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Microbes Influencing Mitochondrial Function

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Abstract
The powerhouse of eukaryotic cells or the mitochondrion is a membrane bound organelle with several unique features differentiating it from other organelles. They have their own independent genome, their numbers vary widely by organism and tissue type, and in addition to supplying energy in the form of ATP, mitochondria is also the site of signaling for many cellular processes from growth and differentiation to cell cycle and cell death. Dysfunction of mitochondria has been implicated in many mitochondrial diseases as well as cardiac dysfunction and aging. Liu et al (Ying, Buck et al. 2014) demonstrate novel effects of microbial metabolites on the activation of surveillance pathways in mitochondria in nematode worms in order to initiate mitochondrial repair. Human physiology also relies on complex interactions with multiple species of microbes and perhaps also uses similar tactics to respond and change the behavior of our cells.

Keywords: drug metabolism and detoxification, mitochondrial repair, microbial stress, pathogen response

Caenorhabditis elegans exist in rich microbial environments and their mitochondria are targeted by many bacterial species for its rich contents of iron (heme and sulphur proteins) that is necessary for bacterial growth. In fact, disruptions in *C. elegans'* mitochondrial function gets interpreted as a xenobiotic or pathogenic attack and results in induction of several drug-detoxification and metabolizer genes such as cytochrome P450 (*cyp-14A3*), ugt-61, and Pseudomonas pathogen response gene *igr-1*.
Mitochondrial stress induction is further accompanied by an increase in hsp-6p gene expression. Both hsp-6p levels and the nuclear versus mitochondrial localization of transcription factor ATFS-1 that induces *hsp-6p* levels during mitochondrial stress can be used as a read-out of defense against stress. As a consequent of mitochondrial stress, ATFS-1 localization in the nucleus gets favored. Interestingly, the disruption of mitochondria has been associated with many diseases from aging and neurodegeneration to cancer in humans as well; therefore, understanding the mechanism behind this stress in *C. elegans* response can help us learn more about human pathophysiology.

This protective defense pathway is also measured by the activation of mitochondrial unfolded protein response (UPR^{mt}). UPR^{mt} is generally initiated by diverse stimuli from disruptions in protein homeostasis, enzymes, and metabolites.
In their manuscript, Liu et al identifies two unique intracellular metabolic pathways that are required for UPR^{m} induction. These findings are enabled through a genome-wide RNAi screen for genes that are important to initiate response to mitochondrial dysfunction (for example *hsp-6p* and *ugt-61*). The first gene whose inactivation through RNAi screen disrupted response to mitochondrial dysfunction was *sptl-1* which encodes serine palmitoyltransferase in the sphingolipid biosynthesis pathway. This pathway is responsible for the production of ceramide, a lipid found in cell membrane and involved in physiological responses to cell death and mitochondrial degradation. *Sptl-1* ablated animals were unable to sense microbial attach and activate the mitochondrial surveillance

pathway under microbial stress. More specifically, among the different isoforms of ceramides, C24 was the only form that rescued this deficiency of mitochondrial surveillance.

The second gene belonged to the mevalonate pathway since statin treatments (human cholesterol-lowering drugs that inhibit mevalonate pathway) abrogated the animal's ability to respond to mitochondrial damage and activate UPR^{mt}. The induction of UPR^{mt} in response to malvonate depletion is similar in yeasts as well (Rauthan, Ranji et al. 2013). Therefore, the induction of ceramide and mevalonate and their localization to sites of injury show that they are two key components of mitochondrial surveillance pathway and likely targets of microbial toxins and virulence factors.

Alternately, Liu et al also reported that forcing the ATFS-1 into the nucleus from the mitochondria can induce UPR^{mt} and rescue the protective response under blocked sphingolipid pathway conditions. In addition, forcing ATFS-1 into the nucleus also protected the worms from harmful effect of statins. These data point to the important regulatory role of ATFS-1 and its disruption in these two metabolic pathways during microbial stress. What exactly causes ATFS-1 stabilization, degradation, and transportation out of the nucleus under microbial stress is however unknown and unanswered, Figure 1 schematic.

Statins are clinically used to reduce cholesterol by inhibiting its biosynthesis through the mevalonate pathway as well as other human diseases. However, there are several reported statin-induced side effects that include liver toxicity and myopathy. Therefore, the findings from this study, i.e. the mitochondrial connection, can be influential in our understanding of side effects and related therapies. In addition, identifying these bacterial metabolites can have therapeutic potentials in treatment of mitochondrial diseases, dysregulated detoxification, and innate immunity.

Figure 1

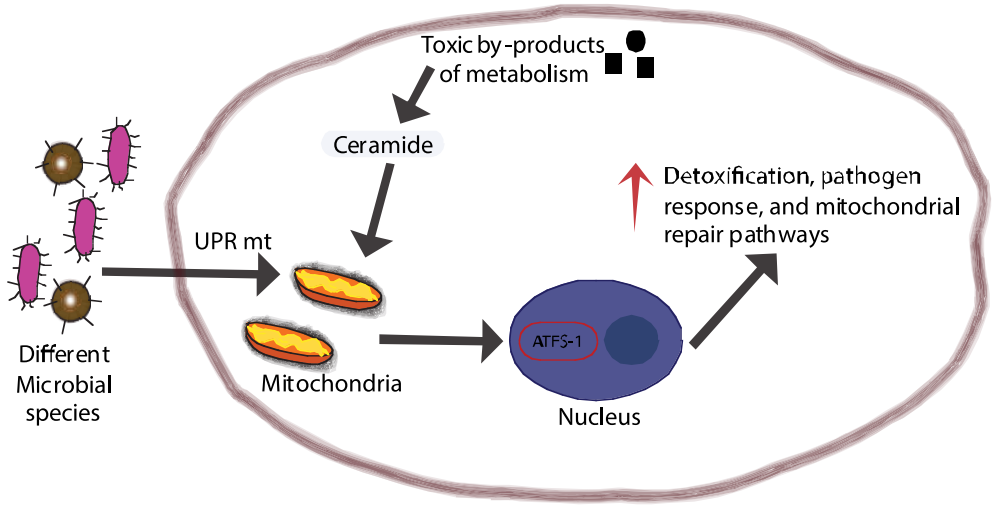

Figure 1. Schematic illustration of microbial and metabolite stress on mitochondrial response. Upon exposure of cells to various types of microbial species and the toxic by-products of metabolism, the protective mitochondrial response (UPR^{mt}) to such metabolites is induced. This occurs through ATFS-1 translocation to the nucleus that turns mitochondrial repair pathways as well as detoxification and pathogen response signaling. Liu et al shows that two intracellular pathways, mevalonate pathway and

ceramide biosynthesis. Cholesterol-lowering drug called statin can inhibit the products of the two pathways, shedding light on further therapeutic potentials.

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