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EDITORIAL

Pharmacological treatments of the ''Fibrotic-NASH'': Towards a delivery on time?

The molecular mechanisms involved in the development and progression of NAFLDs are complex and multifactorial. Intrahepatic but also extrahepatic mechanisms play an important role. Cross talks between the liver, adipose tissue and gut have been involved. In the future, pharmacological innovations may be available for patients with fibrotic-NASH. An increasing number of pre-clinical and clinical studies are in progress targeting ''metabolism-inflammation-fibrogenesis''. Some compounds target inflammation and/or fibrosis (CCR2/CCR5 antagonist, galectin-3 inhibitor...), others the metabolism (FGF21 agonists, PPAR pan-agonists, ACC inhibitor....), or the gut-liver axis (FXR agonists, non-tumorigenic analogues of FGF19 ...) [1,2]. The combination of two or more of these compounds is a rational strategy under development.

To optimize the action of these future treatments, the association with a lifestyle change would be a promising and synergistic approach. Recent reviews summarize the benefits of nutritional management and physical activity on NAFLDs [3]. Weight reductions of $\geq$ 10% can induce a near universal NASH resolution and fibrosis improvement by at least one stage. However, modest weight loss (> 5%) can also produce important benefits on the components of the NAFLD activity score (NAS). The ''ideal'' diet (Mediterranean diet?) and the most effective ''regular'' physical activity remain to be determined on long-term studies. These adapted lifestyle modifications (ALM) towards a healthy diet and habitual physical activity would also be a therapeutic approach to reduce the cardiovascular complications (or even cancers?) associated with NAFLD.

These ALM together with future pharmacological approaches could also help the correction of the altered biological clock associated with obesity and obesity complications. Indeed, the developments of insulin resistance and NAFLD have been associated with alterations of the central brain clock and several peripheral tissue clocks [4—7]. The oscillation of the intestinal microbiome and related metabolites, in addition to the modification of its composition (dysbiosis), have an impact on liver functions and NAFLDs development. The peripheral clocks in muscle, adipose tissue and liver regulate local insulin sensitivity and the peripheral clock in the pancreas regulates insulin secretion [4,5]. Gut microbiota impacts on the biological clock, at the same time as the appropriate timing of metabolic fluxes, hormone secretion, bile acid turnover, autophagy and inflammation with behavioural cycles of fasting/feeding and sleeping/waking is required to prevent the development of hepatic steatosis. The later indicates significant interactions of the gut and circadian processes in NAFLD pathophysiology. ''Deranged'' physiological rhythms (chrono-disruption) may favor the development and progression of NAFLDs. A ''resetting/synchronization'' of exercise and diet intake (time-related dietary patterns (chrononutrition)) with diet composition constitute an attractive strategy that should be evaluated in order to optimize the beneficial effects on NAFLD. Specific NAFLD therapeutic targets, currently under clinical evaluation, also have an impact on the biological clock, such as PPAR, FXR, GLP-1 receptor agonists and FGF19 analogues.

However, a recent study has demonstrated a cell-autonomous mammalian 12 hr clock regulating hepatic gene, distinct from the circadian period of 24 h, which could coordinate metabolic and stress rhythms. This regulation may depend on metabolic stress and endoplasmic reticulum [8]. Among the unfolded protein response (UPR) branches, the transmembrane protein of the endoplasmic reticulum inositol requiring enzyme 1 (IRE-1) could play an important role. Downregulation of the 12 hr gene expression strongly correlates with human hepatic steatosis and steatohepatitis, implying its importance in maintaining metabolic homeostasis.

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The exponentially increasing advances in the pathophysiology of the NAFLDs will therefore allow the expansion of therapeutic targets including ''chronotherapy''.

Disclosure of interest

The author declares that he has no competing interest.

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