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POSTER ABSTRACTS

311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Bone Marrow CD8 $^+$ Tissue-Resident Memory T Cell Promote B Cell Differentiation and Inhibit Platelet Production in Patients with Immune Thrombocytopenia

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Immune thrombocytopenia (ITP) is a prevalent autoimmune disease in which enhanced anti-platelet T cell activity and dysfunction of CD8 $^+$ T cells are involved(Audia et al., 2013; Semple & Freedman, 1991). Persistent secretion of antibodies by long-lived plasma cells and memory B cells in the bone marrow contributes to ITP pathogenesis (Roeser, Lazarus, & Mahevas, 2023). However, the role of memory T cells, especially tissue-resident memory T cells (TRM), in ITP remains underexplored. TRM develop in specific tissues and play crucial role in local immunity. TRM exert their effects through mechanisms including the induction of local humoral responses, contributing to autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (Chang et al., 2021; Gu, Song, Roh, Jung, & Kim, 2021). Bone marrow contains one of the largest pools of memory CD8 $^+$ T cells. However, the involvement of bone marrow TRM in ITP pathogenesis remains poorly understood.

In this study, we observed a significantly higher proportion of CD8 $^+$ TRM (CD8 $^+$CD45RA $^-$CD45RO $^+$CD69 $^+$) in the bone marrow of ITP patients compared to healthy controls. However, no significant differences were observed in CD4 $^+$ TRM, CD8 $^+$ TCM and CD8 $^+$ TEM between the two groups. CD8 $^+$ TRM from ITP patients exhibited increased levels of IFN-γ, NLRP3, IL-1β, TNF-α, and decreased levels of IL-10 compared to those from healthy controls. Furthermore, CD8 $^+$ TRM proportions were significantly higher in glucocorticoid responders than non-responders, suggesting a potential role of CD8 $^+$ TRMs in mediating glucocorticoid therapeutic effects.

Transcriptome sequencing revealed upregulated genes, including IGLC2, ASAP2, HIST2H2AA4, IGLV2-11, C1QA, ATP5MC1, IL5RA, and CYC1, and downregulated genes, including CCR9, HSPE1P18, RGCC, and ITGAE, in TRM cells from ITP patients compared to controls. GO/KEGG analysis of the top 500 upregulated genes highlighted pathways associated with B cell-associated immunity. To explore the effect of TRM on B cells, bone marrow CD19 $^+$ B cells were co-cultured with autologous TRM or memory T cells without TRM (TM) in the presence of IgM, and the proportion of memory B cells (CD19 $^+$CD27 $^+$CD38 $^-$) and plasma cells (CD19 $^-$CD24 $^-$CD38 $^+$) were measured by flow cytometry. The supernatants were collected, and cytokines and IgG level were tested by ELISA. Results showed that TRMs from ITP patients promoted the differentiation of memory B cells and IgG antibody production compared with those from healthy controls. However, no significant difference was observed in the proportion of naive B cells and plasma cells between the two groups. TRM, but not TM augmented B cell differentiation into memory B cells or plasma cells both in ITP patients and healthy controls. Additionally, TRM-primed B cells showed a stronger effect on antibody production and resulted in a higher level of IgG in supernatant compared with TM primed B cells. In line with these findings, the levels of B cell activating factor (BAFF), a proliferation inducing ligand (APRIL), and sCD40L, which were critical cytokines for B cell survival and differentiation, were significantly higher in supernatants from ITP patients than those from healthy controls. Moreover, the levels of BAFF, APRIL and CD40L in co-culture system with TRM were significantly increased compared to the system with TM, providing insights into the impact of TRM on B cell differentiation and function.

To further investigate the role of TRM in regulating platelet production in ITP patients, we cocultured TRM with CD34 $^+$cells in the presence of thrombopoietin (TPO), stem cell factor (SCF) and interleukin (IL)-3. Results showed that TRM did not suppress the production of CD41 $^+$ megakaryocytes from CD34 $^+$ cells, but reduced megakaryocyte apoptosis and increased the percentage of polyploidy (≥4N) megakaryocytes compared with TM. Additionally, TRM inhibited reticulated platelet formation and platelet production. Notably, dexamethasone (DXM) modulation alleviated certain suppressive effects on platelet production.

In summary, our findings reveal the involvement of impaired bone marrow CD8 $^+$ TRM in the pathogenesis of ITP through the promotion of B cell differentiation and inhibition of platelet production. These results shed new light on the potential of immune therapy targeting TRM in the management of ITP.

Disclosures No relevant conflicts of interest to declare.

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