Relevance of hepatic estrogen receptor alpha in liver metabolic adaptation during pregnancy

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Background and Aims: Males and females show different susceptibility, progression and outcome of several acute and chronic liver diseases. Among the factors that may account for these differences are estrogens, acting mainly through estrogen receptor alpha (ERa) at the hepatic level. We previously demonstrated that, in the liver of females, hepatic ERa acts as a sensor of food availability and regulates the hepatic metabolism according to the needs of the several stages of reproduction, thus linking metabolism and reproduction to each other. In particular, hepatic ERa activation by nutrients such as amino acids (AA) is necessary for the proper progression of the estrous cycle. The role of hepatic ERa in the regulation of liver metabolism and reproduction could be even more complex and relevant during pregnancy; however, it still needs to be investigated. Deregulations of hepatic estrogen signaling could also be implicated in pathological liver conditions related to pregnancy, such as intrahepatic cholestasis and acute fatty liver of pregnancy. In this view, a better understanding of the role of hepatic ERa during physiological progression of pregnancy could be crucial for the development of strategies to prevent or limit the progression of these conditions. Therefore, the aim of this study was to assess the specific relevance of hepatic ERa in the physiological adaptation of liver metabolism in different stages of pregnancy.

Method: To assess the specific relevance of hepatic ERa in the metabolic adaptation during pregnancy, we compared female control (CTRL) and liver-specific ERa-knockout (LERKO) pregnant mice at different timepoints (gestational day 6.5, 14.5 and 17.5). Virgin females at proestrus (the phase of the estrous cycle in which circulating 17beta-estradiol levels are highest) were used as the reference group.

Results: Results show that in the livers of female pregnant mice most of the genes analyzed, that are involved in lipid metabolism, glucose homeostasis and amino acid metabolism, display different expression patterns according to the progression of pregnancy. Moreover, hepatic ERa concurs to regulate the expression of some of the genes analyzed, especially those involved in AA metabolism. These findings are in line with our previous data and further demonstrate the tight connection between ERa and AA metabolism in the female liver.

Conclusion: Altogether, our results suggest that liver adapts its metabolism according to the different stages of pregnancy, to sustain the energetic needs of the developing embryo. Moreover, a contribution of hepatic ERa can be observed in the regulation of some of the analyzed pathways, hinting to this receptor as a possible key player in the orchestration of the metabolic adaptation during pregnancy.