News Release

Title

Development of a novel therapy for treating acute liver failure using M2 macrophages inducers identified from the stem cells of human exfoliated deciduous teeth

Key Points

○ A single intravenous administration of monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (sSiglec-9) identified from stem cells derived from human exfoliated deciduous teeth (SHED), a population of self-renewing mesenchymal stromal cells (MSCs), markedly improved hepatic injury in a D-galactosamine (D-Gal) induced rat acute liver failure (ALF) model.

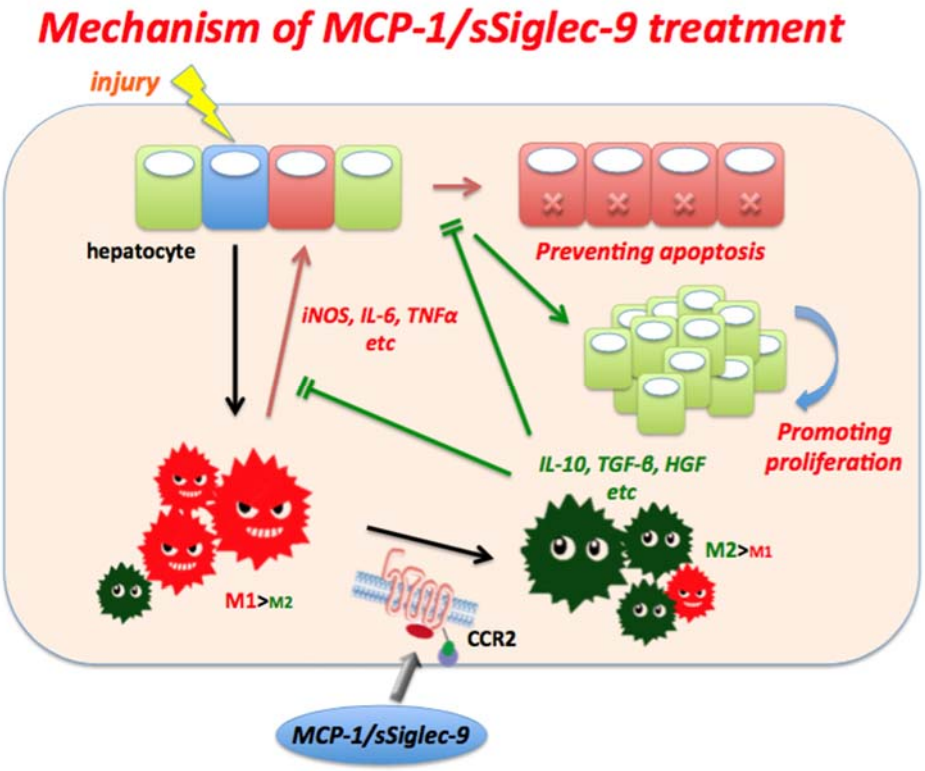
○ Combination of MCP-1/sSiglec-9 induced anti-inflammatory M2, suppressed the apoptosis and promoted the proliferation of hepatocytes, and dramatically improved the survival rate of ALF rats.

○ The conditioned medium from MCP-1/sSiglec-9-activated M2 bone marrow macrophages suppressed the D-Gal- and LPS-induced apoptosis of primary hepatocytes and promoted their proliferation *in vitro*.

○ Our study suggests that MCP-1/sSiglec-9 may be a promising therapeutic strategy for ALF.

Summary

Graduate student Takanori Ito, Assistant Professor Masatoshi Ishigami, Professor Hidemi Goto (Department of Gastroenterology and Hepatology of Nagoya University Graduate School of Medicine, Dean: Masahide Takahashi) and Professor Hideharu Hibi (Department of Oral and Maxillofacial Surgery of Nagoya University Graduate School of Medicine) found that a single intravenous administration of monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (sSiglec-9) identified from stem cells derived from human exfoliated deciduous teeth (SHED), a population of self-renewing mesenchymal stromal cells (MSCs), markedly ameliorated hepatic inflammation and destruction in D-galactosamine (D-Gal), which is known to be one of the hepatotoxin, induced rat acute liver failure (ALF) model. This work has been carried out as a collaboration study with Professor Akihito Yamamoto (Department of Tissue regeneration (former Oral histology), Institute of Biomedical Science, Tokushima University Graduate School). In ALF, a poorly controlled inflammatory response causes extensive hepatic destruction, which leads to systemic inflammation, multiple organ failure, and subsequent death. There are currently no effective treatments for ALF other than liver transplantation in clinical practice. We found that M2 cells synergistically induced by MCP-1 and sSiglec-9, but not IL-4, protected primary hepatocytes from hepatotoxin-induced cell death and furthermore promoted their proliferation *in vitro*. Consistently, ALF rat treated with MCP-1 and sSiglec-9 dramatically ameliorated liver injury through the induction of the tissue-regenerating M2 circumstances. Notably, depletion of M2 abolished MCP-1/sSiglec-9-mediated restoration of hepatic function and improvement of the survival rate. Thus, our data suggest that the M2 macrophages induced by MCP-1/sSiglec-9 may provide therapeutic benefits for treating patients with ALF.



Research Background

ALF induced by various causes (e.g. drugs, hepatitis viruses, autoimmune hepatitis) is unfavorable and intractable liver disease that is characterized by massive hepatocyte destruction and an uncontrolled inflammatory response. Although there are some supportive treatments, such as blood purification, liver transplantation is currently the only available treatment in progressive liver failure. However, its application is limited due to the shortage of donors and exorbitant cost. Therefore, alternative treatments for patients with ALF are urgently needed. We previously reported that a single intravenous administration of the conditioned medium of SHED (SHED-CM) improved rat ALF model without the cell-transplantation. However, it was unclear which among the various factors derived from SHED are responsible for ALF recovery. Here, we investigated the therapeutic activity of MCP-1/sSiglec-9, a major component of SHED-CM, in rat ALF model.

Research Results

Rat ALF was induced by the intraperitoneal injection of D-Gal, and the survival rate of this model was approximately 30%. Rats receiving a single intravenous administration of MCP-1/sSiglec-9, 24 h after D-Gal injection exhibited markedly reduced liver damage and improved survival rates. Quantitative RT-PCR and immunohistochemical staining analysis revealed that MCP-1/sSiglec-9 treatment strongly suppressed pro-inflammatory mediator expression and increased M2 marker expression, suppressed the apoptosis and promoted the proliferation of hepatocytes. In addition, the conditioned medium from MCP-1/sSiglec-9-activated, but not from interleukin-4-induced, M2 macrophages suppressed the D-Gal- and LPS-induced apoptosis of primary hepatocytes and promoted their proliferation *in vitro*. Taken together, the unique combination of MCP-1/sSiglec-9 ameliorates rat ALF by inhibiting hepatocellular apoptosis and promoting liver regeneration through the induction of anti-inflammatory/tissue-repairing M2 macrophages.

Research Summary and Future Perspective

Our data suggest that MCP-1 and sSiglec-9 may be a promising therapeutic strategy for ALF. The goal of our study is to develop the novel anti-autoimmune drug based on the MCP-1 and sSiglec-9.

Publication

Takanori Ito, Masatoshi Ishigami, Yoshihiro Matsushita, Marina Hirata, Kohki Matsubara, Tetsuya Ishikawa, Hideharu Hibi, Minoru Ueda, Yoshiki Hirooka, Hidemi Goto, Akihito Yamamoto. Secreted Ectodomain of SIGLEC-9 and MCP-1 Synergistically Improve Acute Liver Failure in Rats by Altering Macrophage Polarity. *Scientific Reports*, published online on Mar.8, 2017.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2016/ccr2_20170308jp.pdf