学位論文　全文要約

Mechanosignaling YAP/TAZ-TEAD Axis Regulates the Immunomodulatory Properties of Mesenchymal Stem Cells

（メカノシグナル YAP/TAZ-TEAD 経路は間葉系幹細胞の免疫調整能を制御する）

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Aim; Mesenchymal stem cells (MSCs) have attracted medical attention due to their multipotency and self-renewing property. Besides, MSCs exert anti-inflammatory/immunomodulatory functions by producing cytoprotective cytokines such as TSG-6. Recently, F-actin and YAP/TAZ have been recognized as key players in the mechanotransduction cascade, controlling cell lineage commitment in MSCs. However, it is unclear whether YAP/TAZ mechanosignaling affects anti-inflammatory/immunomodulatory capacities of MSCs. Thus, this present study aimed to investigate the roles of YAP/TAZ and their binding target transcriptional factor, TEAD, concerning the immunomodulatory capacities of MSCs.

Methods; Human bone marrow-derived MSCs were cultured with YAP/TAZ disrupting conditions, including soft gel, floating culture, high cell density, disrupting the F-actin integrity with chemical inhibitors, or using siRNAs. Then, TSG-6 and IDO mRNA expression levels were quantified by qPCR. MSCs transfected with YAP/TAZ or TEAD siRNAs were co-cultured with T cells. T cell proliferation was assessed by measuring the bromodeoxyuridine (BrdU) incorporation using a cell proliferation ELISA kit. We conducted whole transcriptome sequencing to investigate how YAP/TAZ down-regulation affects TNFα-induced immunomodulatory factors in MSCs. Then, we also evaluated the in vivo anti-inflammatory efficacy of MSCs in a dextran sulfate sodium (DSS) induced mice colitis model.

Results; Disruption of YAP/TAZ signaling facilitated TSG-6 and IDO mRNA expression in MSCs, and the elevation was strengthened by TNF-α stimulation. MSCs transfected with YAP/TAZ or TEAD siRNA inhibited T cell activity. RNA-seq analysis and inhibition assays demonstrated that the immunomodulatory capacities caused by YAP/TAZ-TEAD axis disruption were due to the NF-κB signaling pathway activation. The administration of human MSCs transfected with TEAD siRNA, which exhibited enhanced

immunomodulatory properties in vitro, significantly ameliorated inflammatory bowel disease symptoms, such as body weight loss and acute colon inflammation, in the DSS-induced mice colitis model.

Conclusion; YAP/TAZ-TEAD axis negatively regulate MSCs anti-inflammatory/immunomodulatory function. Understanding and manipulating these signaling pathways can pave the way for novel and promising MSCs-based therapies for immune system disorders.

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