Cytokine and Growth Factor Reviews 47 (2019) 54–61

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

TNFR2 signaling modulates immunity after allogeneic hematopoietic cell transplantation

Antonella Mancusi[a,1], Maite Alvarez[b,c,1], Sara Piccinelli[a], Andrea Velardi[a], Antonio Pierini[a,*]

[a] Hematology and Clinical Immunology and Bone Marrow Transplant Program, Department of Medicine, University of Perugia, Perugia, 06132, Italy
[b] Program of Immunology and Immunotherapy, Center for Applied Medical Research (CIMA), Pamplona, Spain
[c] Navarra Institute for Health Research (IDISNA), Pamplona, Spain

ARTICLE INFO

Keywords:
Tumor necrosis factor-α
Tumor necrosis factor receptor 2
Allogeneic hematopoietic cell transplantation
Regulatory $CD4^+$ $FOXP3^+$ T cells
Graft versus tumor
Graft versus host disease

ABSTRACT

Tumor necrosis factor-α (TNF-α) signaling through TNF receptor 2 (TNFR2) plays a complex immune regulatory role in allogeneic hematopoietic cell transplantation (HCT). TNF-α is rapidly released in the circulation after the conditioning regimen with chemotherapy and/or radiotherapy. It activates the function of donor alloreactive T cells and donor Natural Killer cells and promotes graft versus tumor effects. However, donor alloreactive T cells also attack host tissues and cause graft versus host disease (GVHD), a life-threatening complication of HCT. Indeed, anti-TNF-α therapy has been used to treat steroid-refractory GVHD. Recent studies have highlighted another role for TNFR2 signaling, as it enhances the function of immune cells with suppressive properties, in particular $CD4^+Foxp3^+$ regulatory T cells (Tregs). Various clinical trials are employing Treg-based treatments to prevent or treat GVHD. The present review will discuss the effects of TNFR2 signaling in the setting of allogeneic HCT, the implications for the use of anti-TNF-α therapy to treat GVHD and the clinical perspectives of strategies that specifically target this pathway.

1. Introduction

Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine that plays a crucial role in immunity and inflammation [1–5]. Because of its pro-inflammatory activity, TNF-α is involved in the pathogenesis of immune-mediated diseases. Indeed, anti-TNF-α therapies are widely used for the treatment of autoimmune diseases [5,6]. However, recent studies show that TNF-α exerts a more complex immune regulatory role. TNF-α is expressed as a type II transmembrane protein, which can be converted to a soluble form. Both transmembrane and soluble TNF-α have biological activity and they act through two receptors, TNF receptor 1 (TNFR1) and 2 (TNFR2) [1–5]. TNFR1 is widely expressed and contains a cytoplasmic 'death domain', which recruits the adaptor molecule TNFR1-associated death domain protein (TRADD). TNFR1 interacts with different signaling complexes through TRADD, triggering either cell survival or cell death, depending on the cellular context [4,5]. TNFR1-deficient mice are defective in immunity to infection and inflammation [7]. TNFR2 is expressed by immune, endothelial and neuronal cells, and it binds preferentially to transmembrane TNF-α [1–5]. TNFR2 binds directly the TNFR-associated factor 2, leading to activation of the nuclear factor 'kappa-light-chain-enhancer' of activated B cells and mitogen-activated protein kinase pathways [4,5]. Studies in TNFR2-deficient mice highlight the important role of TNFR2 in immune regulation. In fact, TNFR2-deficient mice are affected by exacerbated inflammation [7]. In mouse models of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis, TNFR2-deficiency is associated with severe disease, while TNFR1-deficiency with resistance to disease [8–10].

TNF-α effects on the function of immune cells after allogeneic hematopoietic cell transplantation (HCT) have been extensively investigated. Allogeneic HCT is the only cure for high-risk hematologic malignancies [11]. Donor alloreactive T cells are responsible for both beneficial and adverse reactions. Antigen presenting cells present host alloantigens to donor T cells. Once activated and expanded, alloreactive

Abbreviations: TNF-α, tumor necrosis factor-α; TNFR2, TNF receptor 2; HCT, hematopoietic cell transplantation; GVHD, graft versus host disease; Tregs, $CD4^+Foxp3^+$ regulatory T cells; TNFR1, TNF receptor 1; TRADD, TNFR1-associated death domain; GVT, graft versus tumor; NK, natural killer; IFN-γ, interferon-γ; IL-2, interleukin-2; IL-12, interleukin-12; KIRs, killer cell immunoglobulin-like receptors; DCs, dendritic cells; Bregs, regulatory B cells; MDSCs, myeloid-derived suppressor cells; IL-10, interleukin-10

* Corresponding author.
E-mail address: antonio.pierini@unipg.it (A. Pierini).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.cytogfr.2019.05.001
Received 20 March 2019; Accepted 9 May 2019
Available online 15 May 2019

T cells can eradicate malignant cells (graft-versus-tumor [GVT] effect), preventing relapse. However, they also attack host tissues and cause graft versus host disease (GVHD), a major cause of non-relapse mortality [11,12]. Approximately 30% of patients have an HLA-identical sibling donor. The remaining patients need an alternative donor, that could be a matched unrelated donor, an unrelated umbilical cord blood unit or a HLA haplotype mismatched ("haploidentical") related donor [11,13,14]. Whatever the transplant protocol, relapse and GVHD are still the main causes of allogeneic HCT failure.

Preclinical and clinical studies showed that Natural Killer (NK) cells can exert a GVT effect without causing GVHD. NK cells are the first lymphocyte population to reconstitute after allogeneic HCT providing [15]. NK cells kill virus-infected and malignant cells in a MHC unrestricted manner and produce inflammatory cytokines such as interferon-γ (IFN-γ) and TNF-α, which contribute to the elimination of target cells and the regulation of the immune responses [16,17]. NK-cell activation is regulated by a balance of signals mediated by activating and inhibitory receptors. Human NK cells express inhibitory receptors for HLA class I molecules, including killer cell immunoglobulin-like receptors (KIRs) [16]. NK cells are "licensed/educated" by the interaction with self-HLA molecules and became reactive to transformed cells, that down-regulate HLA class I expression, or allogeneic targets that lack self-HLA molecules (so-called "missing self recognition") [16,18,19]. After haploidentical transplantation, mismatches of the HLA-class I KIR ligands in the graft-versus-host direction (that is the donor possesses a HLA-class I KIR ligand that is absent in the recipient), trigger donor-versus-recipient NK cell alloreactions. These NK cell alloreactions are associated with reduced relapse and improved survival, particularly in patients with acute myeloid leukaemia [14,20–22]. Interestingly, alloreactive NK cells kill recipient hematopoietic targets but spare other tissues. They can even protect from T cell-mediated GVHD as they kill recipient antigen presenting cells [20–22]. Other studies showed that NK cells protect from GvHD by inhibiting the function of alloreactive T cells, while retaining the anti-tumor response [23,24]. At the same time, activated NK cells can indirectly contribute to T-cell mediated GVHD by production of INF-γ and TNF-α. Moreover, a recent study has suggested that activated unlicensed host type NK cells promote allogeneic reconstitution and tolerance after HCT in a GM-CSF dependent manner [25].

GVHD prevention and treatment are mainly based on pharmacological immune suppression, which also affects the GVT effect [11–14]. Recent advancements in the prevention of GVHD are based on the adoptive transfer of regulatory $CD4^+CD25^+FOXP3^+$ T cells (Tregs) that can prevent GVHD caused by the co-infusion of effector T cells even in the absence of post-transplant immune suppression. Tregs play a key role in the maintenance of self-tolerance and in immune homeostasis through their capability of suppressing the function of $CD4^+$ and $CD8^+$ effector T cells, B cells, NK cells, and antigen presenting cells [26–29]. Moreover, recent studies show that Tregs localize in the hematopoietic stem cell niche, where they contribute to HSCs maintenance and promote engraftment and B cell differentiation [30–32]. After allogeneic HCT, Tregs can inhibit the function of antigen presenting cells and suppress activation and expansion of alloreactive T cells in lymph nodes and in peripheral tissues [33–36]. Studies in preclinical models and clinical trials of HCT demonstrated that infusion of donor Tregs suppresses alloreactions against normal tissues, thus preventing GVHD [36–39]. Most importantly, Tregs do not impair alloreactions against tumor cells and, consequently, the GVT effect is preserved. The mechanism through which Treg adoptive transfer helps separating GVT from GVHD is under investigation. Moreover, infusions of low-dose IL-2, that selectively activate Tregs, have been used to treat chronic GVHD [40].

TNF-α levels are increased in patients with acute GVHD and correlate with disease progression [12,41–43]. After the conditioning regimen with chemotherapy and/or radiotherapy, TNF-α is rapidly released by tissue macrophages and it activates donor alloreactive T cells that attack host tissues and cause GVHD. Donor T-cell derived TNF-α may also contribute to this detrimental activity [44]. The anti-TNF-α monoclonal antibody infliximab and the human recombinant TNF-α receptor etanercept have been used to treat steroid-refractory GVHD [42,45,46]. However, their clinical use has been limited by the lack of response in some patients, the high-risk of life-threatening infections, and the possibility of GVHD progression or even exacerbation [45]. Studies in murine models of allogeneic HCT demonstrated that TNF-α is also required for optimal GVT activity. Anti-TNF-α antibody administration is associated with early relapse in mice inoculated with a leukemia cell line [47,48]. Similar results were obtained when the transplant recipients were TNFR1-deficient or received TNF-α-deficient T cells [44,48].

The present review describes how TNFR2 signaling can affect the activity of various subsets of immune cells in the setting of allogeneic HCT. These subsets include effector T cells and NK cells, but also cells with regulatory and immune suppressive properties. We also discuss the clinical perspectives of strategies that specifically target this pathway in HCT.

2. TNFR2 signaling in effector T cells and NK cells

In addition to CD28-related molecules, several TNFR family members can act as co-stimulatory molecules for TCR-dependent T cell activation [49,50]. Studies in TNFR2-deficient mice and -deficient T cells showed that TNFR2 expression is upregulated on activated T cells and TNFR2 can act as a co-stimulatory molecule for T cell activation. In the early phase of T cell response, TNFR2 signaling promotes survival and regulates the threshold for clonal expansion through induction of interleukin-2 (IL-2) and anti-apoptotic molecules. As a consequence, TNFR2 deficiency is also associated with reduced pools of memory T cells in mice. Moreover, TNFR2 signaling activates $CD8^+$ T cell effector functions, as it induces production of INF-γ and expression of Fas-L and granzyme B [49–59]. Upon TCR stimulation, effector $CD4^+$ T cells upregulate TNFR2 expression and become more resistant to suppression mediated by Tregs [60,61]. One study showed that TNFR2 expression by effector $CD4^+$ T cells is required to induce full-fledged experimental colitis in mice [62]. TNFR2 signaling has also anti-inflammatory effects as it may contribute to clonal contraction and apoptosis of effector T cells. Chronic exposure to TNF-α or chronic TNFR2 stimulation has been associated with impairment of TCR signaling with a reduction of cytokine production, including IL-2 [50,53,63–67]. TNFR2 stimulation can also induce activated cell death of $CD8^+$ T cells [59,68–70]. Finally, TNFR2 signaling inhibits naïve $CD4^+$ T cell differentiation into Th17 cells, which are essential for immunity against fungal and extracellular bacterial infections, but are also involved in chronic inflammation and autoimmunity [71].

Some studies suggest TNFR2 signaling also plays a role in NK cell activation. NK cell differentiation, maturation and activation are reduced when TNF-α is blocked [72] and their ability to kill tumor cells is impaired in murine TNF-$\alpha^{-/-}$ cells [73]. A recent study showed that NK cell degranulation and IFN-γ production are defective in rheumatoid arthritis patients after treatment with infliximab, adalimumab or etanercept [74]. Other studies also showed that IFN-γ release by NK cells is impaired in TNF-α or TNFR2 knockout mice. Exogenous administration of TNF-α fails to restore IFN-γ release in TNFR2 deficient NK cells [75,76]. Blockade of TNF-α or TNFR2, but not of TNFR1, reduced hepatic NK cell cytotoxicity [77]. However, the mechanisms that regulate TNFR2 expression on NK cells are still under investigation. TNFR2 is differently expressed by various NK cell subsets. Human $CD56^{dim}$ NK cells and their mouse $CD27^{dim}$ counterpart are mature cells endowed with the highest cytotoxic function. They display higher TNFR2 levels compared with the human $CD56^{bright}$ and mouse $CD27^{high}$ NK cell subsets, respectively. In contrast, TNFR1 expression is similar among these different subsets [76]. These studies suggest that $CD56^{dim}$ NK cells have a lower threshold towards to TNFR2 signaling. Additionally, upon

activation, NK cells produce both transmembrane and soluble TNF-α, and further increase the expression of TNFR1 and TNFR2 [74,77]. Several studies have shown that interleukin-12 (IL-12) can increase TNFR2 expression on NK cells and can enhance NK cell activation in conjunction with TNF-α or a TNFR2 agonist [75,76,78]. Interestingly, TNFR2 signaling is involved in the crosstalk between dendritic cells (DCs) and NK cells, which results in a bidirectional activation of the two cell population [77,78]. Recent studies have highlighted the importance of DC-NK cell crosstalk to generate strong anti-tumor responses. Thus, TNF-α/TNFR2 pathway can be exploited to enhance NK-cell immunity against cancer [79–82].

3. TNFR2 signaling in immune regulatory cells

Recent studies suggest that TNF-α promotes the function of immune cells with regulatory and suppressive properties, in particular of $CD4^+$ Tregs. Mouse and human Tregs express higher levels of TNFR2 compared with effector T cells and priming with TNF-α in combination with IL-2 increases the expression of CD25 and FoxP3, and enhances mouse Treg proliferation and suppressive function in vitro. $TNFR2^+$ Tregs display an activated phenotype and suppress Tcon proliferation and function more efficiently than $TNFR2^-$ Tregs [60,83–89]. Further, TNFR2 can provide a co-stimulus to TCR signaling for effective mouse Treg development in the thymus [90]. Several reports show that TNF-α/TNFR2 pathway is required for optimal function of mouse Treg in vivo. For example, Tregs are capable of controlling colitis induced by the transfer of naïve $CD4^+$ T cells into $Rag1^{-/-}$ mice, while TNFR2-deficient Tregs are not [91,92]. In murine models of autoimmune diabetes, TNF-α produced by pathogenic T cells induces Tregs and exert a paradoxical protective effect [93]. The role of TNF-α/TNFR2 pathway has been extensively investigated in Treg-mediated prevention of GVHD. In a mouse model of HSC transplantation, mouse Tregs lost the ability to control GVHD caused by co-infused T cells when treated with a TNFR2 blocking antibody, or when they were TNFR2 deficient. In addition, Tregs did not control GVHD when TNF-α deficient T cells had been infused. Thus, Tregs need exogenous TNF-α production for their in vivo function [94]. Another study showed that activation with TNF-α could even improve control of GVHD exerted by mouse Treg. When donor Tregs were primed with TNF-α, they prevented GVHD and improved survival at an unfavorable Treg:Tcon ratio compared with unprimed Tregs [95]. Finally, Chopra et al. treated irradiated recipient mice with a TNFR2 agonist protein. The treatment expanded radiation-resistant host Tregs and was associated with reduced GVHD severity and prolonged survival after transplant. The beneficial effect of treatment with TNFR2 agonist was abolished in TNFR2 deficient recipients or where recipients were depleted of Tregs [96]. The last two studies also reported that the GVT effect was unaffected by Treg stimulation. Fig. 1 summarizes how TNFR2 signaling in mouse Tregs impacts on GVHD prevention. Some studies reported that the interaction between TNFR2 and transmembrane TNF-α induced Treg expansion [97,98]. However, there are contradictory data about the effects of TNF-α on human Tregs in vitro [89]. Thus, the role of the TNF-α/TNFR2 pathway in human Treg function needs further investigation in preclinical models. TNFR2 is also a marker of a subset of $CD8^+FoxP3^+$ T cells that are endowed with suppressive activity on effector T cells [50,99]. $CD8^+FoxP3^+$ T cells can be induced in vitro with anti-CD3 antibodies or anti-CD3/CD28 beads. Such cells express TNFR2 and TNF-α/TNFR2 interaction is involved in their induction [100,101].

TNF-α/TNFR2 pathway can affect the function of other subpopulations of immune cells with suppressive and tolerogenic properties that can contribute to GVHD control, such as regulatory B cells (Bregs) and myeloid-derived suppressor cells (MDSCs). Bregs exert their immune suppressive function mainly by releasing interleukin-10, playing an important role during infection and autoimmunity [102–106]. The occurrence of Bregs after allogeneic HCT has been correlated with reduced GVHD incidence [106]. Several studies suggest that Bregs can regulate T cell polarization toward a regulatory FoxP3 + phenotype [106,107]. Both host and donor type IL-10 producing B cells can play an important role in the prevention of GVHD as IL-10 deficiency in the B cell compartment exacerbates GVHD [104]. Interestingly, TNFR2 signaling enhances IL-10 release by Bregs, and TNFR2 expression has been proposed as a marker to identify and select IL-10 producing Bregs [105]. Recent studies suggest that TNF-α promotes survival and enhances suppressive activity of MDSCs. They are a heterogeneous population of myeloid progenitors and immature myeloid cells that activate and expand in pathologic conditions, including cancer, inflammation, chronic infection, and autoimmune diseases [108,109]. Expansion and activation of MDSCs are mainly induced by growth factors and cytokines produced by tumor cells and activated T cells. Once activated, they gain the ability to suppress T cell responses and accumulate in lymphoid organs and in tumors, where they can also promote angiogenesis and metastasis. Some studies suggest MDSCs can also induce Tregs, and can suppress allogeneic T cells that cause GVHD [108,110–112]. TNF-α has been shown to block differentiation of immature myeloid cells and to promote MDSC survival, expansion and suppressive activity in mouse models of chronic inflammation and tumor [113–115]. Several studies suggest transmembrane TNF-α specifically promotes optimal MDSC function via TNFR2 [116–118].

4. Modulation of TNFR2 signaling to improve outcomes of allogeneic HCT

TNF-α promotes activation and proliferation of T cells and these effects are mainly mediated by signaling through TNFR2. After allogeneic HCT, TNF-α triggers donor T cell alloreactions, which target malignant cells but also normal host tissues. Moreover, TNF-α can also boost NK cell-mediated GVT effect. At the same time, TNF-α activates Tregs, which express higher levels of TNFR2 compared with effector T cells [60,81,85], and can suppress T cell alloreactions and prevent GVHD. Thus, TNF-α/TNFR2 pathway plays a complex immune regulatory role in allogeneic HCT, affecting the balance between GVT and GVHD (Fig. 2).

The role of TNFR2 signaling in Treg activation can also affect the efficacy of TNF-α blocking therapies in immune mediated diseases. In the setting of HCT, etanercept and infliximab are mainly used for the treatment of steroid-refractory GVHD. Indeed, some patients do not respond or even worsen after anti-TNF-α therapy. A pitfall of this therapy could be the inhibition of immune cells with suppressive function, particularly Tregs. The use of these anti-TNF-α drugs as form of GVHD prevention could be particularly detrimental, because Tregs suppress donor alloreactive T cell proliferation and mainly exert their protective effect against GVHD soon after transplant [34,119,120].

As signaling through the two TNF-α receptors may have different effects in the regulation of immune responses, reagents that specifically target TNFR2 have been recently developed [121]. They could represent a new option for the treatment of immune-mediated diseases, such as autoimmune diseases and GVHD. TNFR2 agonists can be exploited to selectively boost Treg function in order to improve prevention and therapy of GVHD. A limitation of Treg-based cell therapies in allogeneic HCT is the paucity of Tregs, as they constitute a small fraction of peripheral blood $CD4^+$ T cells. Consequently, different strategies were developed to expand their number ex-vivo, while preserving their purity and stability as much as possible [122]. Current expansion protocols mainly use anti-CD3/anti-CD8 monoclonal antibody-coated beads plus IL-2 and rapamycin. One study showed that when TNF-α or a TNFR2 agonist antibody are added to those expansion protocols $TNFR2^+$ Tregs are selectively expanded and are highly suppressive [86]. This strategy successfully expanded activated $TNFR2^+$ Tregs from type 1 diabetic patients, who have decreased numbers of them [87]. Moreover, the addition of a TNFR2 agonist to a protocol of Treg expansion including a CD28 superagonist and rapamycin enhances hypo-methylation of the *FOXP3* gene and consequently promotes Treg

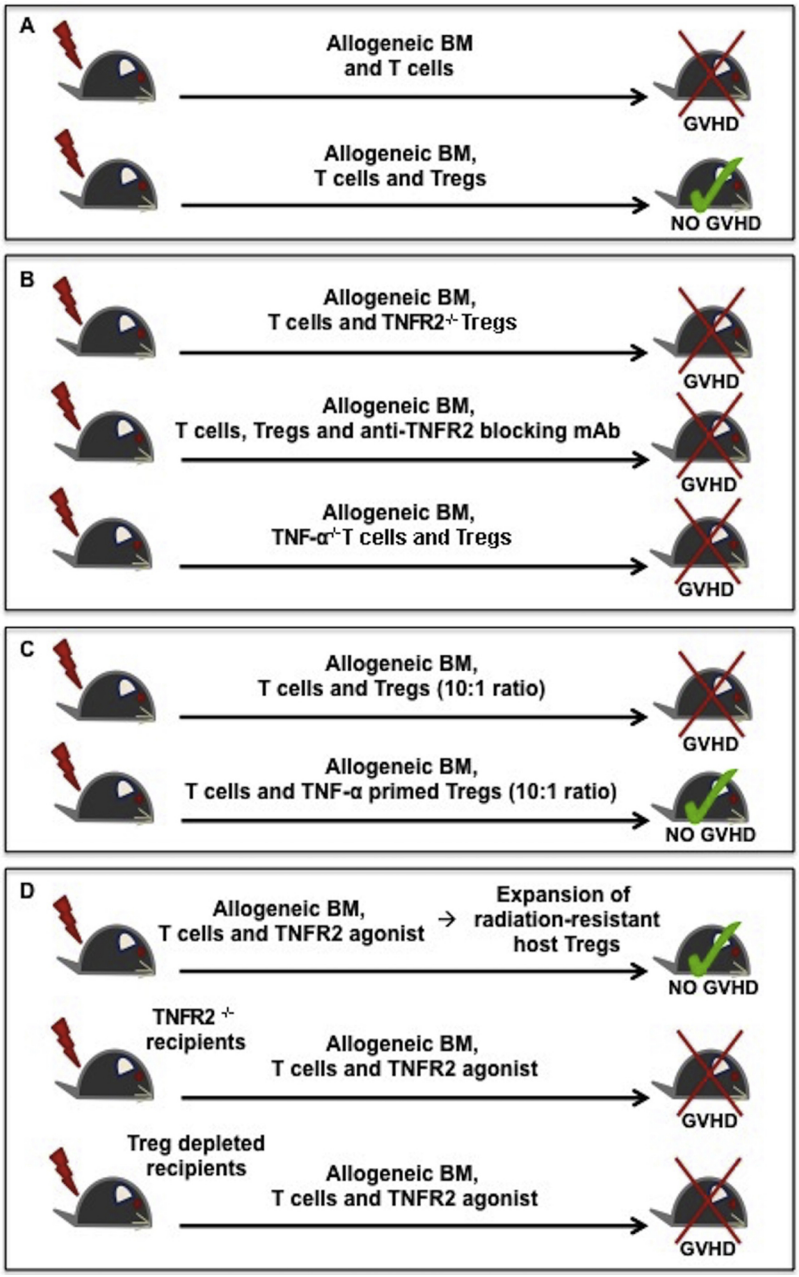

Fig. 1. TNFR2 signaling in mouse Tregs is essential for GVHD control after allogeneic HCT. (A) In mouse models of allogeneic HCT, adoptive transfer of donor Tregs prevents GVHD caused by co-infused donor alloreactive T cells. (B) Leclerc at al. showed that GVHD control is abrogated when mice are infused with either TNFR2 deficient Tregs or a TNFR2 blocking monoclonal antibody or TNF-α deficient T cells. (C) Pierini et al. showed that ex-vivo TNF-α primed Tregs prevents GVHD at an unfavorable Treg:Tcon ratio (1:10), while unprimed Tregs do not. (D) Chopra et al. showed that treatment with a TNFR2 agonist expands radiation resistant host Tregs, which reduce GVHD severity and improve survival. This effect is abrogated when recipient mice are TNFR2 deficient or are depleted of Tregs. BM, bone marrow; mAb, monoclonal antibody.

stability [123]. TNFR2 agonists can be also used to activate NK cells to be infused in patients who relapse after transplant, without the risk to induce GVHD. Indeed, recent studies have used cytokines to expand NK cells before infusing them in tumor-bearing mice. Furthermore, clinical trials with the adoptive transfer of expanded NK cells after chemotherapy are undergoing in patients with leukemia that are unfit for or refractory to standard treatments. These approaches have used IL-2, interleukin-15 (IL-15) and combinations of IL-15, IL-12 and interleukin-18, with promising results [15,124]. They can also be an option to prevent or treat relapse in HCT and could benefit from TNFR2 stimulation. However, further studies are needed to understand the full extent of NK cell activation induced by TNF-α or TNFR2 agonists.

Stimulation with TNF-α or TNFR2 agonists could be also exploited to expand Treg number and/or enhance Treg function in vivo. Tregs are supposed to be preferentially activated when total $CD4^+$ T cells are stimulated with TNF-α or a TNFR2 agonist. Okubo et al. showed that Tregs specifically expanded in a subject treated with Bacillus Calmette Guérin, that induces secretion of TNF-α [86]. Moreover, TNFR2 agonists can promote the function of other immune suppressive cell subsets, such as Bregs, MDSCs and $CD8^+FoxP3^+$ T cells, which can contribute to GVHD control [112]. However, the possible side effects and the effectiveness of the stimulation of the TNF-α/TNFR2 pathway in vivo should be carefully evaluated. In fact, TCR engagement induces upregulation of TNFR2 expression on $CD4^+$ effector T cells, which become more resistant to Treg-mediated suppression [61] and can trigger GVHD. In addition, one may hypothesize in vivo TNFR2 stimulation also enhances the NK cell-mediated tumor killing.

Further studies will ascertain if Treg activation with TNF-α or TNFR2 agonists could also inhibit T cell- and NK cell-mediated GVT effects. However, two recent preclinical studies of HCT showed that stimulation of TNFR2 signaling in mouse Tregs does not impair leukemia clearance [95,96].

5. Concluding remarks

Recent studies suggest TNF-α plays a regulatory role in immune

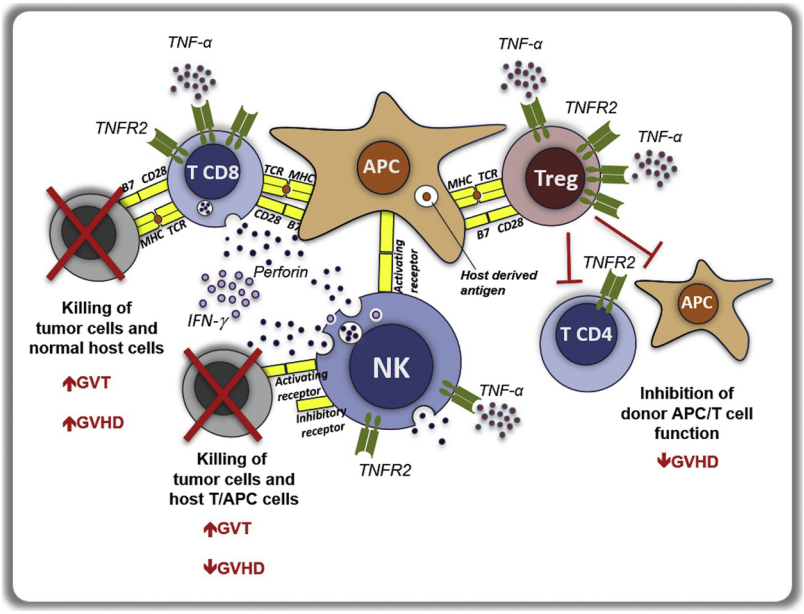

Fig. 2. TNFR2 signaling affects the balance between GVT and GVHD after HCT. After the conditioning regimen with chemotherapy and/or radiotherapy, TNF-α is rapidly released. TNFR2 signaling activates the function of donor alloreactive T cells and NK cells that exert a strong GVT effect. However, donor alloreactive T cells attack normal host cells causing GVHD. These adverse reactions can be prevented by Tregs. Tregs express high levels of TNFR2 and TNF-α strengthens their function.

homeostasis. In the setting of HCT, TNFR2 signaling can affect the balance between GVT and GVHD, because it promotes the function of immune cells endowed with effector functions, but also of immune cells with regulatory and suppressive properties. Promising studies in humanized mouse models are on going to clarify if targeting TNF-α/TNFR2 pathway could be useful to prevent or treat GVHD while retaining the GVT effect.

Conflict of interest

None.

Author contributions

A.M., writing; M.A., writing; S.P., writing; A.V., review and editing; A.P., writing, review and editing.

Funding

The preparation of the article was funded by “Associazione Italiana per la Ricerca sul Cancro (AIRC)”, Italy, Start-Up Grant 2017, project code: 20456. M.A. was supported by the Marie Skłodowska-Curie actions Fellowship, European Union.

References

[1] L.J. Old, Tumor necrosis factor (TNF), Science 230 (1985) 630–632.
[2] F. Bazzoni, B. Beutler, The tumor necrosis factor ligand and receptor families, N. Engl. J. Med. 334 (1996) 1717–1725.
[3] R.M. Locksley, N. Killeen, M.J. Lenardo, The TNF and TNF receptor superfamilies: integrating mammalian biology, Cell 104 (2001) 487–501.
[4] L. Cabal-Hierro, P.S. Lazo, Signal transduction by tumor necrosis factor receptors, Cell. Signal. 24 (2012) 1297–1305, https://doi.org/10.1016/j.cellsig.2012.02.006.
[5] D. Brenner, H. Blaser, T.W. Mak, Regulation of tumour necrosis factor signaling: live or let die, Nat. Rev. Immunol. 15 (2015) 362–374, https://doi.org/10.1038/nri3834.
[6] P.P. Sfikakis, The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions, Curr. Dir. Autoimmun. 11 (2010) 180–210, https://doi.org/10.1159/000289205.
[7] J.J. Peschon, D.S. Torrance, K.L. Stocking, M.B. Glaccum, C. Otten, C.R. Willis, et al., TNF receptor-deficient mice reveal divergent roles for p55 and p75 in several models of inflammation, J. Immunol. 160 (1998) 943–952.
[8] H.P. Eugster, K. Frei, R. Bachmann, H. Bluethmann, H. Lassmann, A. Fontana, Severity of symptoms and demyelination in MOG-induced EAE depends on TNFR1, Eur. J. Immunol. 29 (1999) 626–632.
[9] G.C. Suvannavejh, H.O. Lee, J. Padilla, M.C. Dal Canto, T.A. Barrett, S.D. Miller, Divergent roles for p55 and p75 tumor necrosis factor receptors in the pathogenesis of MOG(35-55)-induced experimental autoimmune encephalomyelitis, Cell. Immunol. 205 (2000) 24–33.
[10] G. Kassiotis, G. Kollias, Uncoupling the proinflammatory from the immunosuppressive properties of tumor necrosis factor (TNF) at the p55 TNF receptor level: implications for pathogenesis and therapy of autoimmune demyelination, J. Exp. Med. 193 (2001) 427–434.
[11] F.R. Appelbaum, S.J. Forman, R.S. Negrin, K.G. Blume, Thomas’ Hematopoietic Cell Transplantation, fourth ed., Wiley-Blackwell, Oxford, UK, 2009.
[12] J.L. Ferrara, J.E. Levine, P. Reddy, E. Holler, Graft-versus-host disease, Lancet 373 (2009) 1550–1561, https://doi.org/10.1016/S0140-6736(09)60237-3.
[13] C. Anasetti, F. Aversa, A. Velardi, Hematopoietic cell transplantation from human leukocyte antigen partially matched related donors, in: F.R. Appelbaum, S.J. Forman, R.S. Negrin, K.G. Blume (Eds.), Eds.), Thomas’ Hematopoietic Cell Transplantation, fourth ed., Wiley-Blackwell, Oxford, UK, 2009, pp. 657–674.
[14] A. Mancusi, L. Ruggeri, A. Velardi, Haploidentical hematopoietic transplantation for the cure of leukemia: from its biology to clinical translation, Blood 128 (2016) 2616–2623, https://doi.org/10.1182/blood-2016-07-730564.
[15] F. Cichocki, M.R. Verneris, S. Cooley, V. Bachanova, C.G. Brunstein, B.R. Blazar, et al., The past, present, and future of NK cells in hematopoietic cell transplantation and adoptive transfer, Curr. Top. Microbiol. Immunol. 395 (2016) 225–243, https://doi.org/10.1007/82_2015_445.
[16] E. Vivier, D.H. Raulet, A. Moretta, M.A. Caligiuri, L. Zitvogel, L.L. Lanier, et al., Innate or adaptive immunity? The example of natural killer cells, Science 331 (2011) 44–49, https://doi.org/10.1126/science.1198687.
[17] M.A. Caligiuri, Human natural killer cells, Blood 112 (3) (2008) 461–469, https://doi.org/10.1182/blood-2007-09-077438 112.
[18] S. Kim, J. Poursine-Laurent, S.M. Truscott, L. Lybarger, Y.J. Song, L. Yang, et al., Licensing of natural killer cells by host major histocompatibility complex class I molecules, Nature 436 (2005) 709–713, https://doi.org/10.1038/nature03847.
[19] N. Anfossi, P. André, S. Guia, C.S. Falk, S. Roetynck, C.A. Stewart, et al., Human NK cell education by inhibitory receptors for MHC class I, Immunity 25 (2006) 331–342, https://doi.org/10.1016/j.immuni.2006.06.013.
[20] L. Ruggeri, M. Capanni, E. Urbani, K. Perruccio, W.D. Shlomchik, A. Tosti, et al., Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants, Science 295 (2002) 2097–2100, https://doi.org/10.1126/science.1068440.
[21] L. Ruggeri, A. Mancusi, M. Capanni, E. Urbani, A. Carotti, T. Aloisi, et al., Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value, Blood 110 (2007) 433–440, https://doi.org/10.1182/blood-2006-07-038687.
[22] A. Velardi, L. Ruggeri, A. Mancusi, F. Aversa, F.T. Christiansen, Natural killer cell allorecognition of missing self in allogeneic hematopoietic transplantation: a tool for immunotherapy of leukemia, Curr. Opin. Immunol. 21 (2009) 525–530, https://doi.org/10.1016/j.coi.2009.07.015.
[23] J.A. Olson, D.B. Leveson-Gower, S. Gill, J. Baker, A. Beilhack, R.S. Negrin, NK cells mediate reduction of GVHD by inhibiting activated, alloreactive T cells while retaining GVT effects, Blood 115 (2010) 4293–4301, https://doi.org/10.1182/blood-2009-05-222190.
[24] F. Simonetta, M. Alvarez, R.S. Negrin, Natural killer cells in graft-versus-host-disease after allogeneic hematopoietic cell transplantation, Front. Immunol. 8 (2017) 465, https://doi.org/10.3389/fimmu.2017.00465.
[25] M. Alvarez, K. Sun, W.J. Murphy, Mouse host unlicensed NK cells promote donor allogeneic bone marrow engraftment, Blood 127 (2016) 1202–1205, https://doi.org/10.1182/blood-2015-08-665570.

[26] J.M. Kim, J.P. Rasmussen, A.Y. Rudensky, Regulatory T cells prevent catastrophic autoimmunity throughout the lifespan of mice, Nat. Immunol. 8 (2007) 191–197, https://doi.org/10.1038/ni1428.
[27] S. Sakaguchi, T. Yamaguchi, T. Nomura, M. Ono, Regulatory T cells and immune tolerance, Cell 133 (2008) 775–787, https://doi.org/10.1016/j.cell.2008.05.009.
[28] M. Miyara, S. Sakaguchi, Human FoxP3(+)CD4(+) regulatory T cells: their knowns and unknowns, Immunol. Cell Biol. 89 (2011) 346–351, https://doi.org/10.1038/icb.2010.137.
[29] D.J. Campbell, M.A. Koch, Phenotypical and functional specialization of FOXP3+ regulatory T cells, Nat. Rev. Immunol. 11 (2011) 119–130, https://doi.org/10.1038/nri2916.
[30] J. Fujisaki, J. Wu, A.L. Carlson, L. Silberstein, P. Putheti, R. Larocca, et al., In vivo imaging of Treg cells providing immune privilege to the haematopoietic stem-cell niche, Nature 474 (2011) 216–219, https://doi.org/10.1038/nature10160.
[31] A. Pierini, H. Nishikii, J. Baker, T. Kimura, H.S. Kwon, Y. Pan, et al., Foxp3+ regulatory T cells maintain the bone marrow microenvironment for B cell lymphopoiesis, Nat. Commun. 8 (2017) 15068, https://doi.org/10.1038/ncomms15068.
[32] Y. Hirata, K. Furuhashi, H. Ishii, H.W. Li, S. Pinho, L. Ding, et al., CD150high bone marrow tregs maintain hematopoietic stem cell quiescence and immune privilege via adenosine, Cell Stem Cell 22 (2018) 445–453, https://doi.org/10.1016/j.stem.2018.01.017 e5.
[33] V.H. Nguyen, R. Zeiser, D.L. Dasilva, D.S. Chang, A. Beilhack, C.H. Contag, et al., In vivo dynamics of regulatory T-cell trafficking and survival predict effective strategies to control graft-versus-host disease following allogeneic transplantation, Blood 109 (2007) 2649–2656, https://doi.org/10.1182/blood-2006-08-044529.
[34] V.H. Nguyen, S. Shashidhar, D.S. Chang, L. Ho, N. Kambham, M. Bachmann, et al., The impact of regulatory T cells on T-cell immunity following hematopoietic cell transplantation, Blood 111 (2008) 945–953, https://doi.org/10.1182/blood-2007-07-103895.
[35] A. Pierini, L. Colonna, M. Alvarez, D. Schneidawind, H. Nishikii, J. Baker, et al., Donor requirements for regulatory t cell suppression of murine graft-versus-host disease, J. Immunol. 195 (2015) 347–355, https://doi.org/10.4049/jimmunol.1402861.
[36] M. Edinger, P. Hoffmann, J. Ermann, K. Drago, C.G. Fathman, S. Strober, et al., CD4+CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation, Nat. Med. 9 (2003) 1144–1150, https://doi.org/10.1038/nm915.
[37] P.A. Taylor, C.J. Lees, B.R. Blazar, The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality, Blood 99 (2002) 3493–3499, https://doi.org/10.1182/blood.V99.10.3493.
[38] M. Di Ianni, F. Falzetti, A. Carotti, A. Terenzi, F. Castellino, E. Bonifacio, et al., Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation, Blood 117 (2011) 3921–3928, https://doi.org/10.1182/blood-2010-10-311894.
[39] M.F. Martelli, M. Di Ianni, L. Ruggeri, F. Falzetti, A. Carotti, A. Terenzi, et al., HLA-haploidentical transplantation with regulatory and conventional T cell adoptive immunotherapy prevents acute leukemia relapse, Blood 124 (2014) 638–644, https://doi.org/10.1182/blood-2014-03-564401.
[40] J. Koreth, K. Matsuoka, H.T. Kim, S.M. McDonough, B. Bindra, E.P. Alyea 3rdet al., Interleukin-2 and regulatory T cells in graft-versus-host disease, N. Engl. J. Med. 365 (2011) 2055–2066, https://doi.org/10.1056/NEJMoa1108188.
[41] J.H. Antin, J.L. Ferrara, Cytokine dysregulation and acute graft-versus-host disease, Blood 80 (1992) 2964–2968.
[42] J.E. Levine, Implications of TNF-α in the pathogenesis and management of GVHD, Int. J. Hematol. 93 (2011) 571–577, https://doi.org/10.1007/s12185-011-0803-1.
[43] H. Kayaba, M. Hirokawa, A. Watanabe, N. Saitoh, C. Changhao, Y. Yamada, et al., Serum markers of graft-versus-host disease after bone marrow transplantation, J. Allergy Clin. Immunol. 106 (2000) S40–4.
[44] C. Schmaltz, O. Alpdogan, S.J. Muriglan, B.J. Kappel, J.A. Rotolo, E.T. Ricchetti, et al., Donor T cell-derived TNF is required for graft-versus-host disease and graft-versus-tumor activity after bone marrow transplantation, Blood 101 (2003) 2440–2445, https://doi.org/10.1182/blood-2002-07-2109.
[45] F.F. Yalniz, M. Hefazi, K. McCullough, M.R. Litzow, W.J. Hogan, R. Wolf, et al., Safety and efficacy of infliximab therapy in the setting of steroid-refractory acute graft-versus-host disease, Biol. Blood Marrow Transplant. 23 (2017) 1478–1484, https://doi.org/10.1016/j.bbmt.2017.05.001.
[46] F. Patriarca, A. Sperotto, D. Damiani, G. Morreale, F. Bonifazi, A. Olivieri, et al., Infliximab treatment for steroid-refractory acute graft-versus-host disease, Haematologica 11 (2004) 1352–1359.
[47] N. Tsukada, T. Kobata, Y. Aizawa, H. Yagita, K. Okumura, Graft-versus-leukemia effect and graft-versus-host disease can be differentiated by cytotoxic mechanisms in a murine model of allogeneic bone marrow transplantation, Blood 93 (1999) 2738–2747.
[48] G.R. Hill, T. Teshima, A. Gerbitz, L. Pan, K.R. Cooke, Y.S. Brinson, et al., Differential roles of IL-1 and TNF-alpha on graft-versus-host disease and graft versus leukemia, J. Clin. Invest. 104 (1999) 459–467, https://doi.org/10.1172/JCI6896.
[49] A.K. Mehta, D.T. Gracias, M. Croft, TNF activity and T cells, Cytokine 101 (2018) 14–18, https://doi.org/10.1016/j.cyto.2016.08.003.
[50] L.L. Ye, X.S. Wei, M. Zhang, Y.R. Niu, Q. Zhou, The significance of tumor necrosis factor receptor type II in CD8+ regulatory t cells and CD8+ effector t cells, Front. Immunol. 9 (2018) 583, https://doi.org/10.3389/fimmu.2018.00583.
[51] H.S. Teh, A. Seebaran, S.J. Teh, TNF receptor 2-deficient CD8 T cells are resistant to Fas/Fas ligand-induced cell death, J. Immunol. 165 (2000) 4814–4821, https://doi.org/10.4049/jimmunol.165.9.4814.
[52] E.Y. Kim, H.S. Teh, TNF type 2 receptor (p75) lowers the threshold of T cell activation, J. Immunol. 167 (2001) 6812–6820, https://doi.org/10.4049/jimmunol.167.12.6812.
[53] R.M. Aspalter, M.M. Eibl, H.M. Wolf, Regulation of TCR-mediated t cell activation by TNF-RII, J. Leukoc. Biol. 74 (2003) 572–582, https://doi.org/10.1189/jlb.0303112.
[54] M.I. Kafrouni, G.R. Brown, D.L. Thiele, The role of TNF-TNFR2 interactions in generation of CTL responses and clearance of hepatic adenovirus infection, J. Leukoc. Biol. 74 (2003) 564–571, https://doi.org/10.1189/jlb.0103035.
[55] E.Y. Kim, H.S. Teh, Critical role of TNF receptor type-2 (p75) as a costimulator for IL-2 induction and T cell survival: a functional link to CD28, J. Immunol. 173 (2004) 4500–4509, https://doi.org/10.4049/jimmunol.173.7.4500.
[56] E.Y. Kim, J.J. Priatel, S.J. Teh, H.S. Teh, TNF receptor type 2 (p75) functions as a costimulator for antigen-driven T cell responses in vivo, J. Immunol. 176 (2006) 1026–1035, https://doi.org/10.4049/jimmunol.176.2.1026.
[57] I. Chatzidakis, G. Fousteri, D. Tsoukatou, G. Kollias, C. Mamalaki, An essential role for TNF in modulating thresholds for survival, activation, and tolerance of CD8+ T cells, J. Immunol. 178 (2007) 6735–6745, https://doi.org/10.4049/jimmunol.178.11.6735.
[58] S.C. McKarns, R.H. Schwartz, Biphasic regulation of Il2 transcription in CD4+ T cells: roles for TNF-alpha receptor signaling and chromatin structure, J. Immunol. 181 (2008) 1272–1281, https://doi.org/10.4049/jimmunol.181.2.1272.
[59] C. Lee-Chang, M. Bodogai, K. Moritoh, X. Chen, R. Wersto, R. Sen, et al., Aging converts innate B1a cells into potent CD8+ t cell inducers, J. Immunol. 196 (2016) 3385–3397, https://doi.org/10.4049/jimmunol.1502034.
[60] X. Chen, M. Bäumel, D.N. Männel, O.M. Howard, J.J. Oppenheim, Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells, J. Immunol. 179 (2007) 154–161, https://doi.org/10.4049/jimmunol.179.1.154.
[61] X. Chen, R. Hamano, J.J. Subleski, A.A. Hurwitz, O.M. Howard, J.J. Oppenheim, Expression of costimulatory TNFR2 induces resistance of CD4+FoxP3- conventional T cells to suppression by CD4+FoxP3+ regulatory T cells, J. Immunol. 185 (2010) 174–182, https://doi.org/10.4049/jimmunol.0903548.
[62] X. Chen, Y. Nie, H. Xiao, Z. Bian, A.J. Scarzello, N.Y. Song, et al., TNFR2 expression by CD4 effector T cells is required to induce full-fledged experimental colitis, Sci. Rep. 6 (2016) 32834, https://doi.org/10.1038/srep32834.
[63] A.P. Cope, M. Londei, N.R. Chu, S.B. Cohen, M.J. Elliott, F.M. Brennan, et al., Chronic exposure to tumor necrosis factor (TNF) in vitro impairs the activation of T cells through the T cell receptor/CD3 complex; reversal in vivo by anti-TNF antibodies in patients with rheumatoid arthritis, J. Clin. Invest. 94 (1994) 749–760, https://doi.org/10.1172/JCI117394.
[64] A.P. Cope, R.S. Liblau, X.D. Yang, M. Congia, C. Laudanna, R.D. Schreiber, et al., Chronic tumor necrosis factor alters T cell responses by attenuating T cell receptor signaling, J. Exp. Med. 185 (1997) 1573–1584, https://doi.org/10.1084/jem.185.9.1573.
[65] P. Isomäki, M. Panesar, A. Annenkov, J.M. Clark, B.M. Foxwell, Y. Chernajovsky, et al., Prolonged exposure of T cells to TNF down-regulates TCR zeta and expression of the TCR/CD3 complex at the cell surface, J. Immunol. 166 (2001) 5495–5507, https://doi.org/10.4049/jimmunol.166.9.5495.
[66] E. Bryl, A.N. Vallejo, C.M. Weyand, J.J. Goronzy, Down-regulation of CD28 expression by TNF-alpha, J. Immunol. 167 (2001) 3231–3238, https://doi.org/10.4049/jimmunol.167.6.3231.
[67] R.M. Aspalter, H.M. Wolf, M.M. Eibl, Chronic TNF-alpha exposure impairs TCR-signaling via TNF-RII but not TNF-RI, Cell. Immunol. 237 (2005) 55–67, https://doi.org/10.1016/j.cellimm.2005.10.001.
[68] Y.C. Twu, M.R. Gold, H.S. Teh, TNFR1 delivers pro-survival signals that are required for limiting TNFR2-dependent activation-induced cell death (AICD) in CD8+ T cells, Eur. J. Immunol. 41 (2011) 335–344, https://doi.org/10.1002/eji.201040639.
[69] S. Punit, P.E. Dubé, C.Y. Liu, N. Girish, M.K. Washington, D.B. Polk, Tumor necrosis factor receptor 2 restricts the pathogenicity of CD8(+) t cells in mice with colitis, Gastroenterology 149 (2015) 993–1005, https://doi.org/10.1053/j.gastro.2015.06.004 e2.
[70] M. Fotin-Mleczek, F. Henkler, D. Samel, M. Reichwein, A. Hausser, I. Parmryd, et al., Apoptotic crosstalk of TNF receptors: TNF-R2-induces depletion of TRAF2 and IAP proteins and accelerates TNF-R1-dependent activation of caspase-8, J. Cell. Sci. 115 (2002) 2757–2770.
[71] P.G. Miller, M.B. Bonn, S.C. McKarns, Transmembrane TNF-TNFR2 impairs Th17 differentiation by promoting Il2 expression, J. Immunol. 195 (2015) 2633–2647, https://doi.org/10.4049/jimmunol.1500286.
[72] A. Jewett, B. Bonavida, Pivotal role of endogenous TNF-alpha in the IL-2-driven activation and proliferation of the functionally immature NK free subset, Cell. Immunol. 151 (1193) (1993) 257–269, https://doi.org/10.1006/cimm.1993.1236.
[73] C.N. Baxevanis, I.F. Voutsas, O.E. Tsitsilonis, M.L. Tsiatas, A.D. Gritzapis, M. Papamichail, Compromised anti-tumor responses in tumor necrosis factor-alpha knockout mice, Eur. J. Immunol. 30 (2000) 1957–1966, https://doi.org/10.1002/1521-4141(200007)30:7<1957::AID-IMMU1957>3.0.CO;2-7.
[74] G. Nocturne, S. Boudaoud, B. Ly, J. Pascaud, A. Paoletti, X. Mariette, Impact of anti-TNF therapy on NK cells function and on immunosurveillance against B-cell lymphomas, J. Autoimmun. 80 (2017) 56–64, https://doi.org/10.1016/j.jaut.2017.02.001.
[75] J. Xu, A.K. Chakrabarti, J.L. Tan, L. Ge, A. Gambotto, N.L. Vujanovic, Essential role of the TNF-TNFR2 cognate interaction in mouse dendritic cell-natural killer cell crosstalk, Blood 109 (2007) 3333–3341, https://doi.org/10.1182/blood-

2006-06-026385.
[76] W. Almishri, T. Santodomingo-Garzon, T. Le, D. Stack, C.H. Mody, M.G. Swain, TNFalpha augments cytokine-induced NK cell IFNgamma production through TNFR2, J. Innate Immun. 8 (2016) 617–629, https://doi.org/10.1159/000448077.
[77] P. Shivakumar, T. Mizuochi, R. Mourya, S. Gutta, L. Yang, Z. Luo, et al., Preferential TNFalpha signaling via TNFR2 regulates epithelial injury and duct obstruction in experimental biliary atresia, JCI Insight 2 (2017) e88747, , https://doi.org/10.1172/jci.insight.88747.
[78] D.M. Tufa, D. Chatterjee, H.Z. Low, R.E. Schmidt, R. Jacobs, TNFR2 and IL-12 coactivation enables slanDCs to support NK-cell function via membrane-bound TNF-alpha, Eur. J. Immunol. 44 (2014) 3717–3728, https://doi.org/10.1002/eji.201444676.
[79] J.P. Bottcher, E. Bonavita, P. Chakravarty, H. Blees, M. Cabeza-Cabrerizo, S. Sammicheli, et al., NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control, Cell 172 (2018) 1022–1037, https://doi.org/10.1016/j.cell.2018.01.004 e1014.
[80] D. Mittal, D. Vijayan, E.M. Putz, A.R. Aguilera, K.A. Markey, J. Straube, et al., Interleukin-12 from CD103(+) Batf3-dependent dendritic cells required for NK-Cell suppression of metastasis, Cancer Immunol. Res. 5 (2017) 1098–1108, https://doi.org/10.1158/2326-6066.CIR-17-0341.
[81] D.J. Theisen, J.T. Davidson 4th, C.G. Briseno, M. Gargaro, E.J. Lauron, Q. Wang, et al., WDFY4 is required for cross-presentation in response to viral and tumor antigens, Science 362 (2018) 694–699, https://doi.org/10.1126/science.aat5030.
[82] K.C. Barry, J. Hsu, M.L. Broz, F.J. Cueto, M. Binnewies, A.J. Combes, et al., A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments, Nat. Med. 24 (2018) 1178–1191, https://doi.org/10.1038/s41591-018-0085-8.
[83] F. Annunziato, L. Cosmi, F. Liotta, E. Lazzeri, R. Manetti, V. Vanini, et al., Phenotype, localization, and mechanism of suppression of CD4(+)CD25(+) human thymocytes, J. Exp. Med. 196 (2002) 379–387, https://doi.org/10.1084/jem.20020110.
[84] X. Chen, J.J. Subleski, R. Hamano, O.M. Howard, R.H. Wiltrout, J.J. Oppenheim, Co-expression of TNFR2 and CD25 identifies more of the functional CD4+FOXP3+ regulatory T cells in human peripheral blood, Eur. J. Immunol. 40 (2010) 1099–1106, https://doi.org/10.1002/eji.200940022.
[85] X. Chen, J.J. Subleski, H. Kopf, O.M. Howard, D.N. Männel, J.J. Oppenheim, Cutting edge: expression of TNFR2 defines a maximally suppressive subset of mouse CD4+CD25+FoxP3+ T regulatory cells: applicability to tumor-infiltrating T regulatory cells, J. Immunol. 180 (2008) 6467–6471, https://doi.org/10.4049/jimmunol.0903548.
[86] Y. Okubo, T. Mera, L. Wang, D.L. Faustman, Homogeneous expansion of human T-regulatory cells via tumor necrosis factor receptor 2, Sci. Rep. 3 (2013) 3153, https://doi.org/10.1038/srep03153.
[87] Y. Okubo, H. Torrey, J. Butterworth, H. Zheng, D.L. Faustman, Treg activation defect in type 1 diabetes: correction with TNFR2 agonism, Clin. Transl. Immunol. 5 (2016) e56, https://doi.org/10.1038/cti.2015.43.
[88] B. Zaragoza, X. Chen, J.J. Oppenheim, A. Baeyens, S. Gregoire, D. Chader, et al., Suppressive activity of human regulatory T cells is maintained in the presence of TNF, Nat. Med. 22 (2016) 16–17, https://doi.org/10.1038/nm.4019.
[89] A. Mancusi, S. Piccinelli, A. Velardi, A. Pierini, The effect of TNF-α on regulatory t cell function in graft-versus-host disease, Front. Immunol. 9 (2018) 356, https://doi.org/10.3389/fimmu.2018.00356.
[90] S.A. Mahmud, L.S. Manlove, H.M. Schmitz, Y. Xing, Y. Wang, D.L. Owen, et al., Costimulation via the tumor-necrosis factor receptor superfamily couples TCR signal strength to the thymic differentiation of regulatory T cells, Nat. Immunol. 15 (2014) 473–481, https://doi.org/10.1038/ni.2849.
[91] W.J. Housley, C.O. Adams, F.C. Nichols, L. Puddington, E.G. Lingenheld, L. Zhu, et al., Natural but not inducible regulatory T cells require TNF-alpha signaling for in vivo function, J. Immunol. 186 (2011) 6779–6787, https://doi.org/10.4049/jimmunol.1003868.
[92] X. Chen, X. Wu, Q. Zhou, O.M. Howard, M.G. Netea, J.J. Oppenheim, TNFR2 is critical for the stabilization of the CD4+Foxp3+ regulatory T cell phenotype in the inflammatory environment, J. Immunol. 190 (2013) 1076–1084, https://doi.org/10.4049/jimmunol.1202659.
[93] Y. Grinberg-Bleyer, D. Saadoun, A. Baeyens, F. Billiard, J.D. Goldstein, S. Grégoire, et al., Pathogenic T cells have a paradoxical protective effect in murine autoimmune diabetes by boosting Tregs, J. Clin. Invest. 120 (2010) 4558–4568, https://doi.org/10.1172/JCI42945.
[94] M. Leclerc, S. Naserian, C. Pilon, A. Thiolat, G.H. Martin, C. Pouchy, et al., Control of GVHD by regulatory T cells depends on TNF produced by T cells and TNFR2 expressed by regulatory T cells, Blood 128 (2016) 1651–1659, https://doi.org/10.1182/blood-2016-02-700849.
[95] A. Pierini, W. Strober, C. Moffett, J. Baker, H. Nishikii, M. Alvarez, et al., TNF-α priming enhances CD4+FoxP3+ regulatory T-cell suppressive function in murine GVHD prevention and treatment, Blood 128 (2016) 866–871, https://doi.org/10.1182/blood-2016-04-711275.
[96] M. Chopra, M. Biehl, T. Steinfatt, A. Brandl, J. Kums, J. Amich, et al., Exogenous TNFR2 activation protects from acute GvHD via host T reg cell expansion, J. Exp. Med. 213 (2016) 1881–1900, https://doi.org/10.1084/jem.20151563.
[97] D.X. Nguyen, M.R. Ehrenstein, Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis, J. Exp. Med. 213 (2016) 1241–1253, https://doi.org/10.1084/jem.20151255.
[98] F.S. Kleijwegt, S. Laban, G. Duinkerken, A.M. Joosten, A. Zaldumbide, T. Nikolic, et al., Critical role for TNF in the induction of human antigen-specific regulatory T cells by tolerogenic dendritic cells, J. Immunol. 185 (2010) 1412–1418, https://doi.org/10.4049/jimmunol.1000560.
[99] L. Cosmi, F. Liotta, E. Lazzeri, M. Francalanci, R. Angeli, B. Mazzinghi, et al., Human CD8+CD25+ thymocytes share phenotypic and functional features with CD4+CD25+ regulatory thymocytes, Blood 102 (2003) 4107–4114, https://doi.org/10.1182/blood-2003-04-1320.
[100] V. Ablamunits, B. Bisikirska, K.C. Herold, Acquisition of regulatory function by human CD8(+) T cells treated with anti-CD3 antibody requires TNF, Eur. J. Immunol. 40 (2010) 2891–2901, https://doi.org/10.1002/eji.201040485.
[101] D.A. Horwitz, S. Pan, J.N. Ou, J. Wang, M. Chen, J.D. Gray, et al., Therapeutic polyclonal human CD8+ CD25+ Fox3+ TNFR2+ PD-L1+ regulatory cells induced ex-vivo, Clin. Immunol. 149 (2013) 450–463, https://doi.org/10.1016/j.clim.2013.08.007.
[102] M. Matsumoto, A. Baba, T. Yokota, H. Nishikawa, Y. Ohkawa, H. Kayama, et al., Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation, Immunity 41 (2014) 1040–1051, https://doi.org/10.1016/j.immuni.2014.10.016.
[103] Y. Iwata, T. Matsushita, M. Horikawa, D.J. Dilillo, K. Yanaba, G.M. Venturi, et al., Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells, Blood 117 (2011) 530–541, https://doi.org/10.1182/blood-2010-07-294249.
[104] M. Weber, P. Stein, S. Prufer, B. Rudolph, A. Kreft, E. Schmitt, et al., Donor and host B cell-derived IL-10 contributes to suppression of graft-versus-host disease, Eur. J. Immunol. 44 (2014) 1857–1865, https://doi.org/10.1002/eji.201344081.
[105] O. Ticha, L. Moos, H. Wajant, I. Bekeredjian-Ding, Expression of tumor necrosis factor receptor 2 characterizes TLR9-driven formation of Interleukin-10-producing B cells, Front. Immunol. 8 (2017) 1951, https://doi.org/10.3389/fimmu.2017.01951.
[106] Y. Hu, G.L. He, X.Y. Zhao, X.S. Zhao, Y. Wang, L.P. Xu, et al., Regulatory B cells promote graft-versus-host disease prevention and maintain graft-versus-leukemia activity following allogeneic bone marrow transplantation, Oncoimmunology 6 (2017) e1284721, , https://doi.org/10.1080/2162402X.2017.1284721.
[107] J. Zheng, Y. Liu, Y.L. Lau, W. Tu, CD40-activated B cells are more potent than immature dendritic cells to induce and expand CD4(+) regulatory T cells, Cell. Mol. Immunol. 7 (2010) 44–50, https://doi.org/10.1038/cmi.2009.103.
[108] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived suppressor cells as regulators of the immune system, Nat. Rev. Immunol. 9 (2009) 162–174, https://doi.org/10.1038/nri2506.
[109] F. Veglia, M. Perego, D. Gabrilovich, Myeloid-derived suppressor cells coming of age, Nat. Immunol. 19 (2018) 108–119, https://doi.org/10.1038/s41590-017-0022-x.
[110] V. Fleming, X. Hu, R. Weber, V. Nagibin, C. Groth, P. Altevogt, et al., Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression, Front. Immunol. 9 (2018) 398, https://doi.org/10.3389/fimmu.2018.00398.
[111] S.L. Highfill, P.C. Rodriguez, Q. Zhou, C.A. Goetz, B.H. Koehn, R. Veenstra, et al., Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13, Blood 116 (2010) 5738–5747, https://doi.org/10.1182/blood-2010-06-287839.
[112] B.R. Blazar, K.P.A. MacDonald, G.R. Hill, Immune regulatory cell infusion for graft-versus-host disease prevention and therapy, Blood 131 (2018) 2651–2660, https://doi.org/10.1182/blood-2017-11-785865.
[113] X. Zhao, L. Rong, X. Zhao, X. Li, X. Liu, J. Deng, et al., TNF signaling drives myeloid-derived suppressor cell accumulation, J. Clin. Invest. 122 (2012) 4094–4104, https://doi.org/10.1172/JCI64115.
[114] M. Sade-Feldman, J. Kanterman, E. Ish-Shalom, M. Elnekave, E. Horwitz, M. Baniyash, Tumor necrosis factor-α blocks differentiation and enhances suppressive activity of immature myeloid cells during chronic inflammation, Immunity 38 (2013) 541–554, https://doi.org/10.1016/j.immuni.2013.02.007.
[115] K.S. Atretkhany, M.A. Nosenko, V.S. Gogoleva, R.V. Zvartsev, Z. Qin, S.A. Nedospasov, et al., TNF neutralization results in the delay of transplantable tumor growth and reduced MDSC accumulation, Front. Immunol. 7 (2016) 147, https://doi.org/10.3389/fimmu.2016.00147.
[116] X. Hu, B. Li, X. Li, X. Zhao, L. Wan, G. Lin, et al., Transmembrane TNF-α promotes suppressive activities of myeloid-derived suppressor cells via TNFR2, J. Immunol. 192 (2014) 1320–1331, https://doi.org/10.4049/jimmunol.1203195.
[117] J. Polz, A. Remke, S. Weber, D. Schmidt, D. Weber-Steffens, A. Pietryga-Krieger, et al., Myeloid suppressor cells require membrane TNFR2 expression for suppressive activity, Immun. Inflamm. Dis. 2 (2014) 121–130, https://doi.org/10.1002/iid3.19.
[118] L. Chavez-Galan, D. Vesin, H. Uysal, G. Blaser, M. Benkhoucha, B. Ryffel, et al., Transmembrane tumor necrosis factor controls myeloid-derived suppressor cell activity via TNF receptor 2 and protects from excessive inflammation during BCG-Induced pleurisy, Front. Immunol. 8 (2017) 999, https://doi.org/10.3389/fimmu.2017.00999.
[119] M. Hamadani, C.C. Hofmeister, B. Jansak, G. Phillips, P. Elder, W. Blum, et al., Addition of infliximab to standard acute graft-versus-host disease prophylaxis following allogeneic peripheral blood cell transplantation, Biol. Blood Marrow Transplant. 14 (2008) 783–789, https://doi.org/10.1016/j.bbmt.2008.04.006.
[120] S.W. Choi, P. Stiff, K. Cooke, J.L. Ferrara, T. Braun, C. Kitko, et al., TNF-inhibition with etanercept for graft-versus-host disease prevention in high-risk HCT: lower TNFR1 levels correlate with better outcomes, Biol. Blood Marrow Transplant. 18 (2012) 1525–1532, https://doi.org/10.1016/j.bbmt.2012.03.013.
[121] G.D. Kalliolias, L.B. Ivashkiv, TNF biology, pathogenic mechanisms and emerging therapeutic strategies, Nat. Rev. Rheumatol. 12 (2016) 49–62, https://doi.org/10.1038/nrrheum.2015.169.
[122] A. Pierini, D. Schneidawind, H. Nishikii, R.S. Negrin, Regulatory T cell

immunotherapy in immune-mediated diseases, Curr. Stem Cell Rep. 1 (2015) 177–186, https://doi.org/10.1007/s40778-015-0025-1.
[123] P.C.M. Urbano, H.J.P.M. Koenen, I. Joosten, X. He, An autocrine TNFα-tumor necrosis factor receptor 2 loop promotes epigenetic effects inducing human treg stability in vitro, Front. Immunol. 9 (2018) 573, https://doi.org/10.3389/fimmu.2018.00573.
[124] L. Ruggeri, S. Parisi, E. Urbani, A. Curti, Alloreactive natural killer cells for the treatment of acute myeloid leukemia: from stem cell transplantation to adoptive immunotherapy, Front. Immunol. 6 (2015) 479, https://doi.org/10.3389/fimmu.2015.00479.

Antonella Mancusi received her Ph.D. in Molecular Medicine, Basic and Applied Immunology from the San Raffaele University in Milan, Italy. She did her postdoctoral training at the Division of Hematology and Clinical Immunology of the University of Perugia in Perugia, Italy, where she investigated the function of NK cells and Killer Cell Ig-like Receptors in haploidentical hematopoietic transplantation. Her research is focused on the function of regulatory T cells in normal and defective hematopoiesis and in the prevention of graft versus host disease after allogeneic hematopoietic transplantation.

Maite Alvarez received her Ph.D. in Immunology from the University of California, Davis in Davis, USA. She did her postdoctoral training in the laboratory of Dr. Robert S. Negrin at Stanford University in Stanford, USA, where she studied NK cell biology and transplantation. She is currently a research scientist at the Center for Applied Medical Research/Navarra Institute for Health Research in Pamplona, Spain and her research is focused on NK cells and cancer immunotherapy.

Sara Piccinelli, M.D., did her training in Hematology at the Bone Marrow Transplant Program of the University of Perugia in Perugia, Italy. She is currently a PhD student in Molecular Medicine, Biotechnologies of Transplantation at the University of Perugia. Her project is focused on the role of bone marrow regulatory T cells in the maintenance of the hematopoietic stem cell niche.

Andrea Velardi, M.D., is Professor of Hematology and Head of the Bone Marrow Transplant Program at the Division of Hematology and Clinical Immunology of the University of Perugia, Perugia, Italy. The Perugia Bone Marrow Transplant Centre pioneered the haploidentical hematopoietic transplant for patients with acute leukemia, and, within that setting, Dr. Velardi's group discovered that NK cell alloreactivity exerts striking control of leukemia relapse. The impact of this discovery was recognized by the European Society for Blood and Marrow Transplantation with the Van Bekkum Award at the 2002 Annual Meeting, and by the American-Italian Cancer Research Foundation with the Annual Prize for Scientific Excellence in Medicine in 2003. He is currently leading the clinical trials of adoptive immunotherapy with regulatory and conventional T cells in allogeneic hematopoietic transplantation.

Antonio Pierini, M.D., Ph.D., is Assistant Professor at the Division of Hematology and Clinical Immunology of the University of Perugia, Perugia, Italy. He spent his postdoctoral training in the laboratory of Dr. Robert S. Negrin at Stanford University in Stanford, USA, where he worked in regulatory T cell prevention of graft versus host disease. He described regulatory T cell-mediated mechanisms of hematopoietic stem cell niche protection in the bone marrow and how bone marrow regulatory T cells control lymphopoiesis. He is currently involved in the clinical care of leukemia patients enrolled in the clinical trials of allogeneic hematopoietic transplantation with adoptive immunotherapy with regulatory and conventional T cells.