## S19-2 Two Lines of Defense against Oxidative Stress Mediated by Selenoproteins and Nrf2

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The selenocysteine tRNA ($tRNA^{Sec}$) molecule is the sight of synthesis for the amino acid selenocysteine and the adaptor for its translational insertion into selenoprotein enzymes, the majority of which contribute to cellular redox homeostasis. We generated a conditional knockout mouse line for the selenocysteine tRNA gene, *Trsp*, to examine the consequences of selenoprotein depletion on the oxidative environment of the cell. Deletion of *Trsp*, in either macrophage or liver, elevated oxidative stress and activated the transcriptional induction of cytoprotective antioxidant and detoxification enzyme genes including the well-known target genes of Nrf2. Simultaneous disruption of *Trsp* and *Nrf2* severely compromised the cytoprotective response. Mice carrying a liver specific deletion of *Trsp,* on an *Nrf2*-null background, experienced hepatocellular apoptosis and displayed a severely reduced survival rate over loss of *Trsp* alone, demonstrating that reduced selenoprotein activity is counter-balanced by an Nrf2-mediated cytoprotective response, which is essential for maintaining cellular redox homeostasis and viability. This study thus provides conclusive evidence for the compensatory function of individual stress response pathway, and the Nrf2 and selenoprotein systems are both essential for the cytoprotection against oxidative stress.