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A Novel Application of CORDYCEPIN (Cordycepssinensis Extract): Maintaining Stem Cell Pluripotency and Improving iPS Generation Efficiency

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Abstract : Embryonic stem cells (ES) and induced pluripotnet stem cells (iPS) are both pluripotent stem cells. For mouse stem cells culture technology, leukemia inhibitory factor (LIF) was used to maintain the pluripotency of stem cells in vitro. However, LIF is an expensive reagent. The goal of this study was to find out a pure compound extracted from Chinese herbal medicine that could maintain stem cells pluripotency to replace LIF and improve the iPS generation efficiency. From 20 candidates traditional Chinese medicine we found that Cordycepsmilitaris triggered the up-regulation of stem cells activating genes (Oct4 and Sox2) expression levels in MEF cells. Cordycepin, a major active component of Cordycepsmilitaris, also could up-regulate Oct4 and Sox2 gene expression. Furthermore, we used ES and iPS cells and treated them with different concentrations of Cordycepin (replaced LIF in the culture medium) to test whether it was useful to maintain the pluripotency. The results showed higher expression levels of several stem cells markers in 10 μM Cordycepin-treated ES and iPS cells compared to controls that did not contain LIF, including alkaline phosphatase, SSEA1, and Nanog. Embryonic body formation and differentiation confirmed that 10 μM Cordycepin-containing medium was capable to maintain stem cells pluripotency after four times passages. For mechanism analysis, microarray analysis indicated extracellular matrix and Jak/Stat signaling pathway as the top two deregulated pathways. In ECM pathway, we determined that the integrin αVβ5 expression levels and phosphorylated Src levels increased after Cordycepin treatment. In addition, the phosphorylated Jak2 and phosphorylated Sat3 protein levels were increased after Cordycepin treatment and suppressed with the Jak2 inhibitor, AG490. The expression of cytokines associated with Jak2/Stat3 signaling pathway were also up-regulated by Q-PCR and ELISA assay. Lastly, we used Oct4-GFP MEF cells to test iPS generation efficiency following Cordycepin treatment. We observed that 10 Mm Cordycepin significantly increased the iPS generation efficiency in day 21. In conclusion, we demonstrated Cordycepin could maintain the pluripotency of stem cells through both of ECM and Jak2/Stat3 signaling pathway and improved iPS generation efficiency.

Keywords : cordycepin, iPS cells, Jak2/Stat3 signaling pathway, molecular biology
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