



Extracellular Vesicles as Messengers Between Hepatocytes and Macrophages in Nonalcoholic Steatohepatitis

See “Lipid-induced signaling causes release of inflammatory extracellular vesicles from hepatocytes,” by Hirsova P, Ibrahim SH, Krishnan A, et al on page 956.

Nonalcoholic steatohepatitis (NASH) has become the most common liver disease in Europe, the United States, and major regions of Asia. The continuous increase of the underlying metabolic risk factors, including abdominal adiposity, insulin resistance/diabetes, and hyperlipidemia has put large populations at risk to develop advanced liver disease characterized by fibrosis or even cirrhosis.¹ Although chronic viral hepatitis was the leading cause of hepatocellular carcinoma for a long time, currently NASH is becoming an increasingly important cause of end-stage liver disease.² In the clinical context, this has led to a strong increase in the number of patients that were listed for liver transplantation owing to NASH in US centers.³ Despite this alarming increase, the available diagnostic and therapeutic options are limited. Current guidelines in several countries, including the US and Germany, point out that the mainstays of therapy are lifestyle interventions leading to weight loss and increased muscle mass, which are difficult to implement in the large target population.⁴ Thus, translational research and improved therapies are urgently required, and research consortia have been formed in the United States, namely, the NASH clinical research network and in Europe, namely, the consortium for Elucidating Pathways of Steatohepatitis to address this shortcoming.

The pathophysiology of NASH involves 2 cardinal features: hepatocellular injury from lipotoxicity and associated inflammation.⁵ However, it remains unclear how mere lipid overload may promote or even cause hepatocellular injury and inflammation. The 2 (or more)-hit model has been proposed implicating the involvement of ≥ 2 critical events in the development of NASH.⁵ Especially, increased oxidative stress, endotoxemia, or cytokines have been incriminated in the progression from nonalcoholic fatty liver to NASH.⁵

In this issue of *Gastroenterology*, Hirsova et al⁶ present an intriguing view that hepatocellular events may lead to macrophage activation and inflammation via the release of extracellular vesicles (EVs) as a consequence of lipid-associated toxicity. EVs serve as shuttles for membrane and cytosolic components between cells and can either bud from the plasma membrane (microvesicles) or be formed intracellularly as multivesicular endosome that are secreted (exosomes).⁷ These EVs may also qualify as novel serum biomarkers, as shown for immune cell-specific EVs (microparticles) that have been shown to correlate with

histologic liver inflammation in NASH.⁸ Previous reports by the group of the paper discussed here showed that lipid overload can cause hepatocellular injury⁹ and macrophage activation.¹⁰ Now the authors present intriguing data that the 2 cell types may communicate through EVs (Figure 1). Interestingly, both are sensitive to activation of death receptor (DR)5, a cognate receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) that exerts strong proapoptotic activity against a large array of cancer cells while largely sparing normal cells. However, the mode of DR5 activation seems to be different between the 2 events—hepatocellular injury and macrophage activation (ligand-independent in the former vs ligand-dependent in the latter).

Ligand-independent hepatocellular apoptosis is inferred from the findings of caspase cascade activation owing to induction and clustering of DR5 upon palmitic acid treatment that is not inhibited by DR5-Fc fusion protein.⁹ DR5 activation by palmitate seems to be caused by CHOP induction from endoplasmic reticulum stress (Figure 1).⁹ On the other hand, ligand-dependent activation of macrophages implies that TRAIL is present in the EVs released from hepatocytes after treatment with lipids and acts on DR5 on macrophages. TRAIL on EVs released from hepatocytes treated with palmitate did not induce apoptosis in macrophages but instead caused an inflammatory response in a RIP1 and nuclear factor- κ B-dependent manner. This non-canonical TRAIL signaling may account for much of the inflammatory component of NASH (Figure 1). In this line, in comparison with transformed cells, normal cells such as macrophages are usually resistant to the canonical apoptotic action of TRAIL, which is attributable to decoy receptors or intracellular inhibitors, such as cFLIP or XIAP, acting alone or in combination.¹¹

TRAIL-containing EVs released after lipid treatment of hepatocytes seem to be microvesicles rather than exosomes since silencing of Rab27b that mediates multivesicular body docking to the plasma membrane¹² did not affect EV release after treatment with lipids. Release of microvesicles from hepatocytes treated with lipids appears to be owing to caspase 3-mediated activation of Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) inducing plasma membrane blebbing, because short hairpin RNA knockdown of ROCK1 led to reduction of EV release in response to lipid treatment. Furthermore, fasudil, a ROCK1 and ROCK2 inhibitor, attenuated the inflammatory changes associated with NASH.

Thus, the authors suggest a novel mechanism in the development of NASH that links hepatocyte liver injury to macrophage activation and liver inflammation, representing a modified 2-hit model or a “2-cell model.” Based on their results, they suggest EV as a potential therapeutic target in

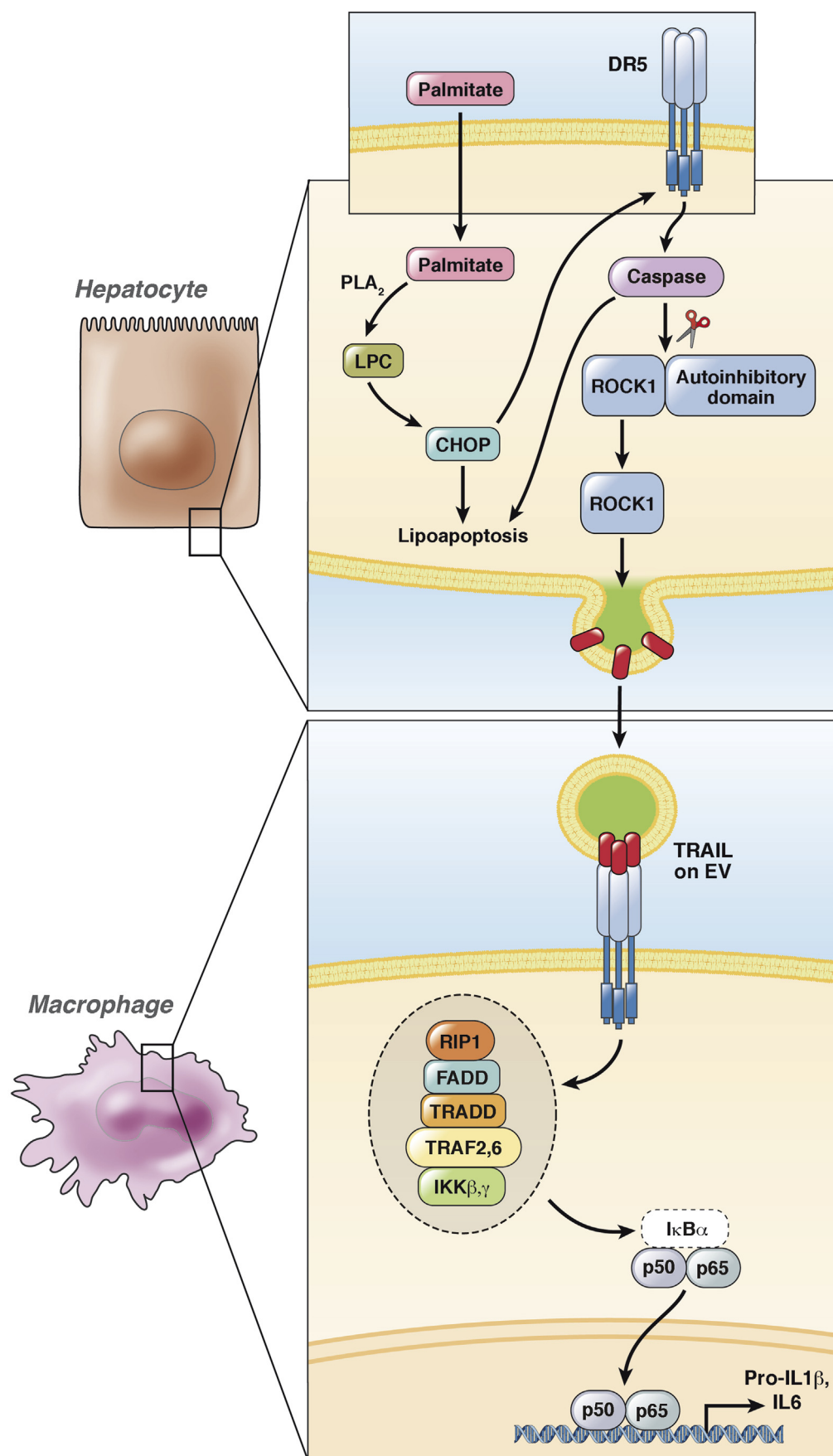


Figure 1. The 2-cell model of NASH development. After palmitic acid incorporation into phosphatidylcholine (PC), CHOP is activated by lysophosphatidylcholine (LPC) produced by phospholipase A₂ (PLA₂) from PC. CHOP can induce DR5 and subsequent caspase activation in a ligand-independent manner. Active caspase removes the autoinhibitory domain from ROCK1, and truncated ROCK1 promotes blebbing of the plasma membrane of hepatocytes (green). TRAIL (red) on blebs activates DR5 on macrophages, and non-apoptotic receptor complex II (in a dotted circle) is formed. IKK induces degradation of I κ B α and releases p50-p65 complex, which induces pro-interleukin (IL)-1 β and IL-6 expression.

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