Title: **Estrogen receptor alpha in the female liver: Dr. Jekyll and Mr. Hyde**

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Abstract

Estrogen signaling concurs to regulate female liver metabolism according to hormonal status and genetic factors, accounting for sex differences in the susceptibility to metabolic dysfunction-associated steatotic liver disease (MASLD).

The good facets of Estrogen receptor alpha in the liver.

In comparison to fertile women, men and post-menopausal women show a greater risk of developing MASLD [1], suggesting that estrogen signaling has a key role in counteracting this pathology [2,3]. The reduction of estrogens in post-menopausal women, indeed, triggers MASLD,

nullifying its sexual dimorphic prevalence [2,3]. The protective role of estrogens is mainly mediated by the estrogen receptor alpha (ERα), whose activation concurs to modulate the hepatic metabolism to the energy requirements characterizing each reproductive stage [4]. In the absence of hepatic ERα regulatory activity, liver metabolic homeostasis is altered with reduced lipid oxidation [5,6], leading to increased accumulation of lipid droplets (LDs). Dysregulation of lipid homeostasis leads to the generation of toxic lipids promoting inflammation and hepatocellular damage [2], a condition resembling the increased incidence of MASLD and steatohepatitis (MASH) observed in women after menopause.

The bad facets of Estrogen receptor alpha in the liver.

The recent work of Cherubini *et al*. [7] shed lights on the relevance of estrogen signaling in promoting MASLD in women carrying the *PNPLA3* p.I148M variant, the main genetic risk factor for MASLD development. Importantly, a multiplicative interaction between carriage of the *PNPLA3* p.I148M variant and female sex determines the whole spectrum of MASLD phenotypes, contributing to sex differences in the susceptibility to the most common cause of liver disease. Transcriptomic analysis in mice revealed higher hepatic *Pnpla3* expression in females during the follicular phase of the cycle characterized by high estrogens. Similarly, higher *PNPLA3* expression was observed in obese women carrying p.I148M variant than in men, suggesting a direct role of estrogens in modulating *PNPLA3* expression. Indeed, ERα activation induced *PNPLA3* expression through a classical mechanism, with the binding of ERα to estrogen responsive element (ERE) [7], resulting in accumulation of PNPLA3 p.I148M protein on LDs, and MASLD development.

Hepatic ERα as a potential target for gender pharmacology

In the context of precision pharmacology, a drug treatment should be specific, personalized and differentiated by type of molecule, dose, route and time of administration, and potential risks of adverse reaction. A pharmacological approach should also take into account the biological variability and, therefore, all the factors that could influence disease development and progression, including sexual hormones. Investigating the potential mechanisms by which hepatic ERα signaling might account for sex differences in MASLD incidence and progression is of great relevance, considering the global burden of metabolic diseases and MASLD, and the fact that

women spend more than one third of their lives in the post-menopausal stage [1,3,8]. Furthermore, MASLD is the most rapidly rising cause of hepatocarcinoma, especially in women [9].

Although, the relevance of sex and hormonal regulation in liver pathophysiology have been greatly underestimated, these findings suggest that liver ERα might be a valuable target for safer, sex-specific pharmacological approaches for MASLD treatment, but this approach should be personalized according to *PNPLA3* p.I148M status as ERα would be beneficial in non-carriers, but detrimental in carriers of this variant.

Given the overlap of MASLD with other forms of steatotic liver disease (SLD), unraveling the interaction between *PNPLA3* p.I148M, sex and estrogen signaling in a broader spectrum of SLD may contribute to define potentially shared mechanisms and therapeutic strategies.

Abbreviations

E2, estrogens; ERα, estrogen receptor alpha; ERE, estrogen responsive element; FA, fatty acids; LDs, lipid droplets; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PNPLA3, patatin-like phospholipase domain containing 3; steatotic liver disease (SLD).

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Author names in bold designate shared co-first authorship.

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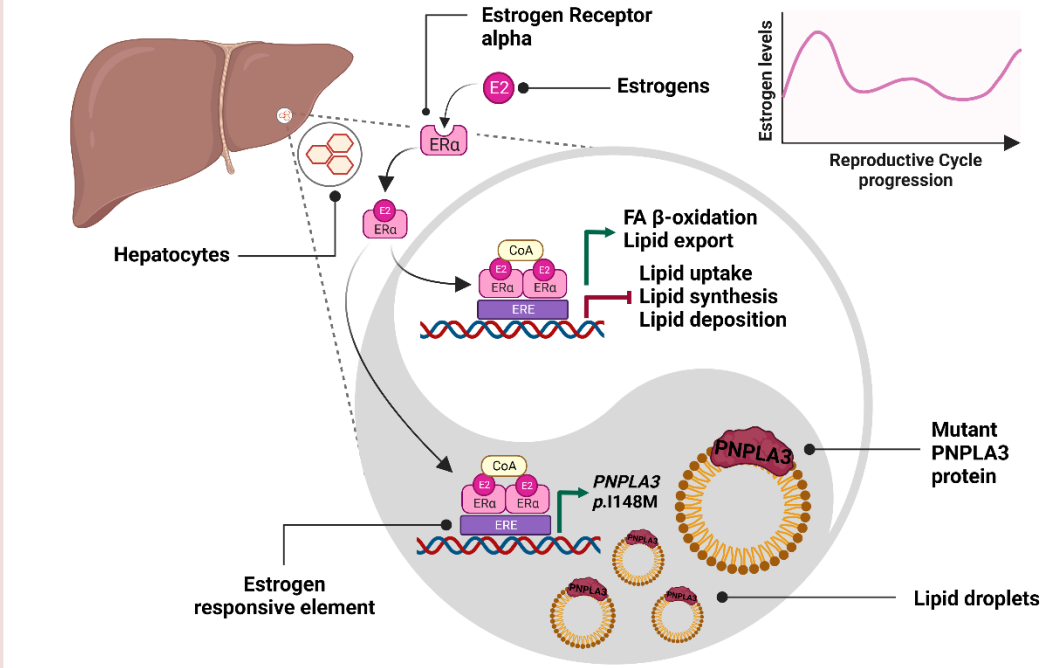

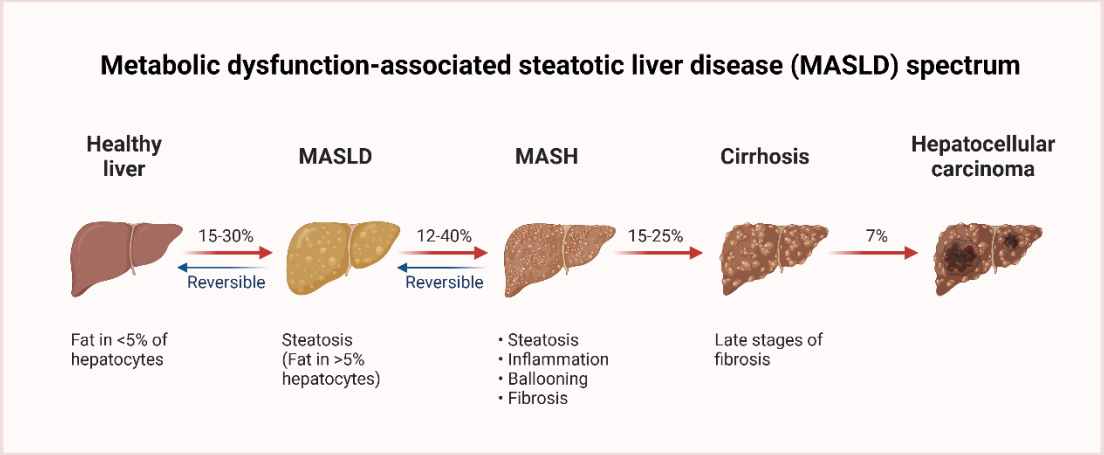

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