

The Protective Role of Decoy Receptor 3 Analogue on Rat Steatotic Liver against Ischemia-Reperfusion Injury by Blocking M1/Th1 Polarization and Multiple Upstream Pathogenic Cascades

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Abstract : TNF superfamily-stimulated pathogenic cascades and macrophage (M1)/kupffer cells (KC) polarization are important in the pathogenesis of ischemia-reperfusion (IR) liver injury in animals with hepatic steatosis (HS). Decoy receptor 3 (DcR3) is a common upstream inhibitor of the above-mentioned pathogenic cascades. The study evaluated whether modulation of these DcR3-related cascades was able to protect steatotic liver from IR injury. Serum and hepatic DcR3 levels were lower in patients and animals with HS. Accordingly, the effects of pharmacologic and genetic DcR3 replacement on the IR-related pathogenic changes were measured. Significantly, DcR3 replacement protected IR-Zucker(HS) rats and IR-DcR3-Tg(HS) mice from IR liver injury. The beneficial effects of DcR3 replacement were accompanied by decreased serum/hepatic TNF, soluble TNF-like cytokine 1A (TL1A), Fas ligand (Fas-L) and LIGHT, T-helper-cell-1 cytokine (INF) levels, neutrophil infiltration, M1 polarization, neutrophil-macrophage/KC-T-cell interaction, hepatocyte apoptosis and improved hepatic microcirculatory failure among animals with IR-injured steatotic livers. Additionally, TL1A, Fas-L, LIGHT and TLR4/NFB signals were found to mediate the DcR3-related protective effects of steatotic livers from IR injury. Using multimodal in vivo and in vitro approaches, we found that DcR3 was a potential agent to protect steatotic livers from IR injury by simultaneous blocking the multiple IR injury-related pathogenic changes.

Keywords : Decoy 3 receptor, ischemia-reperfusion injury, M1 polarization, TNF superfamily

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