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## Mesenchymal stem cells attenuate acute liver injury mediated by NKT cells

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The effects of mesenchymal stem cells (MSC) on phenotype and function of natural killer T (NKT) cells, major effector cells in acute liver injury, is not fully understood. We used two well-established experimental models of NKT-cell mediated acute liver pathology: Concanavalin A (Con A)-induced hepatitis (Con A; 12 mg/kg i.v) and α-galactosylceramide (α-GalCer; 50 μg/kg i.v)-induced liver injury to evaluate effects of MSC on liver damage and NKT cell functions.

MSC (single iv. injection, 500 000/mouse, given immediately after Con A or α-GalCer) significantly attenuate Con A and α-GalCer mediated liver damage, as demonstrated by histopathological analysis and liver enzyme tests. MSC-treatment attenuates influx of inflammatory NKT cells in the liver (TNF-α-, IFN-γ-, T-bet+ CD4+ and CD1d tetramer+ as well as Gata-3+, IL-4-producing NKT cells) and down-regulates inflammatory cytokines (TNF-α, IFN-γ, and IL-4) in the sera of Con A and α-GalCer-treated C57Bl/6 mice. Serum levels of anti-inflammatory IL-10 and percentage of IL-10-producing NKT cells in the liver were significantly higher in MSC-treated mice. MSC did not significantly affect phenotype of macrophages and dendritic cells, suggesting that MSC modulate production of cytokines directly in liver NKT cells. Significantly lower amounts of inflammatory cytokines (TNF-α, IFN-γ, IL-4), and higher amounts of immunosuppressive IL-10 were noticed in supernatants of in vitro α-GalCer (100 ng/mL)-stimulated liver NKT cells cultured with MSC in transwell systems when compared to α-GalCer-stimulated liver NKT cells which were cultured alone. MSC treatment attenuate expression of FASL, CD107 and TRAIL, receptors known to be responsible for NKT cell mediated apoptosis and cytotoxicity. Accordingly, MSC treatment significantly reduced cytotoxic potential of liver NKT cells. The results obtained by xCELLigence system for monitoring real-time cytotoxicity showed that NKT cells isolated from MSCs+α-GalCer-treated mice were significantly less cytotoxic against HEPG2 hepatocyte cells then NKT cells isolated from mice treated with α-GalCer-only. Human MSC managed to significantly attenuate production of inflammatory cytokines in α-GalCer-stimulated peripheral blood mononuclear cells and attenuate their cytotoxicity against HEPG2 cells. In conclusion, MSC protect from acute liver injury by attenuating cytotoxicity and capacity of liver NKT cells to produce inflammatory cytokines.

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