Accepted Manuscript

Genomics of sex hormone receptor signaling in hepatic sexual dimorphism

Daoshan Zheng, Xiao Wang, Per Antonson, Jan-Åke Gustafsson, Zhaoyu Li

PII: S0303-7207(17)30294-0

DOI: 10.1016/j.mce.2017.05.025

Reference: MCE 9956

To appear in: *Molecular and Cellular Endocrinology*

Received Date: 16 December 2016

Revised Date: 17 May 2017

Accepted Date: 23 May 2017

Please cite this article as: Zheng, D., Wang, X., Antonson, P., Gustafsson, Jan.-Å., Li, Z., Genomics of sex hormone receptor signaling in hepatic sexual dimorphism, *Molecular and Cellular Endocrinology* (2017), doi: 10.1016/j.mce.2017.05.025.

Genomics of sex hormone receptor signaling in hepatic sexual dimorphism

Daoshan Zheng[a], Xiao Wang[a], Per Antonson[b], Jan-Åke Gustafsson[b,c], and Zhaoyu Li[a]

[a] Department of Cancer Biology, Mayo Clinic, Jacksonville, FL 32224, USA
[b] Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge 14183, Sweden
[c] Department of Biology and Biochemistry, University of Houston, Houston, TX 77204, USA

Correspondence: Zhaoyu Li, li.zhaoyu@mayo.edu

Highlights

- Numerous sexual differences in hepatic gene expression in the normal mouse liver;
- Hepatic estrogen receptor alpha and androgen receptor differentially drive sexual dimorphic gene expression;
- The most significant sexually dimorphic gene expression occurs at birth during liver development.

Abstract

The liver plays a crucial role in a variety of physiological processes. Sexual dimorphism is markedly defined in liver disorders, such as fatty liver diseases and liver cancer, but barely addressed in the normal liver. Distinct sex hormone signaling between male and female livers is the major driving factor for hepatic sexual dimorphism. Over 6,000 genes are differently expressed between male and female livers in mice. Here we address how sex hormone receptors, estrogen receptor alpha (ERα) and androgen receptor (AR), mediate sexually dimorphic gene expression in mouse livers. We identified 5,192 ERα target genes and 4,154 AR target genes using ChIP-Seq. Using liver-specific ERα or AR knockout mice, we further identified direct and functional target genes of ERα (123 genes) and AR (151 genes) that contribute to hepatic sexual dimorphism. We also found that the most significant sexually dimorphic gene expression was initiated at birth by comparing hepatic gene expression data from the embryonic stage E10.5 to the postnatal stage P60 during liver development. Overall, our study indicates that sex hormone receptor signaling drives sexual dimorphism of hepatic gene expression throughout liver development.