Kill the Messenger: T-cell/B-cell Interactions in cGVHD

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Abstract
Chronic graft-versus-host disease (cGVHD) is a common complication in patients after receiving an allogeneic tissue transplant, such as hematopoietic stem cell transplantation from unrelated donors. cGVHD was viewed predominantly as a T-cell mediated disease but the emerging evidences indicate the crucial role of B-cell and other immune cells in its pathogenesis. In their original paper in *Blood* [1], Flynn *et al.* show that increased frequency of T follicular helper (Tfh) cells and germinal center (GC) B-cells correlates with the development of cGVHD in a murine model and that blocking monoclonal antibodies (mAbs) for interleukin-21 (IL-21), inducble T-cell costimulator (ICOS) and CD40 ligand reverse cGVHD. These data demonstrate the importance of T follicular helper (Tfh) and germinal center (GC) B-cells in the pathogenesis of cGVHD and associated bronchiolitis obliterans syndrome (BOS) and suggest that new therapies using monoclonal antibodies (mAbs) targeting Tfh cells, GC B cells, and their interactions could potentially reverse established pulmonary cGVHD.

Keywords: bronchiolitis obliterans, cGVHD, germinal center, Tfh cells

Chronic graft versus host disease (cGVHD) often follows an allogeneic bone marrow transplant and is caused by the donor derived immune cells attacking the host tissues. It is a common cause of death in long-term survivors of allogeneic bone marrow transplantation [2]. Corticosteroids have been used as first line treatment in cGVHD and several other agents including mammalian target of Rapamycin (mTOR) inhibitors, imatinib, rituximab and pulsed corticosteroids are suggested as second or third line treatment options [3]. Although cGVHD can manifest in many ways, one common symptom is bronchiolitis obliterans (BOS), a disease caused by antibody deposition and subsequent bronchiole constriction in the lungs [4]. Without a proper understanding of the pathogenesis of cGVHD it will continue to be a significant cause of patient mortality. In addition, our murine models of cGVHD and BOS have been lacking, leading to a dearth of *in vivo* data for some clinical manifestations of the disease. Only recently a suitable mouse model for BOS has been identified, which has contributed greatly to our knowledge of BOS [5]. This model is currently the only one shown to develop BOS alongside other classical cGVHD symptoms, allowing the paired study of both diseases in a single model. In their latest article published in *Blood,* Flynn *et al.* further elucidated the pathogenesis of cGVHD by determining the role of T follicular helper cells (Tfh) and their activation of B-cells in germinal centers (GC).

Decades of mouse studies had driven a model that cGVHD was solely driven by T-cell activity; however more recent studies and clinical experience cast doubt on this conclusion. The paucity of adequate cGVHD animal models was a barrier in our understanding, but a new model was shown to be dependent on B-cell activity [5], data which was validated in the clinic by Allen *et al.* [6], and by the emerging data from the use of rituximab (an anti-CD20 monoclonal antibody) for cGVHD prophylaxis [7]. Clinical experience demonstrated that rituximab was not effective in every patient, leading us to wonder why this was the case. Flynn *et al.* showed that anti-CD20 treatment, while depleting CD20+ B-cells, did not significantly reduce symptoms of cGVHD using

this new model. The authors suspected that many B-cells were resistant due to localization or progression to antibody-producing plasma cells which no longer express the CD20 antigen. To circumvent these issues the authors turned to GC B-cells and their critical interaction with Tfh cells as an alternative target.

Tfh cells are known regulators of GC B-cells and in this paper, animals with cGVHD were shown to have increased Tfh counts. Tfh cells migrate into the GC and induce B-cell activation via IL21 production, which is a necessary effector molecule in B-cell maturation. ICOS and CD40 are critical upstream mediators of IL21 expression and are required for B-cell activation via Tfh cells [8]. The authors demonstrated that all three were critical for BOS disease progression, concluding that this interaction might represent an alternate target for clinical studies. Disease progression was shown to be ameliorated in the presence of ICOS and CD40 inhibitors, and use of an anti-IL21 mAB also showed clinical promise in its reduction of cGVHD.

Tfh cell migration to the GC is regulated by the CXCR5/CXCL13 receptor/ligand interaction [9], which may represent another therapeutic target. The authors demonstrated that T-cells deficient in CXCR5 were unable to traffic to the GC, abrogating cGVHD and BOS symptoms. They concluded that CXCR5 expression was necessary for cGVHD and BOS.

In this paper, Flynn *et al.* have demonstrated new clinical targets and have shown novel features of the pathogenesis of cGVHD and BOS. Their discussion of the negative effects of blocking these targets is minimal, despite the widespread expression of some of these targets. However, further research is warranted, in particular to determine clinical side effects of treatment. This study shows great promise, though it will be a long road to determine clinical efficacy. With that being said, their studies could lead to better treatment options for many patients who suffer from cGVHD.

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