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Commentary

Liver Sex Dimorphism and Zonation Shaped by Growth Hormone

Damasia Becu-Villalobos[1,2]

[1]Instituto de Biología y Medicina Experimental CONICET, Buenos Aires, Argentina
[2]Academia Nacional de Ciencias de Buenos Aires, Buenos Aires, Argentina

Correspondence: Damasia Becu-Villalobos, Instituto de Biologia y Medicina Experimental. CONICET, Vuelta de Obligado 2490, Buenos Aires 1428, Argentina. Email Dbecu@ibyme.conicet.gov.ar.

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Abbreviations: GH, growth hormone; lncRNA, long noncoding RNA; snRNAseq, single-nucleus RNA sequencing.

In clinical medicine, the consideration of sex-specific differences in diagnosis and treatment of many diseases is gaining acceptance. In this context, sex differences in liver function and gene expression are important, although not highlighted in medical practice. In humans, significant sex differences in the bioavailability and clearance of drugs and other xenobiotics, as well as sex-biased proneness to different liver disorders, have been described.

Sexually dimorphic gene expression of the liver depends mainly on growth hormone (GH) secretory patterns, and to a lesser extent on sex steroids. The brain is paramount in organizing GH pulses through synchronization of growth hormone–releasing hormone and somatostatin release and feedback responses (1), thus shaping liver sex dimorphism in accordance with the need for sex-specific steroid metabolism, and metabolic or even behavioral performance. High intermittent GH pulses are found in males, while females have a more constant secretory pattern in rodents; this pattern is found also in humans, although to a minor extent. This differential pulsatility is a key factor for the establishment and maintenance of sexual dimorphism in the transcription of liver genes (2-4). More than 1000 liver genes are sexually dimorphic, and of these approximately 90% are GH dependent (2). Sex differences in gene expression range from less than 2-fold to >1000-fold in the mouse, and this should alert to the need of considering sex as a variable when instrumenting different liver therapies, or administering drugs metabolized in a sex-specific manner.

The disruption of GH-dependent sexual dimorphism in liver gene expression has been associated to liver disease, and clinical and experimental data indicate that reductions in circulating GH levels or hepatic response to the hormone are principal components of nonalcoholic fatty liver disease, which is predominant in men compared with premenopausal women, and which may ultimately lead to steatosis, liver fibrosis, and hepatocarcinoma (5).

This field of research has been steadily evolving, and liver sexual dimorphism first described for genes and enzymes, now includes differentially methylated regions of the DNA characterized as GH-STAT5 dependent, differences in chromatin structure, and sex-biased expression of miRNAs and long noncoding RNAs (lncRNAs). In a recent breakthrough published in *Endocrinology* (6) the scenario is further detailed and amplified using single-nucleus RNA sequencing (snRNAseq). This methodology allowed the unraveling of the cell type–specificity and zonation of sexually dimorphic gene expression and increased the sensitivity for single cell–based analysis of lncRNAs, a majority of which are strongly enriched in the nuclei compared to cytoplasm. Most previous analyses included all liver cell types (hepatocytes, cholangiocytes, Kupffer, follicle stellate, endothelial, and immune cells) which might be confounders. Moreover, differential sexual dimorphism of gene expression according to cell zonation of the liver was not considered. Liver zonation is the differential gene expression along the lobule axis. Hepatocytes near the periportal triad are termed *periportal hepatocytes*, and those close to the central vein are the *pericentral hepatocytes*. Due to exposure of different levels of oxygen and metabolites, their function and gene expression may vary. For example, genes participating in gluconeogenesis and ureagenesis are enriched in periportal hepatocytes, sustained by immediacy to fresh blood supply of oxygen and nutrients, while pericentral hepatocytes are enriched for genes involved in glycolytic and xenobiotic metabolism. This spatial division of labor confers optimal liver function, and sex specificity for each zone would be expected, but had not been defined.

The new high-throughput approximation (6) revealed that only hepatocytes, and not the other liver cell subtypes, have sexually dimorphic expression signatures, and furthermore showcased a unique description of gene expression according to zonation. Numerous examples of gene sexual dimorphism in both or only one of the zones, or specific zonation of genes for one or both sexes, as well as zone- or sex-specific dysregulation induced by continuous GH administration, or exposure to a xenobiotic, are meticulously described, and point to an unprecedented plasticity of sex-biased zonation.

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The technological advance provided by snRNAseq could be compared to the resolution and capacity obtained by the Hubble Space Telescope that now allows astronomers to study the nuclei of previously unknown galaxies with extraordinary definition, and to even determine the chemical composition and the kinematic behavior in these central regions. Likewise, Goldfarb et al (6) identify the complex dynamic interaction of the liver disclosing a precise architecture where female and male predominant genes may act in accord, or solely when required in a sex-specific task, and in the specific zone in which their task is optimal. The comprehension of these results broadens our minds to the complexity of liver function and its adaptability to cope with the metabolic demands of females or males.

Liver function may be stressed by alcohol overload, high-fat diets, or chemical exposure. The susceptibility to these stresses is often sex dependent, may be modulated by GH signaling, and is associated with the development of liver diseases. In the present context, it is important to understand that liver pathologies may be not only sex- but also zone- dependent, making it important to determine which specific liver cell types or zonal regions of liver lobules are affected. Furthermore, the study of sex-dimorphic gene expression in the liver may also shed light in the outcome of liver transplants, in which sex mismatch between donors and recipients may be a risk factor for poor graft survival. Though the association is still controversial, a systematic review and meta-analysis on donor-to-recipient gender mismatch as a risk factor for post-transplant graft loss, reported that female donor-to-male recipient (but not male donor-to-female recipient) represented a detrimental role in terms of liver graft survival (7), highlighting the need to clarify sex differences in liver gene expression.

In an era of individualized medicine, recognition of sex-based differences is fundamental in the approach to treating liver disease as well as pre- and post-liver transplant care. Mechanistic studies are needed to beget sex-specific approaches to diagnosis and treatment. The study of Goldfarb et al (6) provides a wealth of novel data to inform such mechanistic studies.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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