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Inhibition of hepatocyte H-2Kb by triptolide leads to natural-killer-cell-mediated cytotoxicity against self-hepatocytes under LPS stimulation

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Abstract

Background and Purpose: Triptolide (TP) is the major active and toxic component of Tripterygium wilfordii Hook. F. Previous studies reported that a toxic pretreatment dose of triptolide leads to hepatic intolerance to exogenous lipopolysaccharide stimulation in mice and liver failure rather than damaging the liver directly. However, the immune mechanisms involved have not been elucidated. Experimental Approach: Flow cytometry analysis, LDH release measurement, blood biochemical analysis, ELISA, qPCR, magnetic beads sorting, plasmid transfection and AAV-DNA transduction were performed to investigate the immune mechanism in TP- and LPS-induced fulminant hepatitis. Key Results: The results show that IFN-γ-mediated necroptosis occurred in C57BL/6N mice treated with 500 μg/kg TP and 0.1 mg/kg LPS to induce fulminant hepatitis. Intracellular IFN-γ levels of natural killer cells increased significantly in mice administered TP and LPS, indicating primary source of IFN-γ in innate lymphocytes in the liver. Flow-cytometry analysis and in vivo depletion of NK cells showed that NK cells in the liver were activated and exhibited potent cytotoxicity. In vivo and in vitro TP administration significantly inhibited hepatocyte major histocompatibility complex class I molecules, H-2Kb, in mice. Further in vitro analysis confirmed that TP-pretreated hepatocytes were susceptible to NK-cell-mediated cytotoxicity, and the induction of hepatocyte H-2Kb significantly decreased NK-cell-mediated cytotoxicity. In vivo induction or of overexpression of hepatocyte H-2Kb also protected against TP- and LPS-induced liver injury. Conclusion and Implications: In conclusion, inhibiting hepatocyte H-2Kb accounted for TP-induced hepatic intolerance to exogenous LPS stimulation and was directly related to NK-cell-mediated cytotoxicity against self-hepatocytes.

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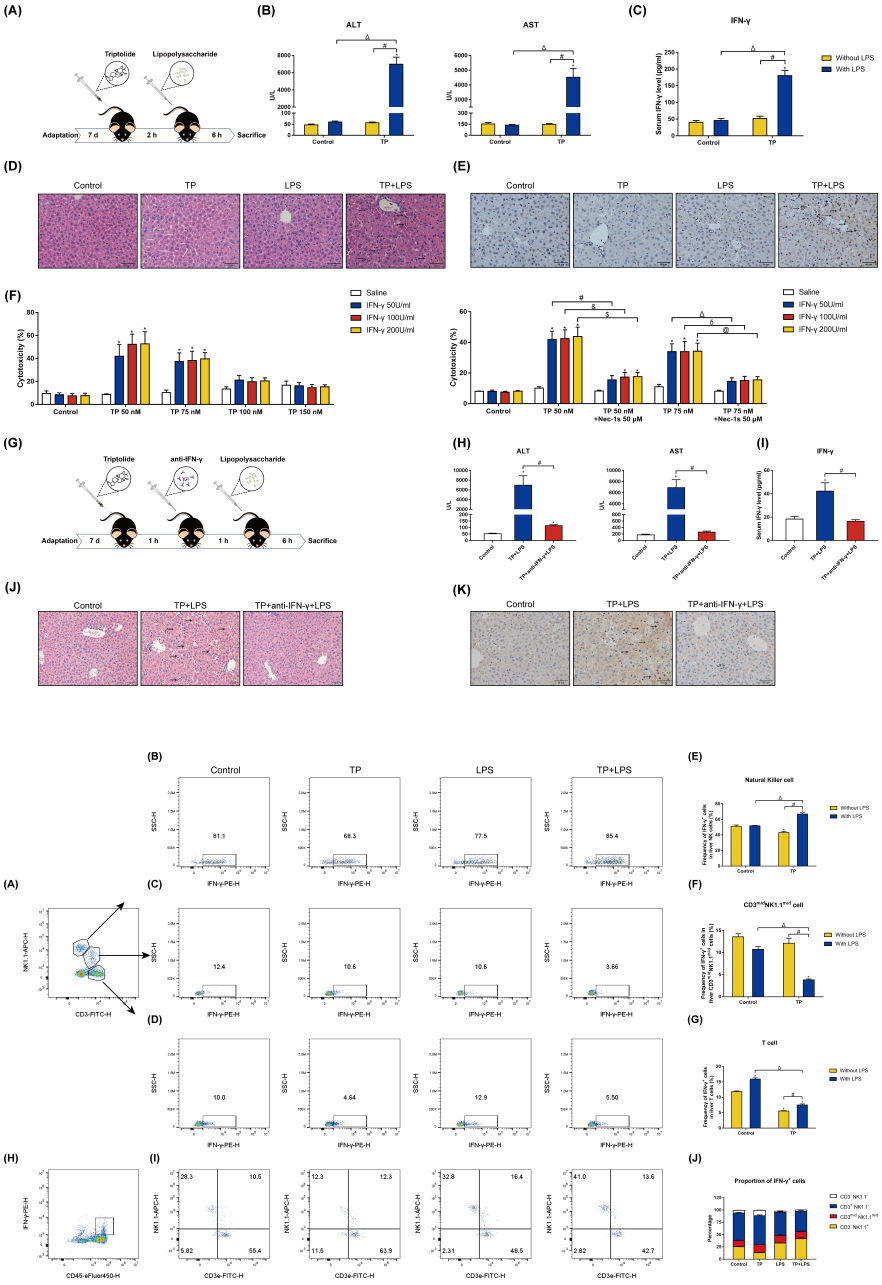

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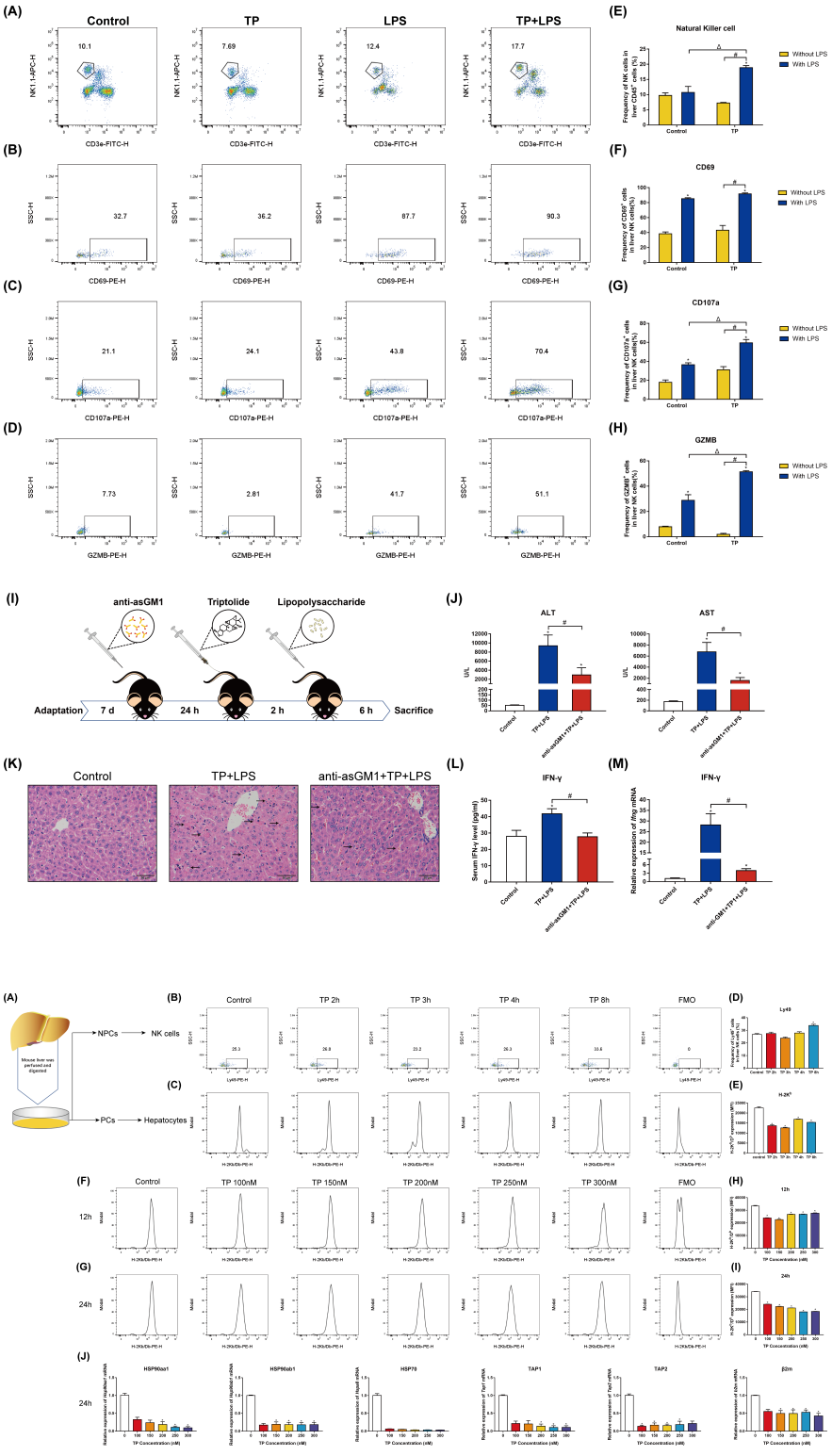

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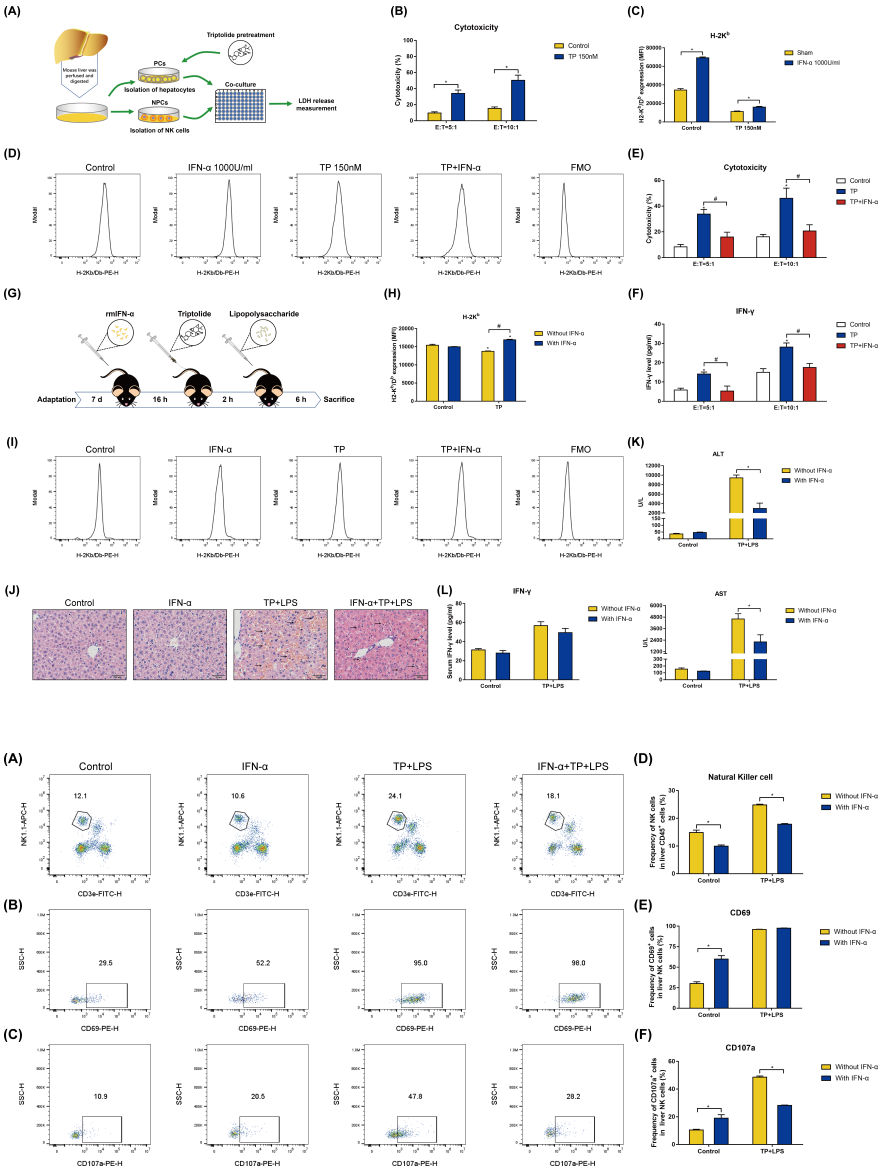

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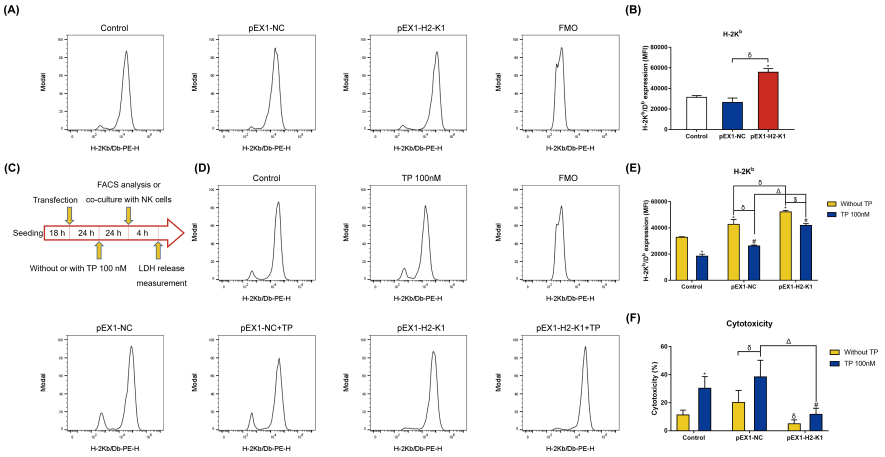

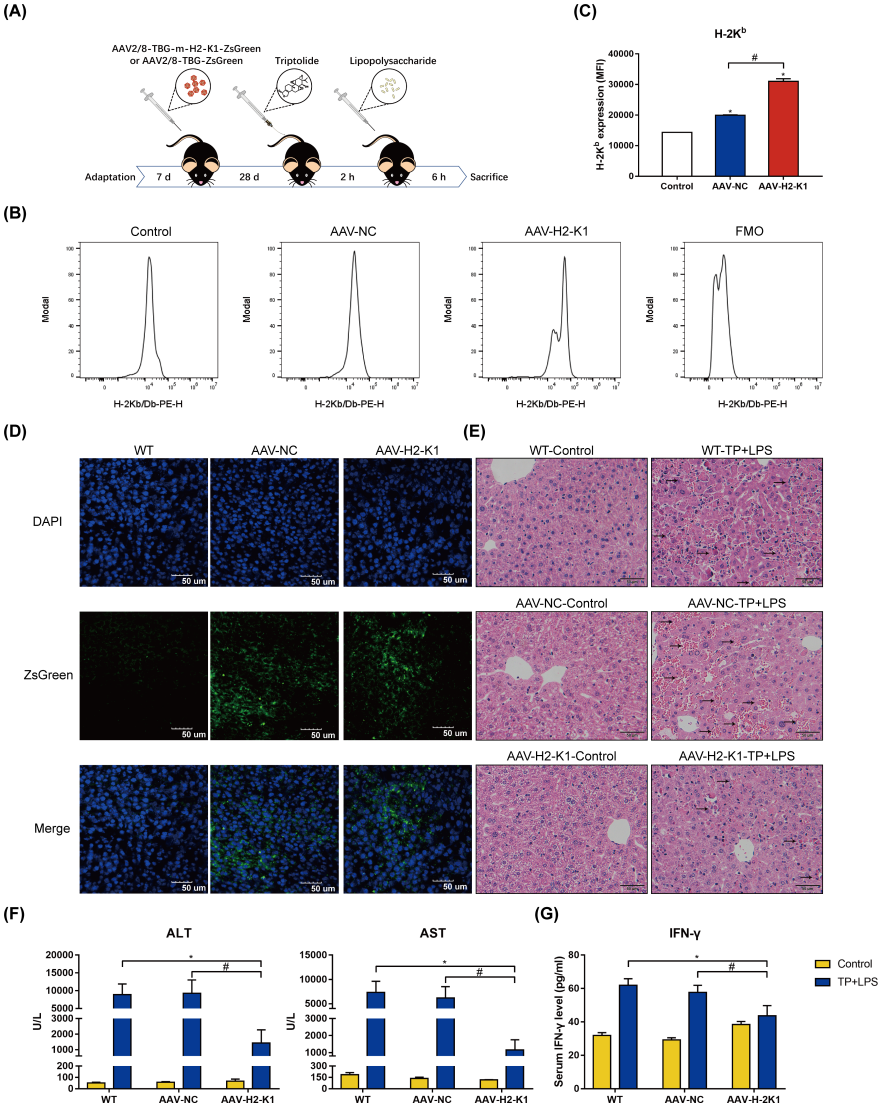

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