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’.1 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 on proteins containing disulfide determinants of structure/function. Elegant quantitative trait loci positional cloning identifying Txnip as the gene responsible for the hyperlipidemia associated with the murine Hyplip1 locus clearly supported this prediction.11

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 al12 show that the absence of Txnip in hearts affected their response to TAC but did not affect cardiac thioredoxin enzyme activity (or the development of fasting induced hyperlipidemia). These findings are contrary to the expectation of the authors that Txnip controls tissue redox state via inhibiting thioredoxin.12

Previous studies have shown that mice having a nonsense mutation in Txnip that deletes functional expression of Txnip protein exhibited marked hyperlipidemia caused in response to prolonged food deprivation.14 The insightful use of ketosis as a surrogate marker for hypertriglyceridemia allowed Bodnar et al to identify Txnip as the gene responsible for the Hyplip1 locus.13 Subsequent studies have shown that mice lacking Txnip expression because of gene targeting also exhibit fasting induced ketosis and hypertriglyceridemia (published previously and R.A.D., unpublished data, 2007). As noted by Yoshioka et al,12 their Txnip knockout mice do not exhibit fasting induced changes in plasma lipids and thus exhibited a metabolic phenotype distinct from other murine models lacking Txnip. Because Txnip ablation causes fasting induced hypertriglyceridemia independent of mouse strain genetic background (published previously11 and R.A.D., unpublished data), the inability of the Txnip knockout mice used by Yoshioka et al12 is unlikely to be caused by strain specific differences. Establishing the mechanistic basis for these important distinctions exhibited by the phenotype of these different Txnip knockout mice should provide valuable insights concerning the physiological function of Txnip.

Role of Txnip in Thioredoxin Function

If correct, the proposal that Txnip acts as an inhibitor of thioredoxin NADPH-dependent reduction of protein disulfides predicts that the redox state of 1 or more of the substrates for this reaction would be altered in the tissues of Txnip knockout mice. Thioredoxin has been shown to bind to the ubiquitous tumor suppressor phosphatase and tensin homolog on chromosome 10 (PTEN) (Figure).16–18 PTEN contains 2 cysteines (Cys71 and Cys124) that must remain reduced to maintain phosphatase activity.19 Oxidation of these cysteines in response to activation of tyrosine kinases associated with insulin and growth factor receptors results in the formation of a disulfide bond, inhibiting PTEN activity.20 PTEN is then reactivated by thioredoxin–NADP(H)–dependent reduction of PTEN active-site cysteines,16,17,21 NADH competitively inhibits thioredoxin–NADPH–dependent reactivation of PTEN.21 Thus, in vivo, thioredoxin function is influenced by the cellular content of Txnip (as well as other proteins that form disulfide links to thioredoxin active site...
cysteines), the relative content of NADPH/NADH and the concentration of thioredoxin protein.

The thioredoxin enzyme activity assay used by Yoshioka et al.10,22 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.12 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.23 These findings are consistent with the proposal that PTEN, a negative regulator of insulin action via Akt,24 is a physiologically important substrate of thioredoxin. The ability of Txnip to regulate thioredoxin-dependent reductive activation of PTEN remains a credible mechanistic link explaining its influence on glucose utilization and tumor suppression.25–27 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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None.

References


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