



Mini Review

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Extracellular Vesicles in Liver Fibrosis and Regeneration: From Mechanistic Promise to Translational Precision

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Abstract

Extracellular Vesicles (EVs) offer a potential means of modifying the hepatic injury microenvironment without administering viable cells. Selected preclinical studies of mesenchymal stromal cell-derived EVs report reduced fibrotic responses, protection against ischaemia-reperfusion injury, and enhanced hepatocyte proliferation. These outcomes, however, are not interchangeable with reversal of established cirrhosis or durable functional regeneration. This mini-review considers representative mechanistic evidence alongside manufacturing and analytical limitations, arguing that clinical translation requires indication-specific products, validated potency assays, and outcomes that distinguish cytoprotection from regeneration.

Keywords: Extracellular vesicles; liver fibrosis; hepatic regeneration; mesenchymal stromal cells; liquid biopsy

Introduction

In hepatology, the central question is not whether EVs are intrinsically regenerative, but which vesicle populations can modify a defined pathological process. Their biological activity depends on source cells, preparation, cargo, and recipient-cell context [1]. Consistent with MISEV2023, the term EV is preferable to “exosome” unless endosomal origin is demonstrated [1]. This focused narrative mini-review examines selected antifibrotic and hepatoprotective studies and considers the requirements for therapeutic development and circulating-EV analysis.

Antifibrotic Cargo: Mechanism Is Not Clinical Reversal

Qu et al. investigated EV preparations from adipose-derived mesenchymal stromal cells (MSCs) engineered to overexpress miR-181-5p. They reported suppression of stellate-cell activation and fibrosis-associated markers, with reduced STAT3 and Bcl-2 expression and autophagy activation involving the STAT3/Bcl-2/Beclin 1 pathway. In mice exposed to carbon tetrachloride, treatment attenuated liver injury and fibrotic responses [2].

Importantly, EVs were administered during fibrosis induction, rather than after established cirrhosis had developed [2]. The findings therefore support experimental antifibrotic activity, not demonstrated reversal of advanced human disease. The reported relationship between autophagy and fibrosis should likewise be interpreted within this specific cellular and experimental setting, rather than as a universal therapeutic principle.

Acute Cytoprotection and Regeneration Are Distinct Outcomes

In a rat hepatic ischaemia-reperfusion model, Yao et al. found that human umbilical cord MSC-EVs reduced neutrophil infiltration, oxidative stress, and hepatocyte apoptosis. Their experiments implicated EV-associated manganese superoxide dismutase in the protective response [3]. These findings provide a mechanistic basis for acute cytoprotection, but do not establish an antifibrotic effect in chronic liver disease.

Tan et al. reported reduced toxicant-induced liver injury and increased hepatocyte proliferation following MSC-derived EV treatment, including increased proliferating cell nuclear antigen expression. In contrast to the antioxidant mechanism above, protection in their models was not attributed to oxidative-stress modulation [4]. Together, these studies caution against assigning a single mechanism to all MSC-EVs. Reduced injury, hepatocyte proliferation, fibrosis regression, and sustained restoration of liver function should remain separate endpoints when interpreting regenerative claims.

Translation Requires Defined Products and Reliable Measurements

Therapeutic development requires more than demonstrating activity in an EV-enriched preparation. Donor and cell-source selection, manufacturing consistency, storage stability, dose, administration route, and safety assessment must be specified. Product identity and purity should be complemented by functional potency testing linked to the proposed mechanism of action [5]. For hepatic applications, we propose that such testing distinguish suppression of stellate-cell fibrogenic activity from support of hepatocyte survival or recovery. Particle abundance alone cannot establish either function.

Circulating EV analysis presents a parallel challenge. Plasma and serum contain abundant lipoproteins and other non-vesicular components that can co-isolate with EVs [1]. Size-exclusion

chromatography can reduce protein contamination and enrich vesicle-containing fractions [6], but does not guarantee complete separation from lipoproteins [1]. Pre-analytical conditions and complementary characterisation therefore require explicit reporting. A circulating signal should not be designated liver-derived without evidence of cellular origin. Diagnostic candidates also require independent clinical validation; analytical detectability alone does not establish diagnostic utility.

These constraints argue for indication-specific development rather than a generic “cell-free” therapeutic category. Studies intended to address established fibrosis should begin treatment after fibrosis is established and examine durability, tissue architecture, and liver function. Controlled clinical evaluation remains necessary before benefits observed in the selected experimental models can be translated into treatment claims [2–5].

Conclusion

EV research offers a coherent framework for linking antifibrotic signalling, acute hepatoprotection, and regenerative responses. Its translational value will depend on keeping these outcomes distinct and matching each claim to a characterised product and an appropriate disease model. Progress should be judged by reproducible biological activity and meaningful functional benefit, not by the cell-free label alone.

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