Pharmacological targeting EZH2 to modulate chronic graft-versus-host disease

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In a recent issue of Blood (Blood 139, 2022), Zaiken et al1 reported that in vivo administration of the EZH2 inhibitor JQ5 effectively reduces chronic graft-versus-host disease (cGVHD), a life-threatening complication that occurs in 30%–70% of patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

cGVHD is a multiorgan chronic autoimmune-like disease that is induced by pathogenic CD4+ T cells and B cells. cGVHD remains the leading cause of nonrelapse mortality and morbidity in patients undergoing allo-HSCT.2 Perturbed B-cell homeostasis contributes to the progression of cGVHD, and inhibition of allo-antibody and auto-antibody production is considered as a promising approach to reduce cGVHD. Ibrutinib, a Bruton tyrosine kinase (BTK) and IL-2 inducible kinase (ITK) inhibitor that blocks B-cell activation, is the only FDA-approved drug for the treatment of steroid resistant cGVHD with an overall response rate of 55% for 44 weeks,3,4 prompting the development of novel treatment approaches.

Epigenetic remodeling occurs during B-cell activation and differentiation. Active and suppressive histone modifications orchestrate the chromatin opening status of cell fate determining genes that direct B-cell identity establishment and maturation.5 Such epigenetic regulation through histone modifications resembles those in T-cell activation and differentiation, which contributes to acute GVHD. Ez2, the catalytic subunit of the polycomb repressive complex 2 that specifically catalyzes the trimethylation of histone 3 at lysine 27, increases in germinal center B cells, regulating germinal center formation and B-cell maturation.6 Inhibition of T-cell Ez2 leads to blockade of acute GVHD in mice.7 Understanding whether pharmacological inhibition of Ez2 controls cGVHD can lead to new strategies to treat the disease.

Zaiken et al1 investigated the impact of pharmacological inhibition of EZH2 on cGVHD in mice manifested with bronchiolitis obliterans (BO). Transplantation with CD19-Cre Ez2fl/fl BM plus WT T cells led to significant lung function improvement compared with WT BM and WT T cells. Likewise, the authors also identified dramatically alleviated lung impairment in mice receiving WT BM together with Ez2 deficient T cells compared with those of Ez2-sufficient WT grafts. Both transplantation approaches led to reduction in follicular helper T cells (Tfh) and germinal center (GC) B cells with an enhanced ratio of follicular regulatory T cells versus Tfh cells, indicating an essential role of Ez2 in GC reaction post-HSCT and cGVHD progression. It should be mentioned that the CD19-Cre led to Ez2 deletion in the early developmental pro-B-cell stage, when the Ez2 level is the highest throughout the B-cell developmental stages.8 Ez2 deficiency at this pro-B stage disrupts B-cell reconstitution, which may also contribute to cGVHD inhibition in mice receiving CD19-Cre Ez2fl/fl BM. The authors tested several Ez2 inhibitors on BO and sclerodermatous cGVHD models by injecting compounds from day 28 to 49 post-HSCT, when B-cell reconstitution already established though compromised in T-cell recipients.9 They found a novel compound JQ5, which competes with SAM binding, significantly improved the pulmonary function and reduced skin lesions associated with blunting GC reaction. Intriguingly, transcriptome study identified a very small number of differentially expressed genes in GC B cells from JQ5-treated mice which co-clustered closer to cGVHD rather than BM-only. Among the several pathways enriched, the positive enrichment of proliferative pathways (mTORC1, Myc) in GC B cells from BM-only recipients and JQ5-treated recipients implied their contribution to the effect of JQ5. Further studies to determine the role of these pathways in GC B cells during cGVHD progression may lead to the identification of downstream effectors of JQ5. Nevertheless, JQ5 treatment later after allo-HSCT curtailed GC reaction without incurring massive transcriptome alteration in GC B cells with dramatic reduction in the H3K27me3 level and the extrinsic help from Tfh cells. This argues for the notion that Ez2 is a master regulator of GC reaction during cGVHD progression.

Besides the suppressive histone modifier Ez2, the bromodomains (BRDs) of the histone acetylation reader BRD and extrametinal (BET) enzymes also upregulated in GC B cells. Zaiken et al evaluated whether targeting this active histone modification reader using the BET-BRD inhibitor JQ1 would affect cGVHD progression. JQ1 reduced GC reaction and improved pulmonary function in the BO cGVHD model. However, unlike JQ5, administration of JQ1 failed to attenuate skin inflammation in the sclerodermatous cGVHD model. Transcriptome study with GC B cells from BO cGVHD mice showed that JQ1 induced distinct transcriptional signature compared with JQ5, as evidenced by the lack of enrichment for pro-proliferation pathways. The beneficial effect of JQ1 therapy on reducing BO cGVHD suggests that BET inhibitors could be potentially translated into patients receiving allo-HSCT.

The histone remodeling during immune cell expansion and differentiation highlights the therapeutic potential for epigenetic drugs in immune cell-mediated diseases such as cGVHD. Zaiken and colleagues’ work demonstrate the significant translational value of EZH2 inhibitors and BET inhibitors for cGVHD treatment. Given that the EZH2 inhibitor tazemetostat is already approved by FDA for the treatment of follicular lymphoma and epitheliod sarcoma,9 findings from Zaiken’s study paves the way for clinical trials targeting this pathway.
the way for clinical use of EZH2 inhibitors in the treatment of cGVHD.

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