A PUTATIVE ENHANCER REGION ACTIVATED BY METFORMIN OVERLAPS WITH SNPS ASSOCIATED WITH VISTAFIN/NAMPT LEVELS

Lídia Lana Ferreira Coura, Marcelo Rizzatti Luizon, Daniela Alves Pereira

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Abstract

Nicotinamide phosphoribosyltransferase (NAMPT) is an adipocytokine with a potential to be a predictive biomarker or a therapeutical target for several diseases, such as nonalcoholic fatty liver disease, type 2 diabetes mellitus, and obesity. Notably, NAMPT was shown to be activated by Metformin, which is the first-line therapy for type 2 diabetes, and is also used as a treatment for other diseases. The single nucleotide polymorphism (SNP) rs1319501 is located in the promoter region of NAMPT gene, and it was found to be associated with plasma NAMPT levels. Notably, the SNPs rs9770242 and rs61330082, which are located 1, 500bp upstream from the transcription start site of NAMPT gene, were in high linkage disequilibrium with the rs1319501 in the European (CEU) population. Moreover, rs61330082 was associated with visfatin/NAMPT levels and adverse cardiometabolic parameters in a cohort of severely obese children. However, whether these noncoding SNPs overlap with active regulatory elements, such as enhancers, is unknown. Therefore, we searched for metformin-responsive regulatory elements in the NAMPT locus, and linked SNPs within them which may be associated with NAMPT levels. First, we examined publicly available ChIP-seq data for active (H3K27ac) and silenced (H3K27me3) histone marks on human hepatocytes treated with metformin, GeneHancer to identify active regulatory elements (enhancers and promoters), and several cis-regulatory elements assignment tools from the Encyclopedia of DNA Elements (ENCODE) to identify enhancers around the NAMPT locus. Next, we performed the functional annotation of noncoding SNPs located in the NAMPT locus using the Genotype-Tissue Expression (GTEx) project data for SNPs linked to NAMPT expression. The SNPs rs1319501, rs9770242 and rs61330082 overlap with a metformin-responsive region enriched for the active histone mark H3K27ac upon metformin treatment, which is located nearby an enhancer element according to GeneHancer (GH07J106288). According to GTEx, the SNPs rs1319501, rs9770242 and rs61330082 are eQTLs for NAMPT expression in the heart tissue. These data support that noncoding variation within a metformin-activated enhancer may increase NAMPT gene expression. However, further studies are needed to reveal whether increased NAMPT expression may represent a beneficial effect. To understand the regulation of NAMPT expression is crucial to reveal its biological functions and the variations under physiological and pathophysiological contexts, which could help to define NAMPT as a biomarker of disease prognosis, a predictive or a pharmacogenetic biomarker. Our study highlights noncoding NAMPT SNPs for further functional studies, which could help to predict NAMPT levels in patients with type 2 diabetes mellitus treated with Metformin.

Funding:

Link to Video: