell-mediated acute autoimmune diabetes independent of the perforin and Fas cytotoxic pathways: possible role of membrane TNF. *Proceedings of the National Academy of Sciences of the United States of America*. 2000; 97(1):279–84. [PubMed: 10618409]
24. Cantor J, Haskins K. Effector function of diabetogenic CD4 Th1 T cell clones: a central role for TNF- α . *Journal of immunology*. 2005; 175(11):7738–45.
25. Isaacs JD. Therapeutic T-cell manipulation in rheumatoid arthritis: past, present and future. *Rheumatology*. 2008; 47(10):1461–8. [PubMed: 18503092]
26. Probert L, Keffer J, Corbella P, Cazlaris H, Patsavoudi E, Stephens S, Kaslaris E, Kioussis D, Kollias G. Wasting, ischemia, and lymphoid abnormalities in mice expressing T cell-targeted human tumor necrosis factor transgenes. *Journal of immunology*. 1993; 151(4):1894–906.
27. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity*. 1999; 10(3):387–98. [PubMed: 10204494]
28. Juhasz K, Buzas K, Duda E. Importance of reverse signaling of the TNF superfamily in immune regulation. *Expert review of clinical immunology*. 2013; 9(4):335–48. [PubMed: 23557269]
29. Vudattu NK, Holler E, Ewing P, Schulz U, Haffner S, Burger V, Kirchner S, Andreesen R, Eissner G. Reverse signalling of membrane-integrated tumour necrosis factor differentially regulates alloresponses of CD4+ and CD8+ T cells against human microvascular endothelial cells. *Immunology*. 2005; 115(4):536–43. [PubMed: 16011522]
30. Harashima S, Horiuchi T, Hatta N, Morita C, Higuchi M, Sawabe T, Tsukamoto H, Tahira T, Hayashi K, Fujita S, Niho Y. Outside-to-inside signal through the membrane TNF- α induces E-selectin (CD62E) expression on activated human CD4+ T cells. *Journal of immunology*. 2001; 166(1):130–6.

31. Horiuchi T, Mitoma H, Harashima S, Tsukamoto H, Shimoda T. Transmembrane TNF- α : structure, function and interaction with anti-TNF agents. *Rheumatology*. 2010; 49(7):1215–28. [PubMed: 20194223]
32. Mitoma H, Horiuchi T, Hatta N, Tsukamoto H, Harashima S, Kikuchi Y, Otsuka J, Okamura S, Fujita S, Harada M. Infliximab induces potent anti-inflammatory responses by outside-to-inside signals through transmembrane TNF- α . *Gastroenterology*. 2005; 128(2):376–92. [PubMed: 15685549]
33. Banerjee D, Liou HC, Sen R. c-Rel-dependent priming of naive T cells by inflammatory cytokines. *Immunity*. 2005; 23(4):445–58. [PubMed: 16226509]
34. Andrews JS, Berger AE, Ware CF. Characterization of the receptor for tumor necrosis factor (TNF) and lymphotoxin (LT) on human T lymphocytes. TNF and LT differ in their receptor binding properties and the induction of MHC class I proteins on a human CD4+ T cell hybridoma. *Journal of immunology*. 1990; 144(7):2582–91.
35. Tartaglia LA, Weber RF, Figari IS, Reynolds C, Palladino MA Jr, Goeddel DV. The two different receptors for tumor necrosis factor mediate distinct cellular responses. *Proceedings of the National Academy of Sciences of the United States of America*. 1991; 88(20):9292–6. [PubMed: 1718003]
36. Ware CF, Crowe PD, Vanarsdale TL, Andrews JL, Grayson MH, Jerzy R, Smith CA, Goodwin RG. Tumor necrosis factor (TNF) receptor expression in T lymphocytes. Differential regulation of the type I TNF receptor during activation of resting and effector T cells. *Journal of immunology*. 1991; 147(12):4229–38.
37. Aspalter RM, Eibl MM, Wolf HM. Regulation of TCR-mediated T cell activation by TNF-RII. *Journal of leukocyte biology*. 2003; 74(4):572–82. [PubMed: 12960285]
38. Kim EY, Teh HS. TNF type 2 receptor (p75) lowers the threshold of T cell activation. *Journal of immunology*. 2001; 167(12):6812–20.
39. Kim EY, Priatel JJ, Teh SJ, Teh HS. TNF receptor type 2 (p75) functions as a costimulator for antigen-driven T cell responses in vivo. *Journal of immunology*. 2006; 176(2):1026–35.
40. Calzascia T, Pellegrini M, Hall H, Sabbagh L, Ono N, Elford AR, Mak TW, Ohashi PS. TNF- α is critical for antitumor but not antiviral T cell immunity in mice. *The Journal of clinical investigation*. 2007; 117(12):3833–45. [PubMed: 17992258]
41. Chen X, Hamano R, Subleski JJ, Hurwitz AA, Howard OM, Oppenheim JJ. Expression of costimulatory TNFR2 induces resistance of CD4+FoxP3- conventional T cells to suppression by CD4+FoxP3+ regulatory T cells. *Journal of immunology*. 2010; 185(1):174–82.
42. Zhang Q, Cui F, Fang L, Hong J, Zheng B, Zhang JZ. TNF- α impairs differentiation and function of TGF- β -induced Treg cells in autoimmune diseases through Akt and Smad3 signaling pathway. *Journal of molecular cell biology*. 2013; 5(2):85–98. [PubMed: 23243069]
43. Lin RH, Hwang YW, Yang BC, Lin CS. TNF receptor-2-triggered apoptosis is associated with the down-regulation of Bcl-xL on activated T cells and can be prevented by CD28 costimulation. *Journal of immunology*. 1997; 158(2):598–603.
44. Atreya R, Zimmer M, Bartsch B, Waldner MJ, Atreya I, Neumann H, Hildner K, Hoffman A, Kiesslich R, Rink AD, Rau TT, Rose-John S, Kessler H, Schmidt J, Neurath MF. Antibodies against tumor necrosis factor (TNF) induce T-cell apoptosis in patients with inflammatory bowel diseases via TNF receptor 2 and intestinal CD14(+) macrophages. *Gastroenterology*. 2011; 141(6):2026–38. [PubMed: 21875498]
45. Richter MV, Topham DJ. The α 1 β 1 integrin and TNF receptor II protect airway CD8+ effector T cells from apoptosis during influenza infection. *Journal of immunology*. 2007; 179(8):5054–63.
46. Twu YC, Gold MR, Teh HS. TNFR1 delivers pro-survival signals that are required for limiting TNFR2-dependent activation-induced cell death (AICD) in CD8+ T cells. *European journal of immunology*. 2011; 41(2):335–44. [PubMed: 21268004]
47. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nature reviews Immunology*. 2015; 15(6):362–74.
48. Li X, Yang Y, Ashwell JD. TNF-RII and c-IAP1 mediate ubiquitination and degradation of TRAF2. *Nature*. 2002; 416(6878):345–7. [PubMed: 11907583]

49. Suresh M, Singh A, Fischer C. Role of tumor necrosis factor receptors in regulating CD8 T-cell responses during acute lymphocytic choriomeningitis virus infection. *Journal of virology*. 2005; 79(1):202–13. [PubMed: 15596816]
50. Wortzman ME, Lin GH, Watts TH. Intrinsic TNF/TNFR2 interactions fine-tune the CD8 T cell response to respiratory influenza virus infection in mice. *PloS one*. 2013; 8(7):e68911. [PubMed: 23874808]
51. Ban L, Zhang J, Wang L, Kuhlreiber W, Burger D, Faustman DL. Selective death of autoreactive T cells in human diabetes by TNF or TNF receptor 2 agonism. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(36):13644–9. [PubMed: 18755894]
52. Gupta S. Tumor necrosis factor-alpha-induced apoptosis in T cells from aged humans: a role of TNFR-I and downstream signaling molecules. *Experimental gerontology*. 2002; 37(2–3):293–9. [PubMed: 11772515]
53. Aggarwal S, Gollapudi S, Gupta S. Increased TNF-alpha-induced apoptosis in lymphocytes from aged humans: changes in TNF-alpha receptor expression and activation of caspases. *Journal of immunology*. 1999; 162(4):2154–61.
54. Klein SA, Dobmeyer JM, Dobmeyer TS, Falke D, Kabelitz D, Fries K, Helm EB, Hoelzer D, Rossol-Voth R. TNF-alpha mediated apoptosis of CD4 positive T-lymphocytes. A model of T-cell depletion in HIV infected individuals. *European journal of medical research*. 1996; 1(5):249–58. [PubMed: 9374446]
55. Gupta S, Bi R, Gollapudi S. Central memory and effector memory subsets of human CD4(+) and CD8(+) T cells display differential sensitivity to TNF-{alpha}-induced apoptosis. *Annals of the New York Academy of Sciences*. 2005; 1050:108–14. [PubMed: 16014525]
56. Lee LF, Lih CJ, Huang CJ, Cao T, Cohen SN, McDevitt HO. Genomic expression profiling of TNF-alpha-treated BDC2.5 diabetogenic CD4+ T cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(29):10107–12. [PubMed: 18632574]
57. Chen X, Baumel M, Mannel DN, Howard OM, Oppenheim JJ. Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells. *Journal of immunology*. 2007; 179(1):154–61.
58. Chen X, Subleski JJ, Hamano R, Howard OM, Wiltout RH, Oppenheim JJ. Co-expression of TNFR2 and CD25 identifies more of the functional CD4+FOXP3+ regulatory T cells in human peripheral blood. *European journal of immunology*. 2010; 40(4):1099–106. [PubMed: 20127680]
59. Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA, Mauri C. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFalpha therapy. *The Journal of experimental medicine*. 2004; 200(3):277–85. [PubMed: 15280421]
60. Valencia X, Stephens G, Goldbach-Mansky R, Wilson M, Shevach EM, Lipsky PE. TNF downmodulates the function of human CD4+CD25hi T-regulatory cells. *Blood*. 2006; 108(1):253–61. [PubMed: 16537805]
61. Nie H, Zheng Y, Li R, Guo TB, He D, Fang L, Liu X, Xiao L, Chen X, Wan B, Chin YE, Zhang JZ. Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-alpha in rheumatoid arthritis. *Nature medicine*. 2013; 19(3):322–8.
62. Flores-Borja F, Jury EC, Mauri C, Ehrenstein MR. Defects in CTLA-4 are associated with abnormal regulatory T cell function in rheumatoid arthritis. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(49):19396–401. [PubMed: 19036923]
63. Nagar M, Jacob-Hirsch J, Vernitsky H, Berkun Y, Ben-Horin S, Amariglio N, Bank I, Kloog Y, Rechavi G, Goldstein I. TNF activates a NF-kappaB-regulated cellular program in human CD45RA- regulatory T cells that modulates their suppressive function. *Journal of immunology*. 2010; 184(7):3570–81.
64. Housley WJ, Adams CO, Nichols FC, Puddington L, Lingenheld EG, Zhu L, Rajan TV, Clark RB. Natural but not inducible regulatory T cells require TNF-alpha signaling for in vivo function. *Journal of immunology*. 2011; 186(12):6779–87.
65. Chen X, Wu X, Zhou Q, Howard OM, Netea MG, Oppenheim JJ. TNFR2 is critical for the stabilization of the CD4+Foxp3+ regulatory T. cell phenotype in the inflammatory environment. *Journal of immunology*. 2013; 190(3):1076–84.

66. Grinberg-Bleyer Y, Saadoun D, Baeyens A, Billiard F, Goldstein JD, Gregoire S, Martin GH, Elhage R, Derian N, Carpentier W, Marodon G, Klatzmann D, Piaggio E, Salomon BL. Pathogenic T cells have a paradoxical protective effect in murine autoimmune diabetes by boosting Tregs. *The Journal of clinical investigation*. 2010; 120(12):4558–68. [PubMed: 21099113]
67. Mahmud SA, Manlove LS, Schmitz HM, Xing Y, Wang Y, Owen DL, Schenkel JM, Boomer JS, Green JM, Yagita H, Chi H, Hogquist KA, Farrar MA. Costimulation via the tumor-necrosis factor receptor superfamily couples TCR signal strength to the thymic differentiation of regulatory T cells. *Nature immunology*. 2014; 15(5):473–81. [PubMed: 24633226]
68. Faustman D, Davis M. TNF receptor 2 pathway: drug target for autoimmune diseases. *Nature reviews. Drug discovery*. 2010; 9(6):482–93. [PubMed: 20489699]
69. Zhao X, Rong L, Zhao X, Li X, Liu X, Deng J, Wu H, Xu X, Erben U, Wu P, Syrbe U, Sieper J, Qin Z. TNF signaling drives myeloid-derived suppressor cell accumulation. *The Journal of clinical investigation*. 2012; 122(11):4094–104. [PubMed: 23064360]
70. Chopra M, Riedel SS, Biehl M, Krieger S, von Krosigk V, Bauerlein CA, Brede C, Jordan Garrote AL, Kraus S, Schafer V, Ritz M, Mattenheimer K, Degla A, Mottok A, Einsele H, Wajant H, Beilhack A. Tumor necrosis factor receptor 2-dependent homeostasis of regulatory T cells as a player in TNF-induced experimental metastasis. *Carcinogenesis*. 2013; 34(6):1296–303. [PubMed: 23385062]
71. Govindaraj C, Scalzo-Inguanti K, Madondo M, Hallo J, Flanagan K, Quinn M, Plebanski M. Impaired Th1 immunity in ovarian cancer patients is mediated by TNFR2+ Tregs within the tumor microenvironment. *Clinical immunology*. 2013; 149(1):97–110. [PubMed: 23948613]
72. Chang LY, Lin YC, Chiang JM, Mahalingam J, Su SH, Huang CT, Chen WT, Huang CH, Jeng WJ, Chen YC, Lin SM, Sheen IS, Lin CY. Blockade of TNF-alpha signaling benefits cancer therapy by suppressing effector regulatory T cell expansion. *Oncoimmunology*. 2015; 4(10):e1040215. [PubMed: 26451304]
73. Croft M. The TNF family in T cell differentiation and function--unanswered questions and future directions. *Seminars in immunology*. 2014; 26(3):183–90. [PubMed: 24613728]

Highlights

- TNF is both protective and pathogenic
- TNF is made by and acts on T cells
- TNF promotes activation and proliferation of naïve and memory T cells
- TNF induces apoptosis of highly activated effector T cells
- TNF can enhance accumulation of Treg cells but block their suppressive effects