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REGULATION OF INTRACELLULAR CYSTINE REDUCTION AND PROTEIN CYSTEINYLATION

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The reduction of intracellular cystine to yield cysteine is critical for protein or glutathione synthesis and many other important biological processes, but its regulation is still unknown. We have shown that the thioredoxin-related protein of 14 kDa (TRP14) is the rate-limiting enzyme for intracellular cystine reduction. Upon TRP14 deficiency, cysteine synthesis through the transsulfuration pathway becomes the major source of cysteine in human cells, and knockout of both pathways is lethal in *C. elegans* subjected to proteotoxic stress. TRP14 can also reduce protein cysteinylation. However, paradoxically TRP14 knock-out mice were protected in acute pancreatitis through activation of Nrf2 and upregulation of the transsulfuration pathway, thus exhibiting less inflammatory infiltrate and edema. Therefore, TRP14 seems to be the enzyme principally responsible for intracellular cystine reduction, and it is also able to regulate protein cysteinylation together with thioredoxin 1.