The pathogenesis of hepatic fibrosis: basic facts and clinical challenges

Globally, the absolute number of patients suffering from chronic liver disease is estimated at 1.5 billion worldwide. The most common liver disease causes are infections with hepatitis B and C, excessive alcohol intake, fatty liver disease, autoimmune attacks, genetic disorders, metabolic disorders, cholestasis, venous obstruction, and parasitic infection. Liver injury is further associated with hepatic fibrosis, which is the excessive formation and deposition of fibrous connective tissue. This process impairs proper metabolic and other homeostatic functions of the parenchyma, disturbs hepatic blood flow, and establishes an inflammatory and tumorigenic microenvironment provoking progression of fibrosis to cirrhosis and hepatocellular carcinoma (HCC). In this scenario, major collagen-producing cells are hepatic stellate cells (HSC), portal fibroblasts, and several pro-fibrogenic progenitors that either invade the inflamed tissue or change their properties and acquire a matrix-producing phenotype.

During the last decades the knowledge on fibrotic mediators, molecular mechanisms and signaling pathways that are involved in the initiation or progression of hepatic fibrosis significantly increased. Accumulating evidence form experimental models has confirmed that liver fibrosis is reversible and that recovery even from cirrhosis may be possible. Stimulated by these findings, numerous anti-fibrotic therapies are currently tested in humans. However, none of them has been thoroughly validated in the clinic or commercialized as a standardized therapy for hepatic fibrosis. Therefore, effective therapies or strategies allowing removing excess extracellular matrix and restoring normal organ functionality are urgently needed.

This special series of *Digestive Medicine Research* contains the first four articles of the ongoing series "The Pathogenesis of Hepatic Fibrosis: Basic Facts and Clinical Challenge". Additional articles will follow in one of the next issues.

In one of these articles, Valentin-Cortez and colleagues discuss the consequences of an altered gut microbiota for the pathogenesis and progression of liver diseases. This article shows that disease-associated modifications in microbiota taxa could become an important biomarker and therapeutic target of patients with chronic liver disease.

The second paper by Poulsen *et al.* provides a brief overview about the roles of chemokines for the pathogenesis of hepatic fibrosis. This article highlight that these soluble mediators are key mediators that orchestrate accumulation and activation of immune cells in the inflamed liver tissue. The authors discuss that the chemokine system offers potent therapeutic targets to either prevent fibrosis or help to stabilize or even reverse progression of fibrosis to improve the quality of life in patients suffering from liver disease.

In a third contribution, Seitz and Neuman highlight the epidemiology and mechanisms contributing to alcohol-driven fibrogenesis and progression to HCC. In their article, the authors illustrate that ethanol-induced hepatocellular damage and progression to HCC is molecularly induced by activation of liver cells by pathogen-associated molecular patterns, ethanol-mediated gastrointestinal dysbiosis, oxidative stress, and epigenetic changes associated with activation of the canonical Wnt signaling pathway that my stimulate β-catenin-dependent tumor growth.

In another narrative review, Melnik and colleagues comprehensively summarized findings of papers published between 2000 and 2021, in which bovine milk-derived exosomes from mesenchymal stem cells and natural killer cells were shown to be effective inhibitors of HSC activation and fibrogenesis. As such, milk exosomes may be promising therapeutic agents either in native form or supplemented with anti-fibrotic acting drugs such as metformin.

Consistently, these four studies demonstrate that the mediators and pathways driving hepatic fibrogenesis offer a multitude of potential targets and treatment options. In future, the better understanding of the underlying processes and mechanisms that contribute to hepatic fibrosis should open new therapeutic avenues, ultimately helping to decrease the enormous morbidity and mortality associated with liver fibrosis and its consequences.

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Footnote

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