SCIENTIFIC SEMINAR

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A sex-genotype interaction drives fatty liver disease susceptibility in women

Fatty liver disease (FLD) caused by metabolic dysfunction is the leading cause of liver disease and the prevalence is rising, especially in women. Although during reproductive age women are protected against FLD, for still unknown and understudied reasons some develop rapidly progressive disease at the menopause. The patatin-like phospholipase domain-containing 3 (PNPLA3) p.I148M variant accounts for the largest fraction of inherited FLD variability. In the present study, we show that there is a specific multiplicative interaction between female sex and PNPLA3 p.I148M in determining FLD in at-risk individuals and in the general population. In individuals with obesity, hepatic PNPLA3 expression was higher in women than in men and in mice correlated with estrogen levels. In human hepatocytes and liver organoids, PNPLA3 was induced by estrogen receptor-α (ER-α) agonists. By chromatin immunoprecipitation and luciferase assays, we identified and characterized an ER-α-binding site within a PNPLA3 enhancer and demonstrated via CRISPR–Cas9 genome editing that this sequence drives PNPLA3 p.I148M upregulation, leading to lipid droplet accumulation and fibrogenesis in three-dimensional multilineage spheroids with stellate cells. These data suggest that a functional interaction between ER-α and PNPLA3 p.I148M variant contributes to FLD in women.

CIC bioGUNE
MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

EXCELENCIA SEVERO OCHOA

Friday
January 26
Atrio 800
12.00H

BRTA
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