Abstract

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Adaptive dysfunction of selenoproteins from the perspective of the triage theory: why modest selenium deficiency may increase risk of diseases of aging.

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BACKGROUND: The triage theory proposes that modest deficiency of any vitamin or mineral (V/M) could increase age-related diseases. V/M-dependent proteins required for short-term survival and/or reproduction (i.e., "essential") are predicted to be protected on V/M deficiency over other "nonessential" V/M-dependent proteins needed only for long-term health. The result is accumulation of insidious damage, increasing disease risk.

OBJECTIVE AND METHODS: We successfully tested the theory against published evidence on vitamin K. Here, we review about half of the 25 known mammalian selenoproteins; all of those with mouse knockout or human mutant phenotypes that could be used as criteria for a classification of essential or nonessential. Five selenoproteins (Gpx4, Txnrd1, Txnrd2, Dio3, and Sepp1) were classified as essential and 7 (Gpx1, Gpx 2, Gpx 3, Dio1, Dio2, Msrb1, and SelN) nonessential.

FINDINGS: On modest selenium (Se) deficiency, nonessential selenoprotein activities and concentrations are preferentially lost, with one exception (Dio1 in the thyroid, which we predict is conditionally essential). Mechanisms include the requirement of a special form of tRNA sensitive to Se deficiency for translation of nonessential selenoprotein mRNAs except Dio1.

CONCLUSIONS: The same set of age-related diseases and conditions, including cancer, heart disease, and immune dysfunction, are prospectively associated with modest Se deficiency and also with genetic dysfunction of nonessential selenoproteins, suggesting that Se deficiency could be a causal factor, a possibility strengthened by mechanistic evidence. Modest Se deficiency is common in many parts of the world; optimal intake could prevent future disease.

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