Abstract

Long-chain fatty acids (LCFAs) are a rich source of metabolic energy for several bacteria including many important pathogens. Because LCFAs also induce oxidative stress, which may be detrimental to bacterial growth, it is imperative to understand the reason for such stress and the strategies employed by bacteria to counteract it. Here, we investigated the above issues in the model bacterium, *Escherichia coli*, where the pathway of LCFA transport and degradation has been extensively characterized. We established that LCFA uptake and degradation is the reason for LCFA-mediated oxidative stress. We proposed that the large amount of reduced cofactors produced during LCFA metabolism increase electron flow in the electron transport chain (ETC) that contributes to elevated levels of reactive oxygen species (ROS). Our results that NADH/NAD+ ratio and the activity of ETC complexes I and II increase in LCFA-utilizing cells provides support to the above proposal. A high-throughput genetic screen on oleate (a C-18 LCFA), using the single-gene deletion library of *E. coli*, revealed that ubiquinone, an electron carrier in the ETC, is highly required for growth in LCFAs. Our detailed genetic and biochemical experiments showed that the increased requirement of ubiquinone on oleate is to counter elevated levels of ROS generated by LCFA degradation. Additionally, we showed that among various oxidative stress combat players in *E. coli*, ubiquinone is the major antioxidant during LCFA metabolism and acts as the cell's first line of defense against LCFA-induced oxidative stress. Interestingly, we find that whereas LCFA degradation generates ROS, it also provides a signal for ubiquinone accumulation. Thus, a feedback loop likely prevents excessive ROS formation during growth in LCFAs. In my talk, I will discuss possible mechanisms by which ubiquinone counteracts ROS during LCFA metabolism. Collectively, our work provides a rationale for investigating the role of ubiquinone as an antioxidant in LCFA-utilizing pathogenic bacteria. Importantly, during the course of our investigation, we identified a novel ubiquinone biosynthetic player and showed its genetic interaction with genes previously known to be involved in this pathway.