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LACTATE RESPONSIVE PROTEIN LRPGC1 REGULATES LIVER LACTATE METABOLISM THROUGH ERRγ-MEDIATED TRANSCRIPTION OF TFAM GENE

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OBJECTIVES

The metabolism of lactic acid (LA) in the liver is essential to prevent lactic acidosis, which is frequently seen in metabolic disorders and severe infection. However, the molecular mechanism through which LA regulates its own metabolism is largely unknown. In this report, we describe an LA-responsive form of metabolic regulator PGC1α, named LRPGC1, which mediates and activates liver LA metabolism.

METHODOLOGY

Subcellular dynamics of LRPGC1 was monitored by living-cell imaging. LA consumption, gene expression levels and mitochondrial activities were analyzed using the PGC1 gene knockout cells. Survival rates were measured in a mouse model of lactic acidosis which received liver-targeted siRNA or selective agonist.

RESULTS

Following LA stimulation, LRPGC1 translocates from the cytoplasm to the nucleus through deactivation of nuclear export signals, and thereby interacts with the nuclear receptor ERRγ (Estrogen-related receptor gamma) and upregulates TFAM, which ensures mitochondrial biogenesis. Knockout of PGC1 gene in HEPG2 hepatocarcinoma cells decreased LA consumption and TFAM expression, which were rescued by LRPGC1 expression. These LRPGC1-induced effects were mediated by ERRγ and mitochondrial activation. The response element for LRPGC1/ ERRγ signalling pathway was identified in a TFAM promoter. Notably, liver-targeted silencing of LRPGC1 reduced the survival of a mouse model of lactic acidosis, whereas pharmacological activation of ERRγ significantly ameliorated the survival of the mouse model.

CONCLUSIONS

Present findings demonstrate LA-responsive transactivation via LRPGC1 that highlights an intrinsic molecular mechanism for LA homeostasis. This novel therapeutic avenue may reverse life-threatening lactic acidosis via activation of LRPGC1/ ERRγ signalling pathway.