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POINT OF VIEW

TNFR2: The new Treg switch?

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ABSTRACT

Three recent publications identified the TNF/TNR2 pathway as a new target to reduce graft-versus-host-disease through regulatory T cells activation or to potentially switch on a strong anti-leukemic effect through regulatory T cells blockade in allogeneic hematopoietic stem cell transplantation. This identified the TNF/TNR2 pathway as a swith and as a new target for immune checkpoint therapy to modulate the immune regulation in this clinical setting.

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Allogeneic hematopoietic stem cell transplantation as a new target opportunity for immune checkpoint therapy

Therapeutic blockade of immune checkpoint pathways is sparking an extraordinary level of energy and enthusiasm among the scientific community and healthcare industry due to its potential outstanding effect in solid tumor oncology[1] as well as in hematologic malignancies.[2] With regard to this last point, PD1 blockade has recently been assessed after allogeneic transplantation but at the cost of a high incidence of refractory GVHD.[3] Importantly, three recent publications prove conclusively not only that a similar strategy could be used to boost the immune response to the tumour after allogeneic hematopoietic stem cell transplantation (alloSCT),[4] but also that such an approach could conversely reduce the immune response in order to control graft-versus-host disease (GVHD), the life-threatening complication of alloSCT.[5,6] These 3 independent publications identified the TNF/TNR2 pathway as a new target for immune checkpoint therapy that allows for immune regulation in both clinical contexts.

Modulate rather than dissociate: How to benefit from both side of alloSCT?

AlloSCT still remains the treatment of choice for several hematological disorders, including leukemia and lymphoma. After myeloreductive conditioning with high-dose chemotherapy +/− irradiation, patients receive a transplant containing hematopoietic stem cells from a healthy donor. This transplant comprises not only hematopoietic stem cells with the potential to durably reconstitute hematopoiesis, but also immunocompetent cells, including mature T cells. These donor T cells have an essential therapeutic role, favoring engraftment, promoting peripheral T cell reconstitution and, importantly, providing a graft-versus-leukemia/tumor (GVL or GVT) effect. Hence, in addition to the cytoreductive contribution of the conditioning therapy, alloSCT can be viewed as an allogeneic immune-based cell therapy for cancer.[7]

This concept that donor T cells play a critical role is supported by the observed increased risk of leukemia relapse when T cells with alloreactivity are reduced or absent as occurs with autografts, syngeneic twin grafts or with T cell depleted allogeneicSCT.[8] However, the infusion of donor T cells is regarded as a double edged sword as the major drawback of this beneficial alloreactive effect on GVL/GVT is an increased risk of GVHD. Depending on the HLA disparity between donor and recipient, alloreactive T cells represent approximately 5–10% of the T cell repertoire present in healthy individuals.[9] When donor T cells are infused into an allogeneic recipient, they undergo activation in response to host alloantigen presenting cells (APC), proliferate and differentiate into cytokine-producing and cytotoxic effectors T cells that have the potential to cause tissue damage in target organs. In order to reduce the risk and prevent GVHD, grafted patients receive immunosuppressive drug therapy but this treatment is only partially effective.[7]

New strategies attempting to dissociate the deleterious from the beneficial effects of donor T cells were investigated intensively over the last 30 years,[10-12] but success was limited and these approaches have had little impact in clinical practice. A radically different approach is therefore required. Fine tuning or modulation of alloreactivity as required by each patient individually to either increase the GVL effect or control GVHD after alloSCT is the very attractive, if challenging, opportunity offered by targeting the TNF/TNFR2 pathway.

How does this issue relate to the therapeutic management of patients after alloSCT? In theory, targeting the TNF/TNFR2 pathway would enable (i) a powerful GVL/GVT effect to be

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induced and amplified to prevent or to treat hematological malignancy relapse or (ii) reduced alloreactivity enabling control of GVHD. Thus, it may be possible to provide each patient with the right balance between the beneficial and harmful effects of alloSCT by tailoring of the intensity of the immune response to each patient's need over the whole course of the disease. The TNF/TNFR2 pathway represents a very promising approach to achieve this unmet clinical need due to its unique effect on regulatory T cells (Treg) a particular sub-population of T cells that is at the center of the immune response after alloSCT.

Acting on Treg to modulate the immune response

In experimental GVHD mouse models, Treg depletion can intensify GVHD.[13,14] Based on this observation, the first worldwide clinical trial of Treg manipulation utilising ex vivo Treg depletion from donor lymphocyte infusions (DLI) through their constitutive expression of CD25 was completed in 2010 in order to improve the GVL effect in patients that relapsed after alloSCT.[15,16] However, the wide spread use of this approach was limited due to the requirment for a dedicated cell therapy unit capable of undertaking good manufacturing practice (GMP) compatible Treg cell depletion. Furthermore, this strategy only targeted Treg present in DLI probably accounting for the low percentage of patients that responded to this treatment. On the other hand, it was shown that cell therapy using Treg infusions could efficiently prevent experimental GVHD[13,14,17] without hampering immune reconstitution or the GVL/GVT effect.[18-21] The therapeutic anti-GVHD effect of Treg relies on their ability to act directly on conventional T cells preventing their activation and differentiation. These pre-clinical models led to the development of clinical trials of Treg-based cell therapy with very promising results.[22-24] However, this approach of Treg collection and ex vivo expansion also requires GMP compliant procedures and at present remains costly.

Thus, if we go back to the possibility of modulating alloreactivity rather than to dissociating GVHD from GVL/GVT, it is clear that Treg are key target cells enabling fine tuning of immune responses after alloSCT. By targeting a pathway that has a major influence on Treg function it would theoretically be possible both to prevent GVHD and to increase alloreactivity improving the GVL effect.

Acting on TNFR2 to modulate Treg effect on both ways: Proof of concept is now done

TNFα, can interact with two transmembrane receptors: TNFR1 and TNFR2 (for review see[25]). TNFR1 is expressed ubiquitously by all cell types and possess a death domain in its intracellular part. Depending on the cellular environment, TNFR1 signaling can induce apoptosis through a caspase 8 dependent pathway. In contrast, TNFR2 expression is more restricted. For instance in immune cells, Treg express higher levels of TNFR2 compared to activated conventional T cells especially for a subset of Treg with the maximal suppressive capacity.[26-29] Interestingly, this was observed not only for tumor-infiltrating Treg[30] but also for myeloid derived suppressor cells (MDSC)[31] as well as for mesenchymal stem cells (MSC)[32] two cell populations also implied in tumor immune evasion. TNFR2 do not have intracytoplasmic death domain and can notably induce activation and proliferation of T cells through NF-kB, AP1, and MAPK pathways.[33] Interestingly, polymorphisms of TNFR2 was demonstrated to be associatied with different immune diseases. For instance, the substitution of arginine by methionine at exon 5 (196M/R) correlates with high concentrations of soluble TNFR2 in rheumatoid arthritis and osteoarthritis patients.[34] The same poymorphism was associatied with increased susceptibility for patients to develop rheumatoid arthritis.[35] Similar observations were made in inflammatory bowel disease[36] and lupus.[37] In alloSCT, the (196M/R) mutation in donors, but not in recipients was shown to increase the incidence of severe GVHD.[38] Altogether, these observations suggested that TNFR2 could be associated with reduced or controled immune response whereas converselly, some mutations on TNFR2 could lead to increased inflammation both during alloreactivity and in autoimmune diseases. Recent seminal publications provided a link between these clinical findings and Treg. Indeed, in different autoimmune disease models TNF has been demonstrated to boost proliferation and the suppressive activity of Treg by interacting with TNFR2.[26-28,39] In addition, Treg express higher levels of TNFR2 compared to other T cells and Treg expressing the highest level of TNFR2 are the most suppressive both in mice and human.[28] Thus, the interaction of TNF with the TNFR2 is at the center of Treg functionality in autoimmunity.

Interestingly, TNF is a cytokine abundantly produced during the cytokine storm following alloSCT.[7] It thus constitutes a likely candidate for modulating Treg functionality during alloSCT. This is precisely what was clearly demonstrated by the three independent publications highlighted above.

In brief, Chopra and colleagues[5] reported the development a novel strategy for inhibiting GVHD based on expanding recipient Treg in vivo before alloSCT by stimulating Treg through their increased expression of TNFR2 using a selective agonist. Using a mouse model they demonstrated that the significant prolongation of graft survival observed was due to a reduction in the severity of GVHD dependent on the targeting TNFR2 to increase Treg activity. Importantly, the use of the TNFR2 agonist had no detrimental effect on the ability of donor T cells present in the transplant to mediate GVL or to eliminate pathogens. Pierini et al[6] observed that activation and suppressive activity of Treg was increased in mice undergoing acute GVHD and that this correlated with the high levels of TNFα present at the same time in the serum. TNFα while inducing Treg proliferation in vivo also limited the capacity of conventional T cells both $CD4^+$ and $CD8^+$ cells to proliferate and differentiate thus reducing their capacity to trigger GVHD. Linking the data from these 2 studies highlights the importance of inflammation following alloSCT leading to the production of TNFα and demonstrates unequivocally that the TNF/TNFR2 pathway is directly responsible.

If positively acting on the TNFR2 expressed by Treg could amplify and activate their suppressive function, thus preventing GVHD, blocking this pathway could conversely reduce their effect promoting GVL/GVT. In the third study, this intruiging hypothesis was explored and revealed a strong donor T cell -> Treg positive feedback mechanism for the first time in the setting of alloSCT. Indeed, the central finding of this study is that

the suppressive activity of Treg depends on TNF produced by conventional donor T cells and TNFR2 expressed by Tregs. The role of the TNF/TNFR2 in this context is supported by a wealth of experimental evidence with all of the clinical and biological indicators being highly consistent and convergent with the concept that Treg are dependent on TNF for their ability to control of GVHD. Indeed, blocking the TNF/TNFR2 pathway increased the clinical GVHD score, increased GVHD-related mortality, led to an increased activated phenotype of donor T cells and to down-modulation of Foxp3 and activation markers expressed by Tregs. Importantly, these results were obtained using 3 different experimental approaches and was validated for polyclonal Treg naturally present in the donor inoculum as well as for therapeutic Treg specific for either the nominal minor histocompatiblilty antigen HY Ag or for recipient alloantigens. Collectively, these results conclusively demonstrate that Treg control of GVHD depends on TNF produced by effector T cells and expression of TNFR2 by injected Treg cells.[4] Thus, anti-TNFR2 treatments, alone or in combination with other immune checkpoint therapy (anti-PD1, anti-PD1L or anti-CTLA/4) represents a new therapeutic option for increasing the GVL/GVT effect in alloSCT (Fig. 1).

Is there a real move towards TNFR2-based therapy?

In summary, we believe that these three publications will clearly be of significant interest for basic immunology as they delineate a novel aspect of Treg biology in the setting of alloSCT. Not only do Treg modulate the immune response following alloSCT but they themselves are in turn modulated by the immune response through TNF signaling. These findings expand the understanding of Treg action, by delineating a negative feedback loop that matches the magnitude of Treg action to donor T cell activity.

For translational and clinical hematology, the findings are a major advance as they have the potential to transform the intensive efforts to bring Treg to therapeutic maturity in alloSCT without having recourse to ex vivo GMP cell therapy approaches ie Treg depletion or expansion. These studies are highly complementary. Indeed, Chopra et al. showed the interest of triggering the TNF/TNFR2 pathway to reduce alloreactivity through Treg activation while Leclerc et al. revealed that Treg activity was inhibited when the TNF/TNFR2 pathway was blocked. Both studies show conclusively that the TNF/TNFR2 pathway is crucial for Treg function in the control of GVHD highlighting the potential therapeutic power of targeting this pathway to enhance or to suppress alloreactivity as needed in the particular clinical scenario that presents after alloSCT. Consequently, when Treg are activated with an anti-TNFR2 agonist molecule, GVHD would be prevented. Conversely, blocking the TNFR2 signaling pathway using a blocking anti-TNFR2 mAb for example would result in increased alloreactivity hence increasing the GVL/GVT effect (Fig. 2). Importantly, it has been shown that effector T cells, once activated, can also express TNFR2, and expression of TNFR2 on effector T cells appears to have a functional consequences in terms of activation and effector functions.[40] Thus, the potential side effect of TNFR2-targeting agents on the function of T cells remains to be carefully monitored. In this line, it is interesting to compare this approach with the therapeutic use of Interleukine-2 (IL-2). Initially identified for its capacity to stimulate T cells in vitro, IL-2 has been used in the clinic for boosting effector immune responses for the treatment of (i) metastatic melanoma and renal carcinoma[41] or (ii) for inducing remission maintenance in patients with acute myeloid leukemia[42] with limited (5–15% of patients) or non-significant benefit, respectively. Low efficacy of IL-2 in cancer can be obviously explained by insufficient T and NK cell activation but also by its now well described proliferating effect on Treg then rendered capable of blocking the anti-tumor immune response.[43] These results are in accordance with the understanding that although IL-2 has a pleïotropic

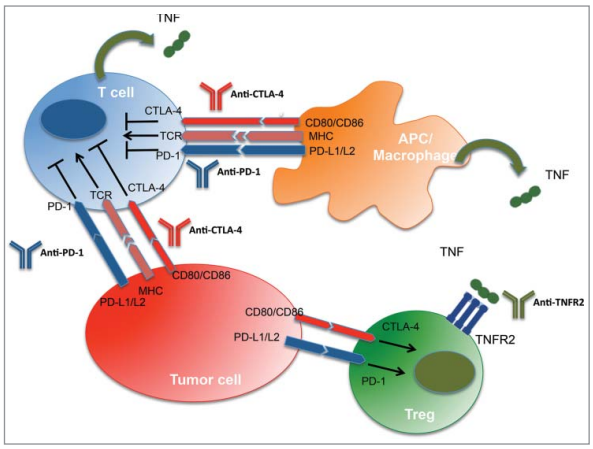

Figure 1. How could anti-TNFR2 treatment come into the arsenal of immune checkpoint therapies? To date, the two most advanced molecules in the clinic are anti-PD-1 and anti-CTLA-4. The engagement of PD-1L and CD80/86 on PD-1 and CTLA-4, respectively, results in inhibition of anti-tumor T-cell response. The same interaction on Treg leads to their activation and thus reinforces the inhibition of anti-tumor response. Anti-PD-1 and anti-CTLA-4 block these inhibition signals. Treatment with anti-TNFR2 may enhance the anti-tumor effect by blocking the effect of Treg. It would be the first immune checkpoint therapy specifically targeting Treg.

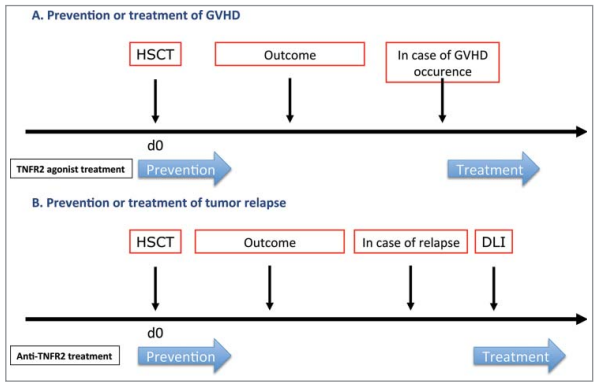

Figure 2. How to act on the TNF/TNFR2 pathway to modulate the immune response in alloSCT? Depending on the clinical situation of patients and the risk for patient to develop or not GVHD, different therapeutic strategies could be envisaged. (A) For patients with elevated risk of GVHD (unrelated donor or with 1 or several mismatch for instance), TNFR2 agonist could be administered to recipients before alloSCT as in the Chopra's publication (4) or at time of grafting. Patients could also be treated at time of GVHD occurrence irrespective of prevention treatment. (B) For patients with elevated risk of relapse (aggressive leukemia, geno-identical alloSCT), anti-TNFR2 could be administered to recipients at time of grafting. In case of relapse, patients could also be treated at time of donor lymphocyte infusion in order to block Treg effect as previously shown by Maury et al. (13, 14).

activity, its major role is to favor Treg survival and suppressive function. Consequently, IL-2 has been used at low doses to block the immune response and GVHD both in mice and in human.[44-46] These two approaches highlight the fact that a single cytokine (IL-2 or TNF) may have dual effects on conventional T cells and on Treg. The dose and timing of IL-2 or TNF administration is supposed to discriminate these to cell populations. However, in the case of TNF, an essential difference is that the therapeutic molecules are different depending on the expected effect: a TNFR2 blocking molecule to increase the GVL effect or a TNFR2 agonistic molecule to avoid GVHD. It is then possible to anticipate a more targeted effect.

Finally, this approach should not be restricted only to the hematopoietic cancers. As mentioned above, solid tumor invasion by TNFR2+ immunosuppressive cells is now well documented.[30-32] Blocking the effect of these cells by blocking the TNFR2 pathway on Treg, MDSC, and MSC could help amplify the anti-tumor immune response. Finally, some cancers especially epithelial cancers also express TNFR2 and the growth of these tumor cells seems to depend on TNFR2.[47,48] A therapeutic approach using a TNFR2 specific blocking agent could therefore act as a double-edged sword: on the one hand by removing the inhibition of the immune response,[49] and on the other hand by directly blocking the tumor growth.

Collectively, this work presented in these new studies reveals a highly innovative discovery in an area of rapid scientific and therapeutic development that offers new avenues of research for in vivo Treg-based immunomodulation using a novel immune checkpoint therapy target.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Authors'contributions

Writing of the manuscript: JLC and KJW

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