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Mechanisms of Concanavalin A-induced mediators of hepatocyte damage in hepatic stellate cells: A dual role of interferon regulatory factor-1

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Concanavalin A (ConA)-induced liver injury in mice has been used extensively as a model to understand the role of immune cells. However, perisinusoidal hepatic stellate cells (HSCs), the primary cell type of liver fibrosis, were recently found to orchestrate ConA-induced liver damage directly and by influencing recruitment and characteristics of immune cells. HSC-released interferon- β (IFN β) and increased hepatic expression of a transcription factor, interferon regulatory factor 1 (IRF1), were determined to be major components of ConA-induced liver injury. The aim of this study was to delineate the mechanisms of the actions of ConA on HSCs with specific focus on IRF1/IFN β axis. HSCs and hepatocytes isolated from WT and IRF1^{-/-} mice were used. HSCs were found to rapidly internalize FITC-labeled ConA; internalized ConA was greatly concentrated in the perinuclear region. ConA increased the expression and nuclear translocation of IRF1 and NF- κ B in wild type (WT) HSCs and the expression of TNF α , IFN β and CXCL1. These effects of ConA were abrogated in HSCs isolated from IRF1^{-/-} mice. ConA induced JAK/STAT signaling in HSCs, and inhibitors of this signaling pathway ameliorated ConA-induced IRF1 expression/nuclear translocation as well as cytokine/chemokine production. Finally, ConA-stimulated WT but not IRF1^{-/-} HSCs induced apoptosis of WT hepatocytes. Conversely, ConA-stimulated WT HSCs were unable to induce apoptosis of IRF1^{-/-} hepatocytes. Our findings suggest that IRF1 plays a dual role in ConA-induced liver injury. On the one hand, ConA stimulates the synthesis of the mediators of hepatocyte injury through JAK/STAT signaling involving IRF1. On the other hand, IRF1 nuclear translocation in hepatocytes induced by ConA-stimulated HSCs instigates apoptosis. While this mechanistic evaluation is performed using ConA, the findings could be relevant to liver injury due to lectins in the food products. In conclusion, HSC can be a potential therapeutic target for acute liver damage of various etiologies including lectins.

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