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508.BONE MARROW FAILURE: ACQUIRED

Myeloid Dendritic Cells Were Expanded and Functionally Stronger in Aplastic Anemia

Lingyun Chen[1], *Jiali Huo*[1], *Xiang Ren*[1], *Shichong Wang, MD*[2], *Yilin Liu*[1], *Jinbo Huang*[1], *Xingxin Li*[1], *Min Wang*[1], *Peng Jin*[1], *Neng Nie*[1], *Jing Zhang*[1], *Yingqi Shao*[1], *Yingchang Mi, MD*[1], *Yizhou Zheng*[1], *Meili Ge*[1]

[1] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences &Peking Union Medical College, Tianjin, China
[2] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences &Peking Union Medical College, Tian Jin, China

At present, the activated T cell-mediated destruction of hematopoietic stem/progenitor cells is the widely-recognized pathogenesis of aplastic anemia (AA). As the most important antigen-presenting cells in humans, dendritic cells (DCs) play an important role in the upstream link of immune pathogenesis in AA patients, so it may be the reason for the breakdown of immune tolerance in AA patients. In addition, abatacept, a cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) fusion protein, can block T cell activation and function by binding CD80 and CD86 and blocking their interaction with CD28. Thus may be a potential direction for targeting DCs to treat AA. However, relevant reports have not been seen so far.

To investigate the potential role of DCs in the pathogenesis of AA, we collected peripheral blood (PB) and bone marrow (BM) and measured the proportion of DCs. Results revealed that compared with healthy donors (HD), the proportion of myeloid DC in PB and BM in AA patients was significantly higher. In contrast, the proportion of plasmacytoid DC decreased significantly. Besides, the expression of CD80 and CD86 on PB DC surface of AA patients was higher than that of HD patients. Next, we cultured monocyte-derived DC in vitro and detected its phenotype and function. We confirmed that compared with HD, the expression rates of the co-stimulatory molecule CD80 and mature molecule CD83 of DC in AA patients were significantly increased, the apoptosis level was significantly decreased, and the ability to promote proliferation of $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes was enhanced. At the same time, AA-DC significantly enhanced the ability of $CD4^+$ T and $CD8^+$ T cells to express CD25 and CD69. In addition, the ability of AA-DC to promote the differentiation of Th0 cells to Th1 and Th17 cells was stronger than HD. The ability to promote the differentiation of Th0 to Treg cells was weaker than HD.

To investigate the feasibility of abatacept targeting DC in the treatment of AA, we compared the proportions of CTLA-4 and found the expression of CTLA-4 on $CD4^+$ T cells and Treg cells in PB of AA patients was significantly decreased. Then, our in vitro tests confirmed that abatacept can bind to CD80 on the surface of DC and significantly down-regulate the expression of CD80. Adding abatacept into the co-culture system of DC and $CD3^+$ T lymphocytes significantly inhibited the proliferation of $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes, and significantly inhibited the expression of CD25 and CD69 in $CD4^+$ T and $CD8^+$ T cells. In addition, the ability of DC to promote the secretion of interferon-γ by $CD4^+$ and $CD8^+$ T cells in AA patients was significantly weakened after the addition of abatacept, while the ability to promote the secretion of interleukin-4 by $CD4^+$ and $CD8^+$ T cells was significantly enhanced.

Finally, we performed RNA-Seq analysis using DCs cultured in vitro from HD and AA patients and using DC from AA patients added with abatacept to uncover the possible molecular mechanism. Result showed that compared with HD, there were significant differences in the expression levels of 58 genes of DC in patients with AA, including 22 up-regulated genes and 36 down-regulated genes. Go analysis inferred that the differentially expressed genes were mainly concentrated in cell migration, cell chemotaxis, regulation of cytokine production, and immune response. Besides, KEGG pathway analysis implied that the signaling pathway of significant enrichment of differentially expressed genes was cytokine-cytokine receptor interaction, NF-κB signaling pathway, chemokine signaling pathway and IL-17 signaling pathway. Meanwhile, compared with AA patients, after adding abatacept, 1058 genes showed significant differences in expression levels. Go analysis inferred that the differentially expressed genes were mainly concentrated in immune response, cytokine secretion, regulation of hemopoiesis, cell activation, differentiation, proliferation, and adhesion. Moreover, KEGG pathway analysis implied that the signaling pathway

enriched in cytokine-cytokine receptor interaction, JAK-STAT signaling pathway, NF-κB signaling pathway and Th1, Th2 and Th17 cell differentiation.
Our finding revealed the increased number and hyperfunction of DC in AA patients may be involved in the immune pathogenesis of AA. Abatacept can block T cell activation by blocking the DC surface co-stimulatory molecule CD80 and is a promising strategy for AA treatment.

Disclosures No relevant conflicts of interest to declare.

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