

Mesenchymal stem cells protect from acute liver injury by attenuating hepatotoxicity of liver NKT cells in IDO dependent manner

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Statement of the Problem: The effects of mesenchymal stem cells (MSCs) on phenotype and function of natural killer T (NKT) cells, is not understood. The aim of the study is to evaluate the protective nature of MSCs against acute liver injury through attenuating hepatotoxicity of liver NKT cells in IDO dependent manner.

Methodology & Theoretical Orientation: We used concanavalin A (ConA) and α -galactosylceramide (α -GalCer) induced liver injury to evaluate effects of MSCs on NKT-dependent hepatotoxicity.

Findings: MSCs significantly reduced Con A- and α -GalCer-mediated liver damage in C57Bl/6 mice, as demonstrated by histopathological analysis and liver enzyme tests, attenuated influx of inflammatory (T-bet+ TNF- α , IFN- γ producing as well as GATA3+, IL-4-producing) liver NKT cells and down-regulated TNF- α , IFN- γ and IL-4 levels in the sera of injured mice. It was observed that the liver NKT cells cultured *in vitro* with MSCs produced lower amounts of inflammatory cytokines (TNF- α , IFN- γ , IL-4) and higher amounts of immunosuppressive IL-10 upon α -GalCer stimulation. MSC treatment attenuated expression of apoptosis-inducing ligands on liver NKT cells suppressed the expression of pro-apoptotic genes in the livers of α -GalCer-treated mice. MSCs reduced cytotoxicity of liver NKT cells against HepG2 hepatocyte cells *in vitro*. The presence of 1-methyl-DL-tryptophan, a specific inhibitor of indoleamine 2,3-dioxygenase (IDO), in MSC-conditioned medium injected to α -GalCer-treated mice, counteracted the hepatoprotective effect of MSCs *in vivo*, and restored pro-

inflammatory cytokine production and cytotoxicity of NKT cells *in vitro*. In line with these findings, human MSCs in an IDO-dependent manner, attenuated the production of inflammatory cytokines in α -GalCer-stimulated human peripheral blood mononuclear cells and reduced their cytotoxicity against HepG2 cells.

Conclusion & Significance: MSCs protects the acute liver injury by attenuating cytotoxicity and capacity of liver NKT cells to produce inflammatory cytokines in IDO dependent manner.

Image

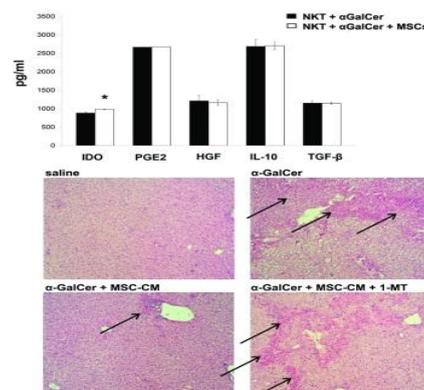


Figure 1: MSCs suppress activity of NKT cells in an IDO-dependent manner. IDO, PGE2, HGF, IL-10, and TGF- β were determined in supernatants by ELISA. C57Bl/6 mice were treated with saline (0.2 mL), α -GalCer (50 μ g/kg), MSC-CM (0.2 mL) or MSC-CM (0.2 mL)+1-MT (1 mM) immediately after α -GalCer administration. Histological tissue samples were analyzed 16 hours after treatment (H&E staining).

Recent Publications

1. Simovic Markovic B, Nikolic A, Gazdic M, Bojic S, Vucicevic L, Kosic M, Mitrovic S, Milosavljevic M, Besra G, Trajkovic V, Arsenijevic N, Lukic M L and Volarevic V (2016) Galectin-3 plays an important pro-inflammatory role in the induction phase of acute colitis by promoting activation of NLRP3 inflammasome and production of IL-1 β in macrophages. *J. Crohn's and Colitis* 10: 593-606.
2. Simovic Markovic B, Nikolic A, Gazdic M, Nurkovic J, Djordjevic I, Arsenijevic N, Stojkovic M, Lukic M L and Volarevic V (2016) Pharmacological inhibition of Gal-3 in mesenchymal stem cells enhances their capacity to promote alternative activation of macrophages in dextran sulphate sodium-induced colitis. *Stem Cells Int.* 2016: 2640746.
3. Volarevic V, Markovic B S, Bojic S, Stojanovic M, Nilsson U, Leffler H, Besra G S, Arsenijevic N, Paunovic V, Trajkovic V and Lukic M L (2015) Gal-3 regulates the capacity of dendritic cells to promote NKT-cell-induced liver injury. *Eur. J. Immunol.* 45: 531-543.
4. Volarevic V, Misirkic M, Vucicevic L, Paunovic V, Simovic Markovic B, Stojanovic M, Milovanovic M, Jakovljevic V, Micic D, Arsenijevic N, Trajkovic V and Lukic M L (2015) Metformin aggravates immune-mediated liver injury in mice. *Arch. Toxicol.* 89: 437-450.
5. Volarevic V, Paunovic V, Markovic Z, Simovic Markovic B, Misirkic-Marjanovic M, Todorovic-Markovic B, Bojic S, Vucicevic L, Jovanovic S, Arsenijevic N, Holclajtner-Antunovic I, Milosavljevic M, Dramicanin M, Kravic-Stevovic T, Ciric D, Lukic M L and Trajkovic V (2014) Large graphene quantum dots alleviate immune-mediated liver damage. *ACS Nano* 8: 12098-12109.



Biography

Bojana Simovic Markovic has experience in immunopathology of liver and gastrointestinal tract research. She has a broad spectrum of publications including original article in the field of mesenchymal stem cell-dependent modulation of immune mediated diseases.