Inhibition of the mevalonate pathway in *C. elegans*: Consequences and implications

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Abstract

The mevalonate pathway in human is responsible for the synthesis of cholesterol and other important biomolecules such as coenzyme Q (a component of the electron transport chain in mitochondria), dolichols (important for N-linked glycosylation of proteins) and isoprenoids (important for the membrane association of small GTPases). This thesis concerns novel findings about the effect of statin on the mevalonate pathway using *C. elegans* as a model organism.

Statins are cholesterol-lowering drugs that inhibit HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway, hence limiting the synthesis of cholesterol and other products from this pathway. *C. elegans* is a particularly powerful model to study the effect of statin on the non-cholesterol outputs of the mevalonate pathway because this pathway is well conserved in worms except for the key fact that the enzymes required for the synthesis of cholesterol are absent. We characterized a *hmgr-1(tm4368)* mutant, which lacks HMG-CoA reductase, and showed that its phenotypes recapitulate the effect of statin on *C. elegans* but in a more severe form. We also showed that inhibition of protein prenylation is a critical consequence of mevalonate pathway inhibition in *C. elegans.*

Since inhibition of the mevalonate pathway, via statins or *hmgr-1* mutation causes growth arrest and sterility, it is relatively easy to screen for resistant mutant. We screened ~150,000 mutagenized haploid genomes and isolated four statin-resistant mutants that carried gain-of-function mutations in *atfs-1*, a positive regulator of the mitochondrial-unfolded protein response (UPR^{mt}). Interestingly, preinduction of this response using ethidium bromide or paraquat in wild type worms or mammalian cells also conferred resistance to statin. Our observations suggest that statin resistance through maintenance of mitochondrial homeostasis is conserved among species, and that the lethal effect of statins in *C. elegans* are caused primarily through impaired protein prenylation leading to mitochondria dysfunction.

We also isolated an additional statin-resistant mutant that carried a partial loss-of-function mutation in *nduf-7,* which encodes a key component of the mitochondrial transport chain complex1 (ETC-1). This mutation also activates the UPR^{mt} and prolonged life span through production of ROS. Interestingly, the gene *ced-4* is required for lifespan extension in the *nduf-7(et19)* mutant but not for UPR^{mt} induction or resistance to statin.

Keywords: *C. elegans,* mevalonate, *atfs-1*, UPR^{mt}, prenylation, *nduf-7*, *ced-4*.

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