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Editorial

IFNγR Signaling as a Therapeutic Target to Prevent GVHD after Allo-HSCT

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Since the first successful bone marrow transplantation was performed by the Nobel laureate, E. Donall Thomas, in 1956, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been a promising therapeutic strategy for hematologic malignancies and marrow failure states. Due to potent anti-alloantigen responses mediated by allogeneic T cells in the graft, allo-HSCT results in the reduction of leukemia relapse through its beneficial anti-leukemia effect or graft-versus-leukemia (GVL). However, a detrimental allogeneic response against healthy host cells, tissues and organs, termed graft-versus-host disease (GVHD), occurs in about 50% of the patients who have undergone allo-HSCT [1-3]. Depletion of these problematic T cells from the donor graft significantly reduces not only GVHD but also donor engraftment, which is associated with a poor immune reconstitution after allo-HSCT, and also increases leukemia relapse. Therefore, the clinical goal is to minimize GVHD while maximizing the beneficial GVL without excluding T cells from the graft.

Although many drugs and drug combinations have been used to prevent or reduce GVHD without abrogating GVL after allo-HSCT, none have dramatically improved outcomes [4]. In addition, the current GVHD prophylaxis and treatment significantly abrogate T cell number and function, thereby increasing donor engraftment failure rate and leukemia relapse. Several groups including our group have recently demonstrated that T cells deficient in IFNγR signaling, such as IFNγR-/-, T-bet-/-, or STAT1-/-, propagate less GVHD while preserving the beneficial GVL [5-9]. Therefore, it is clear that blockade of IFNγR signaling in donor T cells results in reduced GVHD. However, the targeted disruption of IFNγR signaling in donor T cells, donor bone marrow (BM) cells or recipient cells have very different effects upon GVHD severity. In contrast to the GVHD sparing effect of IFNγR deficient donor T cells, allo-HSCT recipient mice, which are deficient in IFNγR signaling, suffer from more aggravated GVHD, especially in the lung, than WT recipients, when transplanted with WT T cells [8]. In addition, a similar observation was reported in the WT recipients of IFNγ-/- T cells [8]. Considering that the primary source of IFNγ is alloreactive donor T cells, these observations suggest that IFNγR signaling in recipients is protective against allogeneic donor T cell-induced GVHD. Interestingly WT T cells cause less GVHD when transplanted along with IFNγR-/- donor BM cells than with WT donor BM cells [7], suggesting that IFNγR signaling in donor BM-derived cells is not protective, but enhances GVHD induction. Thus, the blockade of IFNγR signaling in donor T cells and BM cells or in recipients produces contrary results and it is not easy to predict outcome following systemic pharmacologic interruption of IFNγR signaling after allo-HSCT. Further research, using mouse models, may be necessary to examine GVHD severity after allo-HSCT in which IFNγR deficient recipients are transplanted with allogeneic BM and T cells both of which are also deficient in IFNγR signaling (Table 1).

Although it is well known that IFNγR signaling is a major mediator of GVHD, the underlying mechanisms remain to be elucidated, not only in T cells but also in recipients [8] and in donor BM-derived APCs [7]. While we have demonstrated that genetic blockade of IFNγR signaling alters T cell trafficking to GVHD target organs without affecting their *in vivo* expansion and cytotoxicity, others have shown that the reduced GVHD-inducing potential of IFNγR deficient T cells results from an increase in regulatory T cells (Tregs) [9] and/or preferential T cell differentiation to Th2 over Th1 cells [8,9]. However, all of the evidence reported at present is circumstantial and thus inconclusive.

It has been shown that donor T cell-derived IFNγ is critical for upregulation of indoleamine 2,3-dioxygenase (IDO) in APCs [10-12] and PD-L1 on host parenchymal cells [13,14], both of which are immunosuppressive against donor T cells, suggesting that downregulating IDO and PD-L1 through blockade of IFNγR signaling might result in aggravation of lung GVHD. While it is possible that lack of IDO and PD-L1 might play a role in lung GVHD, it cannot be ignored that the same IFNγR-/- recipients of WT T cells and WT recipients of IFNγ-/- T cells, on the other hand, have significantly less intestinal GVHD than the control groups [8]. Thus, it is also conceivable that the IFNγ-IFNγR axis likely regulate donor T cell trafficking to GVHD target organs in these settings.

Based on the literature, IFNγR signaling is essential for the upregulation of MHC I and II in antigen presenting cells (APCs), such as dendritic cells, macrophages, and B cells [15,16]. Thus, one can speculate that donor BM-derived APCs deficient in IFNγR signaling might be able to stimulate alloreactive donor T cells significantly less

Table 1: Effect of IFNγR signaling on GVHD after allo-HSCT.

donor T cells	donor BM cells	recipients	GVHD mortality	references
WT	WT	WT	++	5-9
IFNγR-/-	WT	WT	+/-	5-9
WT	IFNγR-/-	WT	+/-	7
IFNγ-/-	WT	WT	+++	8
WT	WT	IFNγR-/-	+++	8
IFNγR-/-	IFNγR-/-	IFNγR-/-	unknown	

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than WT BM-derived APCs. Thus, it remains unclear why IFNγR signaling in recipient cells and donor BM-derived cells initiated by the same donor T cell-derived IFNγ leads to different outcomes.

While the mechanisms underlying the reduced/accelerated GVHD after genetic blockade of IFNγR signaling are unclear at present, several groups have used small molecule inhibitors to pharmacologically block IFNγR signaling to mitigate GVHD [5,17-20]. Recently, we have reported compelling preclinical data demonstrating that pharmacologic modulation of IFNγR signaling using INCB018424, a small molecule JAK1/JAK2 inhibitor, is effective at inhibiting GVHD while preserving T cell function and GVL [5,21] as seen in IFNγR deficient T cells [5]. This data suggests that IFNγR signaling pathway is a promising therapeutic target to separate GVHD from GVL. However, a disparity in the effect of IFNγR signaling blockade in donor and recipient compartments remains the major challenge facing the use of systemic IFNγR signaling inhibition to mitigate GVHD and maintain GVL. Thus, elucidation of the mechanisms underlying the function of IFNγR signaling in GVHD will be essential to develop efficient and safe therapeutic strategies to control GVHD and be critical for future clinical trials, which, thus, will represent a significant advance in allo-HSCT.

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