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EDITORIAL

Frontiers in fatty liver: recent advances in pathogenic mechanisms, assessment of patients' prognosis and pharmacotherapy

MASLD: new pathogenic mechanisms, risk assessment tools and drug therapies

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Excessive hepatic fat accumulation in the absence of high alcohol consumption, up to date referred to as nonalcoholic fatty liver disease (NAFLD), has emerged in recent years as one of the most prevalent forms of chronic liver disease on a global scale, with an overall prevalence of about 25% [2, 4, 17]. NAFLD includes a spectrum of hepatic alterations, ranging from the "benign" accumulation of fat in hepatocytes to a progressive liver disease with hepatocellular damage and inflammation, termed nonalcoholic steatohepatitis (NASH), fibrosis development, and cirrhosis or hepatocellular carcinoma (HCC) as end-stages of the disease [1, 13]. Obesity and its associated traits which include hypertriglyceridemia, low HDL cholesterol, hypertension and type 2 diabetes mellitus, define the components of the metabolic syndrome and, together with cardiovascular disease, are intimately linked to the development and progression of NAFLD [6, 7, 12]. Importantly, very recently, the term NAFLD was revised, and a new nomenclature that better defines the etiology of the disease, takes into account alcohol consumption, and the strong epidemiological and pathogenic links between NAFLD, insulin resistance and metabolic dysfunction, have been agreed at an international level. The overarching term steatotic liver disease (SLD), which encompasses all causes of hepatic steatosis, includes now the new denomination "metabolic dysfunction-associated steatotic liver disease" (MASLD) that replaces NAFLD, and "metabolic-associated steatohepatitis" (MASH) for the more advanced stages is previously defined by NASH. Noteworthy, the terms "nonalcoholic" and "fatty" were dropped from these definitions in part because they were considered to be stigmatizing. Curiously, "fatty" was replaced by "steatotic", from the Greek word στέᾱτος ("steatos"), which in that language literally means "fat" [8]. These changes will indeed increase disease awareness and accelerate biomarker and drug discovery in a condition that is reaching epidemic proportions with a heavy toll on patients and health care systems [17]. Being such a complex disease, there are still many aspects that need to be thoroughly addressed. These include, but are not limited to, its pathogenic mechanisms, genetic predisposition, acquired risk factors, the need for an early diagnosis, risk stratification and prognosis, and the elucidation of effective pharmacological treatments. This special issue was conceived to convey to our readers an overview of the most recent advancements in the abovementioned topics. Both review articles and original studies featuring new knowledge and advances in the field are put together in this collection.

The review by Terracciani et al. [14] comprehensively summarized the genetic variants that have been robustly associated with the development and progression of NAFLD. The authors review the wealth of genome-wide association

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Key points
- Genetic determinants and the metabolic syndrome are key drivers of NAFLD.
- Epigenetic and epitranscriptomic dysregulation characterize NAFLD progression.
- Biomarkers are needed for risk assessment and evaluation of therapeutic response.
- There are no licensed drugs for NAFLD, combination therapies look promising.

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studies (GWAS) supporting the impact of single nucleotide polymorphisms (SNPs) in genes like *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, and *HSD17B13*, and the mechanisms by which these variants promote the development of steatosis and liver fibrosis [14]. The impact of obesity, insulin resistance, and the metabolic syndrome on the pathogenesis of the disease is also put into perspective, together with the central role played by fibrosis progression on the outcome of patients, included mortality. An updated description of the latest non-invasive methods to assess disease activity and liver fibrosis, along with their prognostic potential and utility in individual risk stratification, as well as in monitoring treatment response, is provided in this very useful piece.

In this same context, the original study by Sookoian and Pirola [11] investigated the association between the ratio of circulating uric acid (UA) and creatinine (Cr) levels, the sUA/Cr ratio, and NAFLD in a very large population of patients from the USA with elastography confirmed liver steatosis. It was demonstrated that elevated sUA/Cr ratio was significantly associated with liver fat content, concluding that progression of elevated sUA/Cr ratio may indicate worsening of liver steatosis, and may also alert on kidney function decline. Nevertheless, as acknowledged by the authors, the utility of this parameter in face of other canonical risk factors will need further validation [11].

The dysregulation of epigenetic and epitranscriptomic mechanisms is increasingly recognized to play a role in most disease conditions, and accumulating evidence indicates that this is also the case for NAFLD. The covalent modifications of histones, DNA, and RNA have a strong impact in gene expression, and these marks are deposited, erased, and read by a complement of dedicated enzymes and factors. The original report of Herranz et al. [5] performed a comprehensive study of the expression of 419 and 128 epigenetic and epitranscriptomic genes, respectively, in a total of 903 human liver tissues samples from patients with normal liver, obese patients, patients with NAFLD, and NASH patients. This analysis integrated ten different transcriptomic datasets in an unbiased manner. The authors identified significant alterations in the expression of epigenetic and epitranscriptomic genes along the course of the disease, including gene signatures that were markedly correlated with fibrosis progression [5]. This study provides the first integral transcriptomic landscape of these key regulators of gene expression in NAFLD, shedding light into the molecular mechanisms of the disease and also guiding the identification of new biomarkers and potential drug targets.

Additional mechanisms underlying the development and progression of NAFLD were summarized in two comprehensive reviews. Tuero et al. [15] revised the experimental and clinical evidence supporting a role for the gut hormone ghrelin in the context of obesity, insulin resistance, type 2 diabetes, and the metabolic syndrome, conditions in which the circulating levels of ghrelin are decreased. The authors highlight the mechanisms of ghrelin expression regulation, its signaling system, and the tissue targets on which this hormone exerts potent regulatory effects on lipid and energy metabolism, both at the central and peripheral levels. Very interestingly, the multifaceted hepatoprotective properties of ghrelin, including anti-inflammatory, anti-fibrogenic, and anti-lipotoxic effects, are dissected [15]. As proposed by the authors, altogether, these evidences support a potential application of ghrelin in the prevention of NAFLD in patients with metabolic diseases. Atorrasagasti et al. [3], in turn, reviewed the role of "secreted protein acidic and rich in cysteine" (SPARC) in the pathogenesis of obesity, type 2 diabetes, and NAFLD. SPARC is an extracellular matrix multifunctional protein expressed in many different tissues. In the liver it is upregulated in response to injury, including in NAFLD patients. This response seems to limit de novo lipogenesis; however, sustained SPARC expression has been linked to inflammation and fibrosis progression. As summarized by the authors, SPARC also plays a role in different tissues involved in the pathogenesis of obesity and the metabolic syndrome, such as the adipose tissue, muscle, and pancreas. However, this role may change along the course of the disease and with the magnitude of SPARC overexpression [3]. Although the complex pathogenic mechanisms mediated by SPARC overexpression still need to be further elucidated, the consistent association of its expression levels with liver injury and fibrosis suggests a potential application of SPARC as a biomarker of disease progression.

Sangro et al. [10] reviewed the results of the most advanced clinical trials for the pharmacological treatment of NAFLD. As discussed by the authors, the complexity of NASH pathophysiology, with multiple genetic and environmental factors at play, its long natural history, and wide spectrum of severity may explain why few drugs have been successful in NAFLD trials. In fact, no licensed pharmacotherapy is currently available for this condition. This review comprehensively summarizes the variety of molecules with different biological targets that have been evaluated, including antidiabetic drugs as well as drugs targeting liver inflammation and fibrosis. Updated information on the outcome of trials testing inhibitors of glucose tubular reabsorption (SGLT2 inhibitors), GLP-1R agonists, PPAR modulators, FXR agonists, and liver-directed THR-beta agonists is presented in great detail [10]. Anti-inflammatory and antifibrotic agents are also discussed, including the clinical trials evaluating the chemokine two and five receptors antagonist Cenicriviroc. Being liver fibrosis a central event in NAFLD progression and patients' outcome, the identification of direct anti-fibrotic agents has attracted much attention. In this line, in this special issue, Ruiz de Galarreta et al. [9] provide compelling in vitro evidence of the anti-fibrotic properties of Ocoxin, a nutritional supplement containing

natural products with antioxidant and anti-fibrogenic properties. Ocoxin inhibited growth and collagen production in activated liver fibrogenic cells [9], activities that may underlie the beneficial effects on steatosis and inflammation in biopsy-proven NAFLD patients reported before [16]. Nevertheless, as discussed by Sangro et al. [10], although in some cases, drugs specifically targeting the major components of NASH, i.e., steatosis, inflammation, and fibrosis have shown beneficial effects in a proportion of patients; the future of NAFLD treatment may reside in combination strategies. Ideally, these would be tailored according to disease stages, and also should take into account the extrahepatic complications of a multisystem disease.

All in all, the studies collected in this special issue summarize the key aspects of NAFLD pathogenesis, uncover novel disease mechanisms, and discuss cutting-edge approaches for risk assessment, prognosis, and treatment of these patients. Although much has been learned about this disease since 1980, when the term NASH was introduced, one take home message from the research showcased here is the need of further research to develop new biomarkers of disease activity and effective drugs. This can only be achieved through multidisciplinary collaboration which also considers cardiometabolic risk factors.

Data availability The authors declare that all data were generated in-house and that no paper mill was used.

Declarations

Ethics approval Does not apply.

Informed consent Does not apply.

Conflict of interest The authors declare no competing interests.

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