THE APPLICATION OF ENHANCED CELL-FREE THERAPY USING HYPOXIA-PRECONDITIONED BONE MARROW MESENCHYMAL STEM CELLS IN PRIMARY OVARIAN INSUFFICIENCY

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Abstract Body

Primary ovarian insufficiency (POI) is defined as ovarian dysfunction before age 40, accompanied by hypogonadotropic hypogonadism, amenorrhea, and infertility. Although the exact etiology of POI is unknown, one of the most common and major causes of POI is chemotherapy for female cancer patients. Human bone marrow mesenchymal stem cells (hBMMSC) are widely used for tissue regeneration and have demonstrated the effect of restoring ovarian function in POI. hBMMSC has pro-angiogenic, anti-apoptotic, and immunomodulatory properties. These effects are enhanced under hypoxia conditions. The therapeutic efficacy of hBMMSC mainly depends on paracrine actions, and extracellular vesicles (EV) have been identified as the major mediators of stem cell-induced regenerative factors. However, the underlying therapeutic mechanism of hBMMSC-derived extracellular vesicles (hBMMSC-EV) is not fully understood in ovarian regeneration.

In this study, we investigated therapeutic potential in ovarian damage caused by cyclophosphamide (CTX) and underlying molecular mechanisms using hypoxia-preconditioned hBMMSC-EV as an enhanced cell-free therapy. Both normoxic hBMMSC-EV (N-EV) and hypoxic hBMMSC-EV (H-EV) exhibited round-shaped morphology with a mean diameter of 100nm and were positive for CD63, CD81, TSG101, and negative for calnexin. MicroRNA profiling revealed that 19 miRNAs express the most significant difference in abundance between N-EV and H-EV. Among them, six miRNAs were up-regulated in H-EV compared to N-EV, and the target genes predicted by up-regulated miRNAs and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were associated with an anti-inflammation. The number of primordial follicles increased, and apoptosis reduced in H-EV-treated than N-EV-treated ovaries in POI mice. Our findings suggest that hypoxic hBMMSC-EV may be a promising therapy for ovarian regeneration in chemotherapy-induced POI through the miR-mediated mechanism.