Searching for Causality of Knocking Out Txnip Is Txnip Missing in Action?

Roger A. Davis

Thioredoxin is an essential protein present in all known biological systems responsible for mediating the major pathway through which electrons are transferred from NADP(H) to protein disulfide bonds: NADP(H) + R-S-S-R' → NADP + R-SH + HS-R'. Thus, the discovery that thioredoxin-interacting protein (Txnip) bound to and inhibited thioredoxin–NADPH–dependent reduction of protein disulfides predicted that Txnip would both counter thioredoxin-mediated protection from oxidative stress and have pleiotropic physiologic influence on process dependent on proteins containing disulfide determinants of structure/function. Elegant quantitative trait loci positional cloning identified thioredoxin–NADPH–dependent reduction of protein thioredoxin-interacting protein (Txnip) bound to and inhibiting thioredoxin. In this issue of Circulation Research, Yoshioka et al describe how gene-targeted disruption of Txnip influences the response of mice to transverse aortic constriction (TAC) (ie, Txnip knockout mice displayed improved cardiac function 4 weeks after TAC but decreased cardiac function after 8 weeks). The findings that Txnip deletion caused no change in thioredoxin enzyme activity, whereas cardiac glucose uptake in Txnip knockout mice was increased led the authors to conclude that Txnip does not simply act via regulating redox state, but rather it acts as a novel metabolic regulator. This report provides several remarkably important insights regarding the function and targets of Txnip-thioredoxin.

The Txnip Knockout Mouse Model

The 2007 awardees (Mario Capecchi, Martin Evans, and Oliver Smithies) of the Nobel Prize in Physiology and Medicine “for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells” emphasizes the enormous impact that gene targeting has had in providing insights into complex physiological questions concerning the function of specific genes. Using mice lacking Txnip (mRNA and protein) expression because of gene targeting ablation of Txnip, Yoshioka et al describe how gene-targeted disruption of Txnip influences the response of mice to transverse aortic constriction (TAC) (ie, Txnip knockout mice displayed improved cardiac function 4 weeks after TAC but decreased cardiac function after 8 weeks). In response to food deprivation, the Txnip knockout mice displayed improved cardiac function 4 weeks after TAC but decreased cardiac function after 8 weeks. Microarray analysis revealed that the gene expression profile of Txnip knockout mice was different from that of wild-type mice, with a significant number of genes involved in metabolic pathways being upregulated in Txnip knockout mice. These findings suggest that Txnip plays a crucial role in regulating metabolic processes, possibly via its influence on redox state or glucose uptake. Understanding the specific molecular mechanisms by which Txnip modulates metabolic pathways will contribute to our understanding of the physiological function of redox-regulated proteins in the context of metabolic health and disease.
cysteines), the relative content of NADPH/NADH and the concentration of thioredoxin protein.

The thioredoxin enzyme activity assay used by Yoshioka et al., which uses insulin as the substrate, saturating amounts of NADPH, and the sulfhydryl-reducing reagent dithiothreitol would obscure the important complex interactions through which Txnip is likely to influence thioredoxin function and NADPH-dependent protein disulfide reduction.

Role of Txnip in Glucose Utilization

Yoshioka et al. conclude that Txnip ablation increased cardiac glucose uptake, which is in agreement with studies showing that in human skeletal muscle, Txnip regulates both the insulin-dependent and insulin-independent pathways of glucose uptake. These findings are consistent with the proposal that PTEN, a negative regulator of insulin action via Akt, is a physiologically important substrate of thioredoxin. The ability of Txnip to regulate thioredoxin-dependent NADPH reductive activation of PTEN remains a credible mechanistic link explaining its influence on glucose utilization and tumor suppression. Altered PTEN activity via Txnip ablation could also explain the altered response of hearts from Txnip knockout mice to TAC-induced pressure overload.

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Disclosures

None.

References


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