

Extracellular vesicles of iPS cells highly capable of producing HGF and TGF- β 1 can attenuate Sjögren's syndrome via innate immunity regulation

Abstract

Previous studies have demonstrated that extracellular vesicles (EVs) from dental pulp stem cells (DPSCs), which release abundant hepatocyte growth factor (HGF) and transforming growth factor- β 1 (TGF- β 1), contribute to the pathogenesis of Sjögren's syndrome (SS). However, depending on the condition of DPSCs, this effect is often not achieved. In this study, we established induced pluripotent stem (iPS) cells highly capable of releasing HGF and TGF- β 1 and iPS cells barely capable of releasing them, and administered each EV to SS model mice to see if there was a difference in therapeutic effect. EVs were collected from each iPS cell and their characteristics and shapes were examined. When they were administered to SS model mice, the EVs from iPS cells with higher concentrations of HGF and TGF- β 1 showed significantly reduced inflammatory cell infiltration in salivary gland tissues, increased saliva volume, and decreased anti-SS-A and anti-SS-B antibodies. A comprehensive search of microRNA arrays for differences among those EVs revealed that EVs from iPS cells with higher concentrations of HGF and TGF- β 1 contained more of the let-7 family. Thereafter, we examined the expression of toll-like receptors (TLRs), which are said to be regulated by the let-7 family, by qPCR, and found decreased TLR4 expression. Focusing on MAPK, a downstream signaling pathway, we examined cytokine concentrations in mouse macrophage culture supernatants and Western blotting of murine splenic tissues and found higher concentrations of anti-inflammatory cytokines in the EVs-treated group and decreased TLR4, NF- κ B and phosphorylation (p)-p-38 MAPK expression by Western blotting. Alternatively, p-Smad2/3 was upregulated in the EVs-treated group. Our findings suggest that the let-7 family in EVs may suppress the expression of TLR4

and NF- κ B, which may be involved in the suppression of MAPK-mediated pro-inflammatory cytokine production.

Keywords: Extracellular vesicles; Induced pluripotent stem (iPS) cells; Sjögren's syndrome; Toll-like receptors (TLRs).