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EDITORIAL

A Role for Extracellular Vesicles in Liver Fibrosis

Extracellular vesicles comprise exosomes, microvesicles, and apoptotic bodies. Each consists of a lipid bilayer that encases a variety of contents. Exosomes are the smallest of the group (40–120 nM) and arise from the endolysosomal pathway. Microvesicles are middle sized (50–1000 nM) and occur as a result of outward budding of the cell surface. Both contain various RNA species and proteins. Apoptotic bodies are larger (500–2000 nM), form from budding of the apoptotic cell membrane, and contain nuclear fragments and cellular organelles.[1]

Originally described in the early 1980s, extracellular vesicles were initially thought to be a way for cells to expel membrane debris.[2,3] Over the last few years, research on extracellular vesicles reveals them to be complex vehicles for signaling in a wide variety of systems and cell types. With their heterogeneous contents, extracellular vesicles seem to be an important mechanism for intercellular communication. Clear roles have been established in such diverse processes as tumorigenesis, stem cell maintenance, immune function, and neurotransmission.[1,4–6] To represent this diverse palette of functions, they have been termed "signalosomes."[1]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology,* Povero and colleagues[7] bring this powerful new understanding of extracellular vesicles to investigate the question of stellate cell activation. Although stellate cell activation has long been known to be a critical event in the development of fibrosis, the initiating event in this process is less well understood.

Building on their previous report[8] demonstrating that hepatocytes increase the release of extracellular vesicles in response to lipotoxic fatty acids, the authors expand these studies to show that these extracellular vesicles are internalized by stellate cells, leading to their activation. In a series of convincing experiments, they demonstrate the effect is dependent on Vanin 1, a cell-surface protein thought to be critical for internalization of extracellular vesicles. Mechanistic studies further elucidate the effect as a result of the shuttling of peroxisome proliferator-activated receptor-γ (PPAR-γ) targeting microRNAs, specifically miR-128-3p, a critical modulator of stellate cell activation.

This work is important for a number of reasons. First, it establishes extracellular vesicles as a potential modulator of fibrosis in an increasingly common and devastating human problem, nonalcoholic fatty liver disease. Further in vivo studies will be required to verify these findings in both animals and humans. Next, it establishes a direct signaling link from injured or stressed hepatocytes to stellate cells. If confirmed, this would help elucidate the as yet poorly understood issue of the initial events in stellate cell activation.

Further, and perhaps most importantly, these studies suggest targeting extracellular vesicles might have therapeutic potential. As understanding of extracellular vesicle biology improves, methods to inhibit their generation, modify their contents, or decrease their release or uptake may find a role into the clinic.

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Conflicts of interest
The author discloses no conflicts.

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