Immunoglobulin G binding as a quantitative marker of hepatocellular death across acute and chronic liver injury

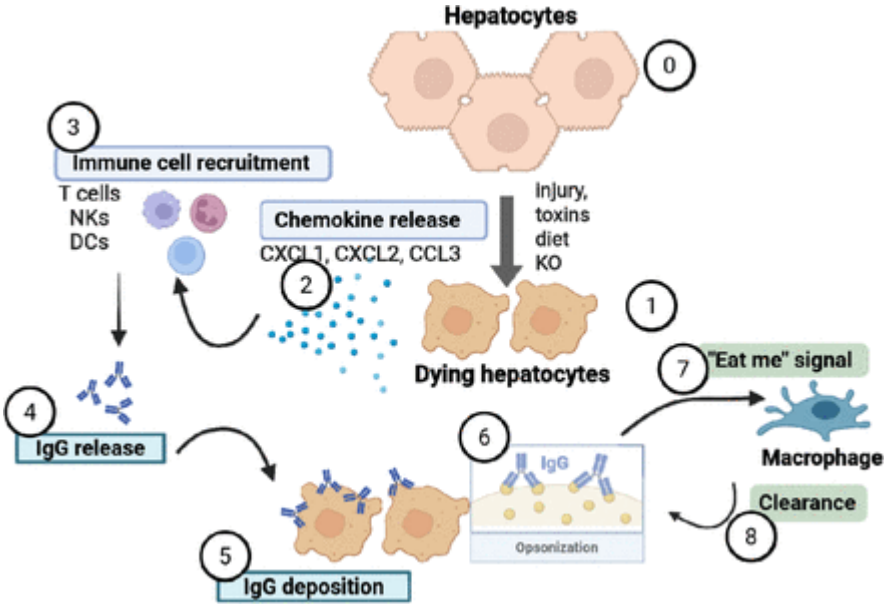
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Abstract

Background & Aims: Accurate detection of hepatocellular death is fundamental for understanding liver injury, intoxication, regeneration, and fibrosis. Conventional markers, such as serum transaminases and histopathological scoring, suffer from limited temporal resolution, high variability, and observer dependence. We evaluated immunoglobulin G (IgG) binding as a quantitative and spatially resolved marker of hepatocyte death in acute and chronic liver injury models.

Methods: Male C57BL/6 mice were subjected to acute carbon tetrachloride (CCl_4) intoxication (1600 mg/kg, single dose), dose-escalation (0-800 mg/kg), and chronic injury paradigms including Western diet (WD), WD+CCl_4, and Mdr2-/- mice with or without a single CCl_4 challenge. The serum ALT and AST levels were measured. Liver sections were stained with IgG, Hematoxylin and Eosin (H&E), bromodeoxyuridine (BrdU), glutamine synthetase (GS), CD26, and alpha-smooth muscle actin (Acta2). Spatial and integrative transcriptomic analyses were performed to characterize the IgG^+ hepatocyte dead regions.

Results: Hepatocellular IgG labeling emerged as early as 6h post-CCl_4, peaked at 72–96h, and declined during regeneration. IgG-positive areas correlated strongly with Ishak necroinflammatory score (r=0.70) and serum transaminase levels (p=0.74-0.85), surpassing both in Receiver Operating Characteristic (ROC) analyses (AUC=0.92-0.95). IgG bound to both apoptotic ($TUNEL^+$) and necrotic ($TUNEL^-$) hepatocytes. In chronic liver injury models, IgG deposition was localized to the injury zones and correlated with ALT/AST, irrespective of etiology. Multiplex imaging revealed IgG-positive necrotic cores surrounded by proliferating hepatocytes and Acta2+ myofibroblasts. Spatial transcriptomics identified immune cell enrichment, FcγR-mediated signaling, phagocytosis, and vascular remodeling within the IgG-marked regions.

Conclusions: IgG immunostaining provides a robust, quantitative, and pathologist-independent readout of hepatocellular death, which scales with injury severity, delineates necrotic zones, and reveals immune-active microenvironments. These findings establish IgG-based detection as a versatile, high-resolution tool for assessing liver injury, regeneration, and fibrosis.