Abstract: S255

Title: DIMETHYL FUMARATE AMELIORATES CGVHD BY INHIBITING TFH DIFFERENTIATION VIA NRF2

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Background:

Chronic graft-versus-host disease (cGVHD) remains a major complication after allogeneic hematopoietic stem cell transplantation. We previously reported that dimethyl fumarate (DMF), an anti-inflammatory drug approved for the treatment of multiple sclerosis and psoriasis, effectively inhibits acute GVHD (aGVHD) while preserving the graft-versus-leukemia effect. However, the role of DMF in cGVHD progression remains unknown.

Aims:

The current study aimed to investigate the role of DMF in the pathogenesis of cGVHD after allo-HSCT.

Methods:

To establish scleroderma-like cGVHD model, lethally irradiated BALB/C recipients were injected with 2.5 × 10^6 T cell-depleted bone marrow cells (TCD-BM) and 5 × 10^5 splenocytes from C57BL/6 mice. For systemic lupus-like cGVHD, C57BL/6 or BALB/c recipients were injected with 1 ×10^7 splenocytes from bm12 mice or 5 ×10^6 BMs together with 3 × 10^7 CD25- splenocytes from DBA2 mice, respectively. For xenograft GVHD, NSG-A2+ mice were transplanted with HLA-A2- human peripheral blood mononuclear cells (PBMCs). To explore the potential mechanisms, we profiled the immune cell responses in thymus and splenocytes by flow cytometry 6-8 weeks post transplantation. Murine and human naïve CD4+T cells were sorted to detect the role of DMF on Tfh development. RNA-Seq and ATAC-seq were integrated to investigate the mechanism of DMF involved in Tfh differentiation. Expression of indicated genes were determined by real-time PCR and immunofluorescence staining. Luciferase reporter assay was performed to assess the regulation of Nrf2 on IL-21 transcription. To validate the therapeutic potential of DMF in clinical cGVHD, PBMCs from cGVHD patients were isolated and treated with DMF.

Results:

The survival of receipts administrated with DMF was significantly prolonged than controls, companied by a lower cGVHD clinical score. Percentages of CD4+CD8+ cells in thymus were significantly elevated in recipients with DMF. Tfh cells and GC B cells were dramatically reduced in both scleroderma-like and lupus-like cGVHD model after DMF treatment. In vitro studies revealed that DMF directly inhibits both murine and human Tfh development by a dose dependent manner. RNA-seq showed that DMF significantly down-regulates Tfh cell-related genes, including Tcf7, Il6ra, Batf, klf2 and Il21, while up-regulates prdm-1 expression. Integrated RNA-seq and public Tfh ATAC-seq datasets, we found DMF reduced the accessibility of IL-21 gene. Luciferase reporter assay showed Nrf2 significantly repressed the transcript activity of IL-21. The inhibitory role of DMF on Tfh development were diminished after Nrf2 depletion. Interestingly, DMF treatment leads to a striking decrease in the frequency of IL-21 secretion and Tfh generation in human cGVHD PBMCs. Moreover, DMF significantly mitigates xenograft GVHD development.

Summary/Conclusion:

DMF administration significantly suppresses Tfh differentiation, germinal center formation and alleviates disease severity in different murine cGVHD models. Mechanistically, DMF treatment downregulates IL-21 transcription by activation of Nrf2, thus orchestrating Tfh-related gene program both in mice and humans. The inhibitory role of DMF on Tfh cell differentiation was diminished in Nrf2 deficient T cells. Importantly, DMF

treatment significantly suppresses IL-21 secretion and Tfh cell generation in PBMCs of active cGVHD patients and further attenuates xenograft GVHD. Collectively, our findings reveal that DMF potently inhibits cGVHD development by repressing Tfh cell differentiation via Nrf2, paving way for the treatment of cGVHD in the clinic.

Keywords: Bone marrow transplant, Chronic graft-versus-host, T cell