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 (UPRmt). 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 UPRmt 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 UPRmt induction or resistance to statin.
Keywords: C. elegans, mevalonate, atfs-1, UPRmt, prenylation, nduf-7, ced-4.