https://doi.org/10.1038/s41575-023-00844-6

Turning our focus to liver fibrosis

Liver fibrosis is a substantial risk factor for liver cancer development. In this issue, we focus on molecular and cellular mechanisms of hepatic fibrogenesis and discuss therapeutic implications.

The ancient Greeks realized what a remarkable organ the liver is — they believed it to be the centre of the soul. As the myth of Prometheus shows, the liver has an extraordinary capacity for tissue regeneration. Our body's factory of metabolism and detoxification — the liver — is resilient, and works tirelessly towards our well-being, regardless of how much 'junk food' or wine we consume. But, it can only bear so much burden and endure so much scarring.

At some point, the liver cannot heal an injury fast enough and must continue its life-saving function with scarred tissue — an asymptomatic condition called fibrosis. If left untreated, fibrosis can progress to cirrhosis, which is irreversible, and eventually to liver cancer. At this late stage, the patient's survival depends on liver transplantation.

However, liver fibrosis is reversible; quality of life and mortality can be improved if it is treated early. As the incidence of liver cancer is increasing, it is time to concentrate our efforts on early diagnosis and individualized treatment. In this Focus Issue of *Nature Reviews Gastroenterology & Hepatology*, we look closely at liver fibrosis and delve into exciting advancements that are moving us towards improved diagnosis and treatment.

Chronic inflammation is a common denominator of chronic liver diseases, such as nonalcoholic fatty liver disease (NAFLD, or, as has been proposed, metabolic dysfunction-associated steatotic liver disease, MASLD[1]), and can lead to hepatic fibrosis. Persistent immune responses promote overproduction of the extracellular matrix (ECM), changing its composition and eventually altering the liver architecture. As developing effective antifibrotic treatments is challenging, targeting immune cells with a predominant role in fibrogenesis is appealing.

Nonalcoholic steatohepatitis (NASH, or, as has been proposed, metabolic dysfunction-associated steatohepatitis, MASH[1]) is associated with hepatocyte injury and lobular inflammation and can progress to fibrosis, then to cirrhosis and eventually to hepatocellular carcinoma, the most common primary liver cancer. Researchers estimate that the global prevalence of NASH will increase by up to 63% by 2030. Despite the vigour of research in the field, preclinical studies have not yet led to an approved therapy to treat fibrosis and, therefore, to improved clinical outcomes. Thus, it is critical to understand why we need to treat NASH-related fibrosis and the limitations we currently face. Promising trials include the phase III MAESTRO-NASH trial, the preliminary results of which were presented during the European Association for the Study of the Liver (EASL) Congress 2023 in Vienna, Austria.

> "it is time to concentrate our efforts on early diagnosis"

Liver fibrosis is a major risk factor for the development of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Hepatic stellate cells (HSCs) have a substantial role in liver physiology and fibrogenesis and are important players in ECM overproduction. HSCs are needed for liver homeostasis and regeneration, but, due to chronic liver injury, they can differentiate into myofibroblasts and cancer-associated fibroblasts (CAFs). The biology behind the contribution of CAFs to liver cancer is elusive owing to their plasticity, and is vital to decipher for the refinement of future targeted therapies.

Cellular stress is also involved in the multifaceted process of fibrogenesis. Several stress pathways are activated in cells (for example, in hepatocytes and HSCs), contributing to chronic injury and liver disease pathogenesis, such as in NAFLD and NASH. Emerging data highlight the potential of targeting cellular stress as a therapeutic avenue, but more studies are needed to show an effect on fibrosis regression.

Continuous translational and clinical research and advanced technologies stand at the forefront of medical care. As these efforts intensify, they pave the way towards individualized medicine for liver fibrosis.

Published online: 26 September 2023

References

1. Rinella, M. E. et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *J. Hepatol.* https://doi.org/10.1016/j.jhep.2023.06.003 (2023).