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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Hepatological coordination of pregnancy-related changes

Pregnancy constitutes a unique state in which almost every organ system in the body undergoes at least some degree of phenotypical change. In conjunction, these changes prepare the body for implantation; germinal, embryonic, and fetal growth; and parturition. Although the role of altered production of sex hormones is well recognized to initiate the organ adaptations involved, remarkably little is known about the molecular mechanisms that mediate the changes in the mother. Remarkably, in the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Lee et al[1] show that the maternal liver plays a coordinating role in preparing the body of the mother for a successful pregnancy. The contribution of the liver in mediating pregnancy-associated changes that was uncovered by Lee et al[1] is surprisingly broad. It involves, apart from the liver itself, the maternal pancreas, spleen, kidney, placenta, and even the composition of the microbiome, among other effects in the expecting mother. The current study is limited to experimental rodents. If the findings observed, however, are reflected by similar effects in human mothers, it would not be unreasonable to suggest that in the future, the classical trio of physiological function groups associated with the liver (detoxification, synthesis, and storage[2]) will be updated with a fourth functional group involving the coordination of pregnancy-related changes.

Central to the paper by Lee et al[1] is the transcription factor achaete-scute homolog-like 1 (Ascl1). This transcription factor is conventionally associated with compartment expansion in the developing neural system, probably through noncell autonomous activation of Notch signaling in neuroblasts, but is also implicated in oncogenesis of various endodermal derivatives.[3] In the present study the authors built on the unexpected observation that this transcription factor becomes specifically expressed in the maternal hepatocytes in the second half of gestation. Exploiting the power of contemporary molecular biology, the authors show that specific deletion of Ascl1 from the maternal hepatocyte genome at midgestation prevents adequate structural and functional adaptation of maternal organs associated with pregnancy. Thus, the authors reveal a cardinal role of hepatic Ascl1 expression in the regulation of maternal physiology during gestation. The importance of these Ascl1-associated changes is further highlighted by the observation that pups born from animals with hepatic deletion of Ascl1 show abnormal postnatal growth, highlighting the importance of liver-dependent pregnancy-associated maternal tissue remodeling for delivering healthy offspring.

Ascl1 is a basic helix-loop-helix transcription factor, thus the inhibitory effects seen following its deletion on pregnancy-associated changes in the maternal organ systems are likely associated with alternative transcription in hepatocytes of the mother animal. Although most investigators active in the field would probably attribute Ascl1 effects to alternative activation of Notch signaling in neighboring cells, the authors provide evidence that at least part of the effects are mediated by reduced production of insulin-like growth factor 2. In the absence of experiments in which the importance of this effect is tested directly (eg, in animals conditionally genetically deficient for this growth factor), the importance of this effect remains uncertain, but the authors acknowledge that the effects of Ascl1 deletion in hepatocytes of pregnant dams probably involves multiple mediators, which remain obscure for now. The clarification of the identities and specific roles of these mediators should add to the understanding of the unexpected role, executed by the liver in ensuring a healthy pregnancy. Disregarding the currently incomplete insight into the exact details of the liver in controlling pregnancy-associated changes in the expecting mother, it is evident from the study published in the current issue of *Cellular and Molecular Gastroenterology and Hepatology* that Lee et al[1] have uncovered a very important novel functionality of the liver in the reproduction of mammals.

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Conflicts of interest
The authors disclose no conflicts.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2021.09.002