Title:	Dithiothreitol causes toxicity in C. elegans by modulating the methionine-homocysteine cycle.
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Abstract:	The redox reagent dithiothreitol (DTT) causes stress in the endoplasmic reticulum (ER) by disrupting its oxidative protein folding environment, which results in the accumulation and misfolding of the newly synthesized proteins. DTT may potentially impact cellular physiology by ER-independent mechanisms; however, such mechanisms remain poorly characterized. Using the nematode model Caenorhabditis elegans, here we show that DTT toxicity is modulated by the bacterial diet. Specifically, the dietary component vitamin B12 alleviates DTT toxicity in a methionine synthase-dependent manner. Using a forward genetic screen, we discover that loss-of-function of R08E5.3, an S-adenosylmethionine (SAM)-dependent methyltransferase, confers DTT resistance. DTT upregulates R08E5.3 expression and modulates the activity of the methionine–homocysteine cycle. Employing genetic and biochemical studies, we establish that DTT toxicity is a result of the depletion of SAM. Finally, we show that a functional IRE-1/XBP-1 unfolded protein response pathway is required to counteract toxicity at high, but not low, DTT concentrations.
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