

DOES MTHSP70 OVEREXPRESSION INHIBIT p53-DEPENDENT APOPTOSIS IN MICE?

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The mitochondrion is central to several aging theories, therefore mitochondrial maintenance is believed to be integral to extension of lifespan. Whether aging is due to accumulation of oxidative damage or apoptosis within the mitochondrion is not known. Increased levels of apoptosis have led to premature aging models such as the mutant p53^{+m} mice and the Ku80 deficient mice, in contrast, mouse models that have decreased levels of apoptosis, such as the p66^{Shc} deficient mouse, are long-lived. A mitochondrial maintenance gene, mitochondrial heat shock protein of 70kDa (*mthsp70*) is essential and a member of the highly conserved HSP70 family. MTHSP70 localizes to the mitochondrion where it functions in protein translocation, folding and degradation of damaged/misfolded proteins. MTHSP70 inhibits p53 transactivation of target genes and prevents p66^{Shc}-mediated events leading to apoptosis, thus MTHSP70 is believed to be an apoptotic antagonist. Previous work in human diploid fibroblasts and in *C.elegans* has shown that overexpression of the gene *mthsp70* extends lifespan and at least in the case of fibroblasts this involves the inhibition of p53's transactivation activity. We have created a *mthsp70* genomic BAC transgenic mouse line to determine whether the lifespan extension observed in *C.elegans* and human fibroblast is also seen in mammals. Treatment of mice with the anti-cancer drug doxorubicin induces p53-dependent apoptosis, particularly in the heart, intestine, liver and spleen. RT-PCR has shown that *mthsp70* overexpression blunts the response of several p53 target genes within 24 hours in the heart of doxorubicin-injected mice. Results will be presented on extent of apoptosis via TUNEL assay and cleaved caspase-3 western, as well as, the structural damage to mitochondria via electron microscopy and the protein damage via protein conformational westerns. It will be intriguing to test if *mthsp70* is a lifespan determinant in mammals and whether the mode of action is through the inhibition of apoptosis and/or the protection of damaged mitochondrial proteins.