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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Impaired Immunosuppressive Effect of Bone Marrow Mesenchymal Stem Cell-Derived Exosomes on T Cells in Aplastic Anemia

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Background: Previous studies have verified the dysfunction of mesenchymal stem cells (MSCs) for immunoregulation in acquired aplastic anemia (AA) patients. Exosomes derived from MSCs can partially substitute MSC acting as immune regulator. Dysfunction of exosomes (Exos) derived from AA-MSC (*AA-Exos*) may play a key role in immunologic dissonance.
Objectives: This study aims to investigate the interaction between exosomes derived from mesenchymal stem cells and T cells of patients with aplastic anemia by examining the immunosuppressive effects of exosomes on T cells both in vitro and in vivo. Besides, this study intends to explore the differently expressed miRNA of exosomes and mRNAs of T cells between patients with AA and healthy donors (HD) to better understand the mechanisms of AA on molecular lever.
Method: In this study, CD3 $^{+}$ T cells were collected and cocultured with AA-Exos and exosomes derived from HD-MSC (HD-Exos). The proliferation, differentiation and activation of CD3 $^{+}$ T cells were detected to compare the immunosuppressive effects between AA-Exos and HD-Exos. An immune-mediated murine model of AA was structured to compare the therapeutic effect of AA-Exos and HD-Exos. Furthermore, total RNA including miRNA from exosomes we purified and total RNA of CD3 $^{+}$ T cells were extracted for RNA-seq in order to construct the miRNA-mRNA network for interactions and functional analysis.
Results: Compared to HD-Exos, AA-Exos exhibit a weakened ability to inhibit the proliferation of CD3+/CD4+/CD8+ T cells (40.73% vs 32.43%,p = 0.0007;46.20% vs 38.08%,p = 0.0009;36.28% vs 29.73%,p = 0.0077). Furthermore, AA-Exos show reduced capacity to suppress T cell activation compared to HD-Exos. In AA-Exos group, the ability of inhibiting CD4+ T cell differentiation towards Th1 is diminished (12.80 vs 10.17%, $p = 0.0047$), while the induction of Th17 cell generation is significantly enhanced (3.613% vs 1.153%, p=0.0015). Additionally, AA-Exos demonstrate weaker capabilities to inhibit CD8+ T cell differentiation towards Tc1 compared to HD-Exos (41.93% vs 35.40%,p=0.0007). The capacity of AA-Exos to induce Treg is also weakene (7.78% vs 10.36%,p=0.041).HD-Exos other than AA-Exos can rescued the AA mice. Administration of HD-Exos effectively improves the bone marrow failure, the BMNC counting revealed that HD-Exos had more potency in ameliorating bone marrow hyperplasia than AA-Exos (8.27×106/L vs 0.85×106/L,p=0.0021).
The RNA cargo of exosomes was believed to be a key mediator exerting their function, especially the carry of miRNA.Importantly, we identified some differentially expressed miRNA involved in immune response under the standard of adjusted $p < 0.05$ &| log2 (foldchange) | > 1.5, such as miR-199, miR-128, miR-486 and miR-375. The Gene Ontology analysis of differentially expressed genes (DEGs) revealed involvement of various cellular processes, such as lymphocyte chemotaxis, lymphocyte migration and response to interferon-gamma. The Kyoto Encyclopedia of Genes and Genomes analysis illustrated upregulation of critical pathways associated with T cell function after co-culturing with AA-Exos compared with HD-Exos, such as graft-versus-host disease, Th17 cell differentiation, and JAK-STAT signaling pathway. A miRNA-mRNA network was established to visualize the interaction between them, in which a total of 61 node and 142 edge network pathways were constructed, including 14 miRNAs and 47 mRNAs. To validate the findings, qPCR was performed on four DEGs, and significant differences were observed in three of them, namely MRPL40, TNF and CCL4L2 (p=0.0116, p=0.0016, p=0.0122, respectively).
Conclusion: In summary, AA-Exos had impaired immunosuppressive effect on T cells, less ability to rescue AA mice and differently expressed miRNA profile, which might partly account for the pathogenesis of AA as well as provide a new target of AA treatment.

Disclosures No relevant conflicts of interest to declare.

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