Title:	Understanding the interconnection between carbon metabolism, electron transport chain and envelope redox homeostasis in Escherichia coli
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Abstract:	Escherichia coli, a common gut microbe, can utilize a wide variety of fermentable and non- fermentable carbon sources (NFCs) for heterotrophic growth. In contrast to fermentable carbon sources, growth on NFCs requires the optimal functioning of electron transport chain (ETC) for energy production. Because different NFCs enter central metabolism at different steps and theoretically generate varied amounts of reduced cofactors, even amongst NFCs, there could be a difference in the requirement of ETC components. Besides a fundamental understanding, the information on the requirement of ETC components for growth on different NFCs can be exploited to manipulate commensal/ pathogenic E. coli strains. Here, we performed a comparative analysis of the existing high-throughput datasets of genetic screens of the single-gene deletion library of E. coli K-12 on multiple carbon sources. Our results showed that the requirement of ETC components for growth is inversely correlated with the energy yield of NFCs; however, the requirement of ubiquinone, a lipid-soluble electron carrier in the ETC, is highest for growth on long-chain fatty acids (LCFAs), an energy-rich NFCs. Our detailed analysis revealed that besides its electron carrier function in the ETC, ubiquinone functions as a key antioxidant during LCFA metabolism. Besides transferring electrons generated by carbon metabolism, ubiquinone plays a pivotal role in taking up electrons from the disulfide bond-forming machinery, which catalyzes disulfide bond formation in the oxidizing environment of the envelope compartment. Because metabolism and disulfide bond formation converge at ubiquinone in the ETC, it is plausible that metabolic conditions that generate a large number of reduced cofactors render ubiquinone unavailable for disulfide bond formation. Disulfide bonds are required for the activity of several proteins including virulence factors, therefore, understanding the interconnection between carbon metabolism and disulfide bond formation is of tremendous importance to envision how carbon metabolism impacts bacterial survival and pathogenesis. In this direction, we investigated the influence of metabolism of LCFA on the redox state of the envelope. We found that LCFA-utilizing cells exhibit characteristics of insufficient disulfide bond formation; these hallmarks are averted in cells exogenously provided with ubiquinone. Importantly, the envelope stress response (ESR) pathways, Cpx and σ E , are activated by envelope signals generated by LCFA metabolism with Cpx being the primary ESR that monitors problems in disulfide bond formation. Taken together, our results demonstrate an intricate relationship between carbon 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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