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GSDMD-NT's pan-membrane blitz on the liver

Rui Min[1,2,4] **and Xing Liu**[1,3,4,*]

[1]State Key Laboratory of Immune Response and Immunotherapy, Shanghai Institute of Immunity and Infection, Shanghai Institute of Materia Medica, CAS, Shanghai 200031, China

[2]University of Chinese Academy of Sciences, Beijing 100049, China

[3]Shanghai Academy of Natural Sciences (SANS), Shanghai 200031, China

[4]These authors contributed equally

*Correspondence: xingliu@ips.ac.cn

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Huang et al. (2025) demonstrate that systemic delivery of lipid nanoparticle (LNP)-encapsulated mRNA encoding the N-terminal pore-forming domain of GSDMD triggers severe pyroptosis in the liver, leading to acute hepatic failure, systemic inflammation, and rapid mortality in mice and non-human primates.[1] Their work reveals a "pan-membrane" pyroptosis phenotype, characterized by non-selective damage to intracellular organelles, significantly expanding our understanding of GSDMD-mediated cell death in vivo.

Pyroptosis is a lytic form of programmed cell death primarily executed by

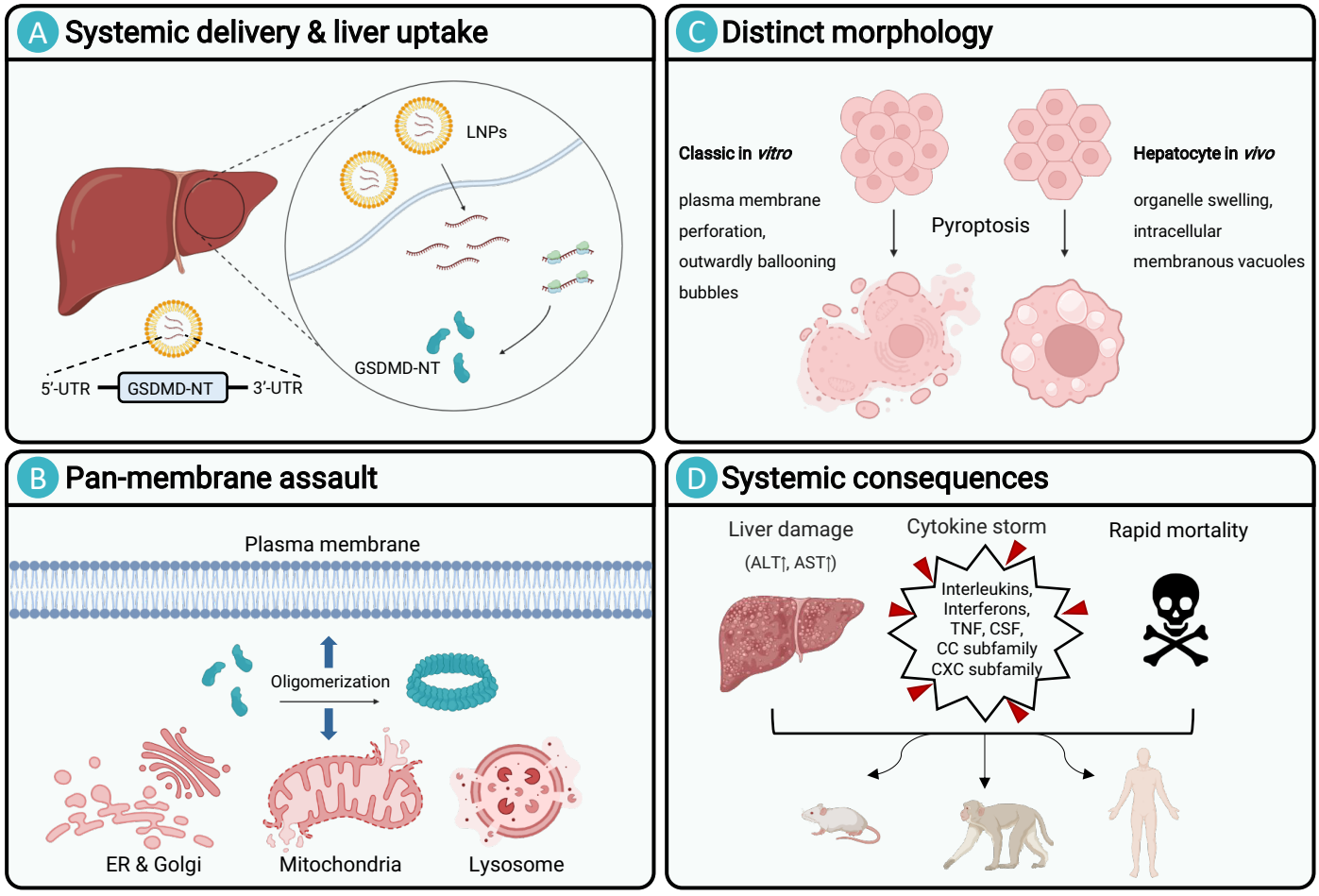

Figure 1. LNP-delivered GSDMD-NT mRNA triggers pan-membrane pyroptosis in vivo Upon systemic administration, LNPs encapsulating mRNA encoding the pore-forming GSDMD-NT are taken up by hepatocytes. Oligomerized GSDMD-NT integrates into multiple intracellular membranes—including the plasma membrane, mitochondria, lysosomes, endoplasmic reticulum, and Golgi apparatus. While pyroptotic cells in vitro typically display outward ballooning bubbles, hepatocytes in vivo exhibit inward membrane invaginations and intracellular vacuolation. This widespread hepatocyte pyroptosis results in acute liver failure, accompanied by a surge of pro-inflammatory cytokines and chemokines in the circulation. These systemic effects trigger multi-organ inflammation, rapid clinical decline, and mortality in both mouse and non-human primate models. These findings suggest similar risks may extend to humans, underscoring the potential hazards of systemic GSDM activation for therapeutic applications such as cancer treatment.

gasdermin (GSDM) proteins, with GSDMD being the well-characterized executioner in inflammatory responses.[2] Upon cleavage by inflammatory caspases, the liberated N-terminal fragment of GSDMD (GSDMD-NT) oligomerizes to form pores in the plasma membrane, disrupting osmotic balance and leading to cell swelling, membrane rupture and the release of pro-inflammatory cytokines.[3] Beyond the plasma membrane, emerging evidence suggests GSDMD-NT can target intracellular organelles, though the physiological relevance of this activity has been unclear.[4] Given its potent lytic function, GSDMD activation is being explored as a strategy for cancer therapy. Inducing pyroptosis in tumor cells can directly kill them and trigger robust anti-tumor immunity by releasing inflammatory signals and tumor-related antigens, potentially transforming immunologically "cold" tumors into "hot", therapy-susceptible ones.[5] Several approaches, including small-molecule agonists, nanoparticle-delivered proteins, and circRNA encoding GSDMs, are being explored to activate pyroptosis in tumors.[5] However, the systemic safety of such powerful pyroptosis-inducing approaches, particularly the risk of off-

target toxicity in vital organs like the liver, remain largely undefined and constitute a major translational concern.

In this study, Huang et al. leveraged LNP-encapsulated mRNA technology to express active human GSDMD-NT in vivo.[1] They aimed to characterize the consequences of systemic GSDMD activation, particularly in the liver—the primary organ for LNP accumulation. The authors first validated that in vitro transfection of GSDMD-NT mRNA triggered robust pyroptosis. Upon intravenous administration in mice, GSDMD-NT mRNA-LNP caused dose-dependent mortality, with animals succumbing within 12–24 hours. Serum biomarkers indicated rapid liver dysfunction, marked by elevated ALT and AST levels. Histopathological analysis revealed extensive hepatocellular death, loss of tissue architecture, and the appearance of cytoplasmic vacuoles. A broad array of pro-inflammatory cytokines and chemokines (e.g., IL-1α, IL-6, TNF-α, CCL2, CXCL10) were significantly upregulated in serum. Many of these elevated cytokines have known roles in promoting liver damage. Thus, heterologous GSDMD-NT expression in the liver induced sudden cell death and a potent systemic inflammatory response, accompanied by acute liver damage.

Using intravital microscopy in mice with fluorescence labeling of cell membrane the authors captured the real-time dynamics of hepatocyte membranes following GSDMD-NT expression. Contrary to the classic cellular swelling and ballooning morphology observed in cultured cells undergoing pyroptosis, hepatocytes in vivo displayed intracellular vacuole formation, rapid karyopyknosis, and infiltration of blood components. This distinct morphology is likely due to the liver's compact tissue architecture and strong intercellular connections. These results highlight how tissue context fundamentally shapes pyroptotic morphology.

A central finding of this work is the "pan-membrane" targeting capability of GSDMD-NT. Through immunofluorescence and transmission electron microscopy, the authors demonstrated that GSDMD-NT localized to and damaged not only the plasma membrane but also mitochondria, lysosomes, the endoplasmic reticulum (ER), Golgi apparatus, and the nuclear envelope. Mitochondria exhibited swelling and indistinct cristae; lysosomes showed swelling, membrane permeabilization, and leakage; the ER and nuclear envelope formed vacuolar structures. These organellar disruptions likely contribute to the observed cytoplasmic vacuolation and appear to precede plasma membrane rupture, suggesting that organelle damage may drive early cell death events.

The pathological changes induced by GSDMD-NT expression were replicated in cynomolgus macaques, where intravenous administration caused dose-dependent liver injury, elevated serum cytokines, and even mortality at higher dosages. Histological staining of liver sections showed vacuolated hepatocytes and organelle damage consistent with the observation in mice. Importantly, the GSDMD inhibitor disulfiram, as well as anti-inflammatory glucocorticoids (triamcinolone and hydrocortisone), attenuated liver damage, reduced cytokine levels, and improved survival in mice injected GSDMD-NT mRNA-LNP. This confirms the specificity and therapeutic malleability of the phenotype. The observed cytokine profile, which includes multiple factors known to promote liver injury, demonstrates that heterologous GSDMD-NT expression in the liver leads to sudden death via acute hepatic damage and systemic inflammation.

The authors extended their platform to other GSDM family members with pore forming ability (GSDMA, GSDMB, GSDMC, GSDME). While the N-terminal fragments of all these proteins induced pyroptosis in vitro, only GSDMB caused significant liver toxicity and mortality in vivo, comparable to GSDMD. GSDMA-NT, GSDMC-NT, and GSDME-NT did not elicit overt liver damage or clinical decline. This highlights member-specific differences in membranolytic selectivity or organ tropism. Together, these data reveal a significant functional heterogeneity among GSDM proteins in their capacity to induce pyroptosis and associated pathology in vivo.

This study provides a comprehensive in vivo portrait of GSDMD-induced pyroptosis in a solid organ, revealing its capacity to cause rapid, catastrophic liver failure through widespread membrane disruption (Figure 1). The concept of "pan-membrane pyroptosis" extends the traditional view of GSDMD as a plasma membrane pore-former and underscores its potential to dismantle cellular integrity by attacking multiple organelles. These findings carry significant implications for emerging GSDM-based therapies, particularly in oncology, where systemic activation or off-target delivery could provoke severe hepatotoxicity. While the differential toxicity profiles among GSDM members may inform the selection of safer candidates for immune activation strategies, several key questions remain unresolved: What determines GSDMD's promiscuity for different membranes? How do tissue-specific factors modulate pyroptotic outcomes? Can organelle-selective GSDMD engagement be harnessed to tune immune responses without causing lethal damage? Future work should also explore delivery strategies that confine GSDM activation to target tissues, and further dissect the long-term consequences of sublethal, "hyperactive" GSDMD signaling on organ homeostasis. As GSDM-targeted agents advance toward clinical translation, this study serves as a critical reminder of the balance between therapeutic potency and systemic safety.

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AUTHOR CONTRIBUTIONS

R.M. and X.L. conceived and drafted the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.