Liver fibrosis, non-parenchymal cells and the promise of exosome therapy

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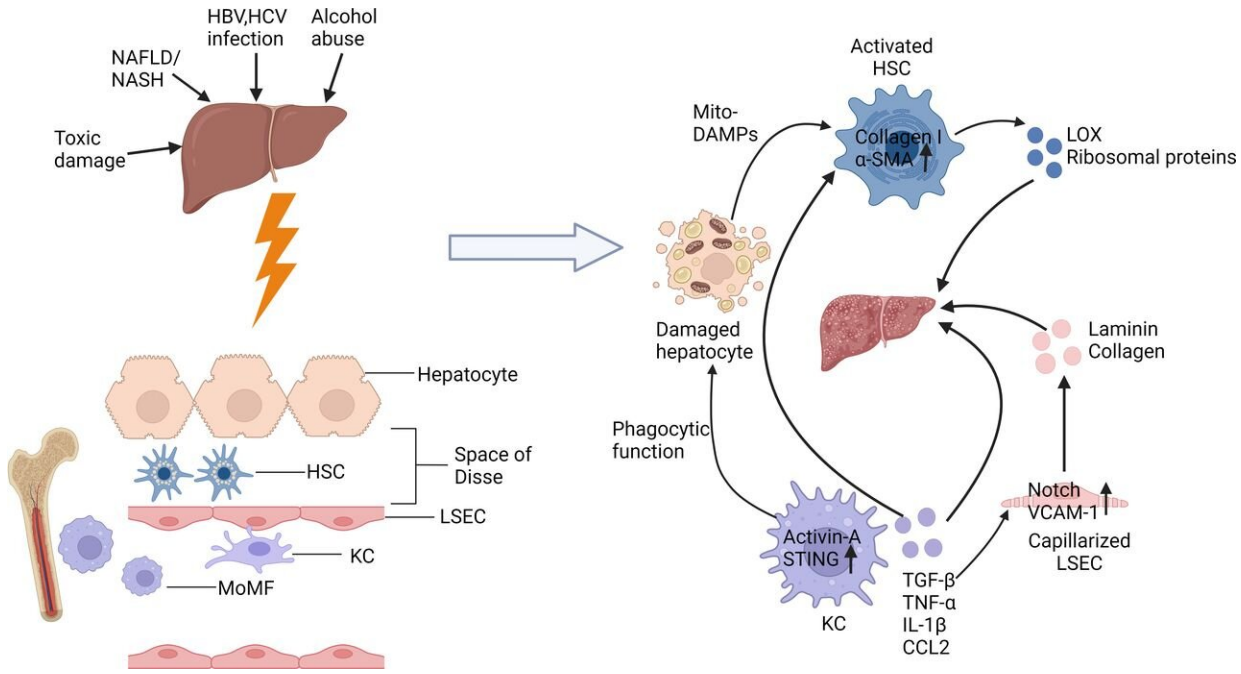


In response to chronic stimuli such as alcohol abuse, viral infection, NAFLD/NASH and toxic damage, liver loses its normal structure and non-parenchymal cells including HSCs, KCs and LSECs undergo phenotypic changes. HSCs and KCs are in activation and LSECs become capillarised with loss of fenestrae and markers followed by release of fibrogenic stimuli such as TGF-β, LOX and so on, which play important roles in the development of liver fibrosis. CCL2, C-C motif chemokine ligand 2; HBV, hepatitis B virus; HCV, hepatitis C virus; HSC, hepatic stellate cell; IL, interleukin; KC, Kupffer cell; LOX, lysyl oxidase; LSEC, liver sinusoidal endothelial cell; Mito-DAMP, mitochondrial damage-associated molecular pattern; MoMF, monocyte-derived macrophage; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic

steatohepatitis; SMA, smooth muscle actin; STING, stimulator of interferon gene; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1. Credit: Yingying Liu and Lin Wang

Liver disease is a major health concern, causing millions of deaths worldwide each year. One serious complication is liver fibrosis, scarring that can lead to liver failure. There is currently no effective treatment, but new research suggests promise for exosomes, tiny sacs released by cells.

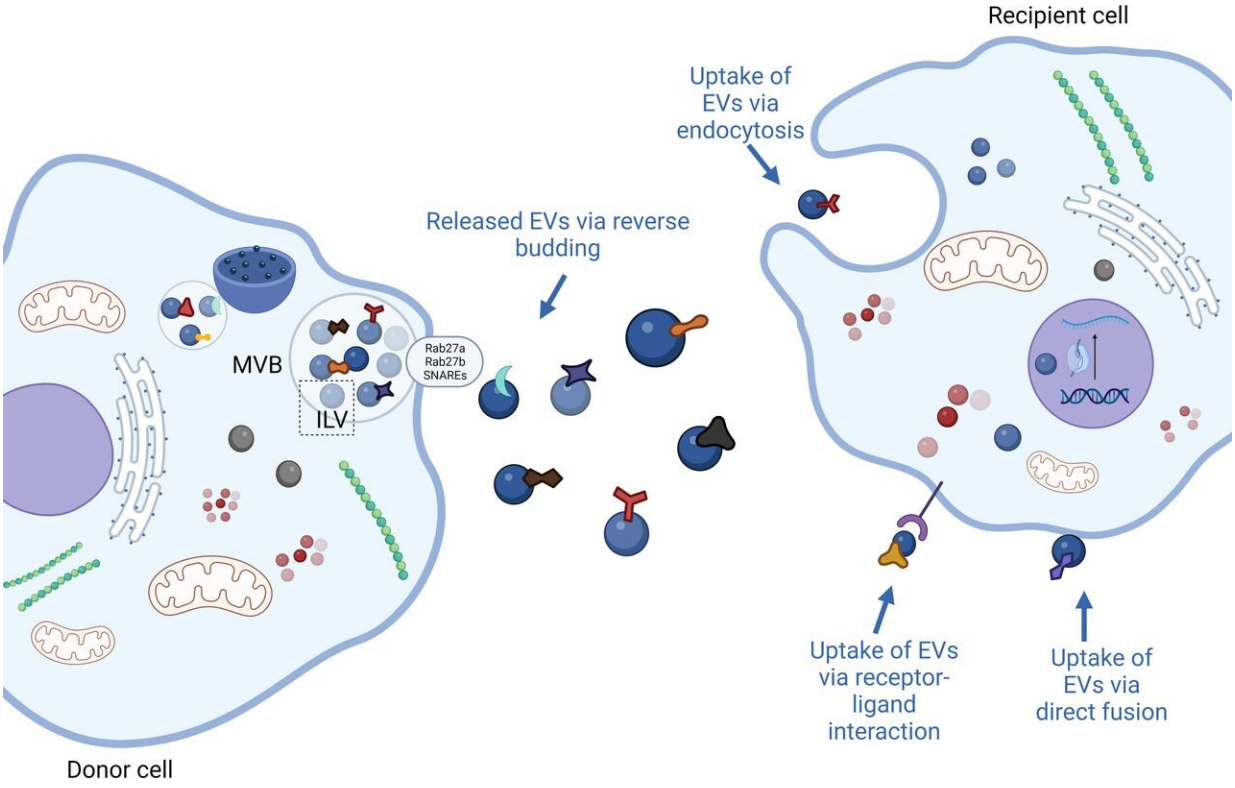
Non-parenchymal cells like hepatic stellate cells (HSCs), Kupffer cells (KCs), and liver sinusoidal endothelial cells (LSECs) play a key role in fibrosis development. These cells are involved in inflammation, scar formation, and tissue repair. Understanding their function is vital for new therapies.

Exosomes are emerging as potential treatments for liver fibrosis. Derived from various cell sources, they can be engineered to target specific non-parenchymal cells. This targeted approach offers several advantages.

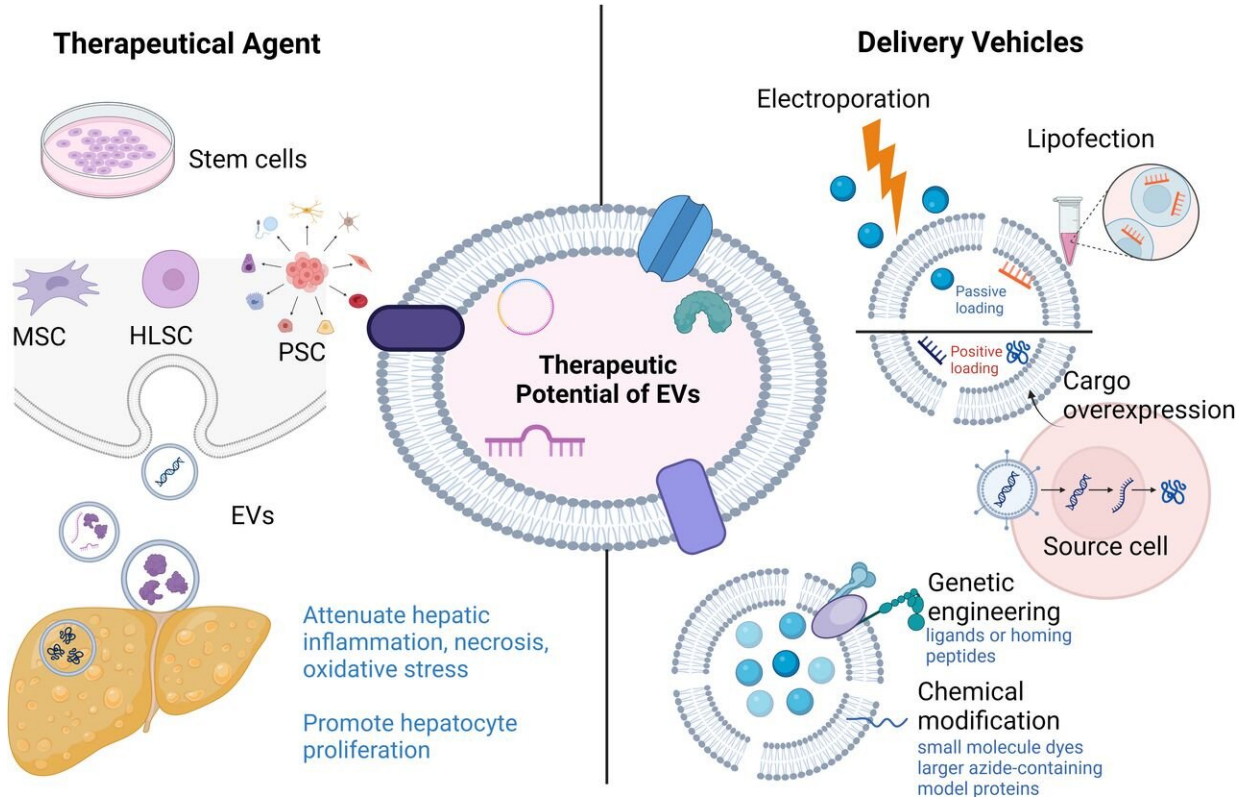
Exosomes can deliver drugs directly to cells involved in fibrosis, reducing side effects on healthy tissue. They can efficiently carry therapeutic cargo like drugs, RNA molecules, and signaling molecules. Additionally, exosomes can be modified to target specific cell types within the liver.

Current research explores exosomes in several ways. Exosomes from stem cells or engineered with antifibrotic molecules can inhibit HSC activation and collagen production. Exosomes can also modulate KCs, promoting their anti-inflammatory phenotype to break down scar tissue.

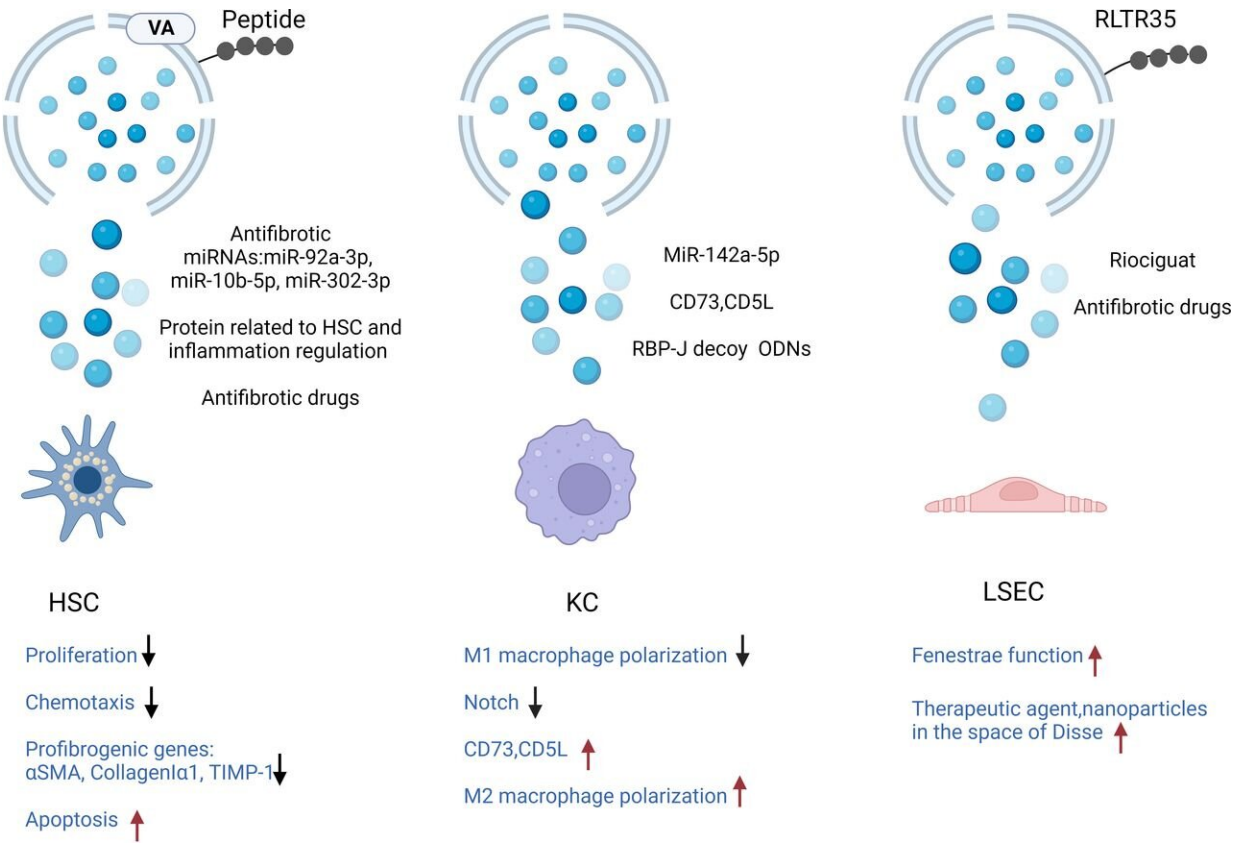
Moreover, exosomes may help repair LSEC fenestrae, pores essential for nutrient exchange and waste removal.



EVs are formed by inward budding or endocytosis of the plasma membrane (PM) into the cell. After that, EVs mature gradually and finally are released to extracellular space in the EV generation pathway. Then, EVs enter target cells and interact with them through various mediators such as surface receptors and signaling events in order to influence phenotypes of recipient cells. EVs, extracellular vesicles; ILV, intraluminal vesicle; MVB, multivesicular body; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor. Credit: Yingying Liu and Lin Wang



EVs can be used as therapeutical agent or delivery vehicles. As therapeutical agent, EVs are always from stem cells and they can attenuate hepatic inflammation, necrosis and oxidative stress and promote hepatocyte proliferation. As delivery vehicles, EVs loading drugs with genetic or chemical modification target liver to improve fibrosis. EVs, extracellular vesicles; HLSC, human liver stem cell; MSC, mesenchymal stem/stromal cell; PSC, pluripotent stem cell. Credit: Yingying Liu and Lin Wang



After treatments of EVs, proliferation, chemotaxis and profibrogenic signals of activated HSCs decrease while expression of antifibrotic miRNA and apoptosis increase. As for KCs, their polarization changes and expression of Notch declines while CD73 and CD5L raise. LSECs restore their fenestrae function and therapeutic agent or nanoparticles are allowed to access the space of Disse to play a role. HSC, hepatic stellate cell; KC, Kupffer cell; LSEC, liver sinusoidal endothelial cell; ODN, oligodeoxynucleotide; SMA, smooth muscle actin. Credit: Yingying Liu and Lin Wang

Exosome therapy offers a promising, innovative approach to treating liver fibrosis. While further research is needed to understand their potential fully, exosomes represent a significant step forward in this fight.

Standardized protocols for exosome production, storage, and clinical use are crucial. Exploring exosome applications and targeting strategies is essential to ensure their safety and efficacy as therapeutic agents or delivery vehicles for liver fibrosis treatment.

Overall, exosomes hold great promise as a novel therapy for liver fibrosis, offering opportunities for targeted treatment and improved patient outcomes. However, it is important to note that no exosome therapy for liver fibrosis has reached clinical trials yet. Continued research and development are essential to advance our understanding and use of exosomes in liver fibrosis therapy.

The work is published in the journal *eGastroenterology*.

More information: Yingying Liu et al, Extracellular vesicles targeting non-parenchymal cells: the therapeutical effect on liver fibrosis, *eGastroenterology* (2024). DOI: 10.1136/egastro-2023-100040

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