Title:	Metabolism of long-chain fatty acids affects disulfide bond formation in escherichia coli and activates envelope stress response pathways as a combat strategy
Authors:	Jaswal, Kanchan (/jspui/browse?type=author&value=Jaswal%2C+Kanchan) Shrivastava, M. (/jspui/browse?type=author&value=Shrivastava%2C+M.) Roy, D. (/jspui/browse?type=author&value=Roy%2C+D.) Agrawal, S. (/jspui/browse?type=author&value=Agrawal%2C+S.) Chaba, Rachna (/jspui/browse?type=author&value=Chaba%2C+Rachna)
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Abstract:	The envelope of gram-negative bacteria serves as the first line of defense against environmental insults. Therefore, its integrity is continuously monitored and maintained by several envelope stress response (ESR) systems. Due to its oxidizing environment, the envelope represents an important site for disulfide bond formation. In Escherichia coli, the periplasmic oxidoreductase, DsbA introduces disulfide bonds in substrate proteins and transfers electrons to the inner membrane oxidoreductase, DsbB. Under aerobic conditions, the reduced form of DsbB is re-oxidized by ubiquinone, an electron carrier in the electron transport chain (ETC). Given the critical role of ubiquinone in transferring electrons derived from the oxidation of reduced cofactors, we were intrigued whether metabolic conditions that generate a large number of reduced cofactors render ubiquinone unavailable for disulfide bond formation. To test this, here we investigated the influence of metabolism of long-chain fatty acid (LCFA), an energy-rich carbon source, on the redox state of the envelope. We show that LCFA degradation increases electron flow in the ETC. Further, whereas cells metabolizing LCFAs exhibit characteristics of insufficient disulfide bond formation, these hallmarks are averted in cells exogenously provided with ubiquinone. Importantly, the ESR pathways, Cpx and σE, are activated by envelope signals generated during LCFA metabolism. Our results argue that Cpx is the primary ESR that senses and maintains envelope redox homeostasis. Amongst the two ESRs, Cpx is induced to a greater extent by LCFAs and senses redox-dependent signal. Further, ubiquinone accumulation during LCFA metabolism is prevented in cells lacking Cpx response, suggesting that Cpx activation helps maintain redox homeostasis by increasing the oxidizing power for disulfide bond formation. Taken together, our results demonstrate an intricate relationship between cellular metabolism and disulfide bond formation dictated by ETC and ESR, and provide the basis for examining whether similar mechanisms control envelope redox status in other gram-negative bacteria.
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