Lu et al. Stem Cell Research & Therapy (2020) 11:268
https://doi.org/10.1186/s13287-020-01784-7

Stem Cell Research & Therapy

RESEARCH Open Access

hUMSC transplantation restores ovarian function in POI rats by inhibiting autophagy of theca-interstitial cells via the AMPK/mTOR signaling pathway

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Abstract

Background: Previous studies of primary ovarian insufficiency (POI) have focused on granulosa cells (GCs) and ignored the role of theca-interstitial cells (TICs). This study aims to explore the mechanism of the protective effects of human umbilical cord-derived mesenchymal stem cells (hUMSCs) on ovarian function in POI rats by regulating autophagy of TICs.

Methods: The POI model was established in rats treated with cisplatin (CDDP). The hUMSCs were transplanted into POI rats by tail vein. Enzyme-linked immunosorbent assay (ELISA) analysis, hematoxylin and eosin (HE) staining, and immunohistochemistry were used to measure the protective effects of hUMSCs. The molecular mechanisms of injury and repairment of TICs were assessed by immunofluorescence, transmission electron microscope (TEM), flow cytometry (FCM), western blot, and quantitative real-time polymerase chain reaction (qRT-PCR).

Results: In vivo, hUMSC transplantation restored the ovarian function and alleviated the apoptosis of TICs in POI rats. In vitro, hUMSCs reduced the autophagy levels of TICs by reducing oxidative stress and regulating AMPK/mTOR signaling pathway, thereby alleviating the apoptosis of TICs.

Conclusion: This study indicates that hUMSCs protected ovarian function in POI by regulating autophagy signaling pathway AMPK/mTOR.

Keywords: Primary ovarian insufficiency, Theca-interstitial cells, Human umbilical cord-derived mesenchymal stem cells, Autophagy, Oxidative stress, AMPK

Background

Primary ovarian insufficiency (POI) is an encompassing disorder associated with conditions ranging from irregular ovulation to premature menopause and covers all non-physiological declines in ovarian reserves [1, 2]. POI refers to the loss of ovarian activity in women before the age of 40 and is manifested as amenorrhea or oligomenorrhea, accompanied by elevated gonadotropin and decreased estradiol (E_2) levels [3]. It has reported that chromosomal abnormalities, immune factors, metabolic abnormalities, surgery, radiotherapy, drugs, and especially chemotherapy drugs can induce POI [4–9]. Cisplatin (CDDP), one of the commonly used chemotherapeutic drugs, has been reported to trigger POI and result in decreased hormonal levels of an acceleration in follicle loss and an enhancement of ovarian aging [10, 11]. Recently, mesenchymal

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