GENETIC MODIFIERS AND LIFESPAN EXTENSION OF MN SUPEROXIDE DISMUTASE (MNSOD) MUTANT MICE

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Mn superoxide dismutase (MnSOD) is encoded by a nuclear gene (*Sod2*) and transported into the matrix of mitochondria to protect the organelle from superoxide damage. Mutant mice (*Sod2*-/-^{tm1}Cje) deficient in MnSOD have increased mitochondrial superoxide radicals, accelerated tissue damage, and a short survival time. A strong correlation exists between the survival time and the genetic background of the mutant mice. Thus, congenic *Sod2*-/- mice on a C57BL/6J (B6) background develop dilated cardiomyopathy and the majority of them die around embryonic day 15 (E15). Those that survive to term usually die within 24 hours after birth. On the other hand, congenic *Sod2*-/- mice generated on a DBA/2J (D2) background develop normally through gestation and do not have dilated cardiomyopathy. However, these mice develop severe metabolic acidosis and have an average lifespan of 8 days. Interestingly, the F1 mice (B6D2F1 *Sod2*-/-) generated from the two parental strains have a cardiac phenotype similar to that of the D2 *Sod2*-/- mice, but with a milder form of metabolic acidosis. Consequently, the mice are able to survive for 3 weeks without any pharmacological intervention.

The phenotypic variation of *Sod2*-/- mice on different genetic backgrounds suggests that genetic modifiers that co-segregate with the long-lived population in D2 and B6D2F1 backgrounds have the ability to minimize mitochondrial damage caused by MnSOD deficiency, and consequently prolonging the lifespan of the mutant mice. To isolate and identify the chromosome regions containing potential genetic modifiers for *Sod2*-/- mice, we carried out serial backcross (introgress) of D2 *Sod2* mice into B6 background for 5 generations. The study results showed that (1) the segregation and mean lifespans of *Sod2*-/- mice from each backcross generation remained stable; (2) the lifespans of *Sod2*-/- mice from each backcross generation were not significantly different from that of D2 *Sod2*-/- mice; and (3) the bimodal lifespan distribution was consistent with the inheritance of two independently segregating genes with dominant effects.

A genome-wide scan using 217 informative MIT markers (average distance 6.7 cM) with 17 short-lived (mean lifespan = 0.5 ± 0.3 days) and 28 long-lived (average lifespan = 11.4 ± 1.0 days) N5-N6 *Sod2*-/- mice identified the distal region of chromosome 13 to be the strongest QTL, and chromosome 10 to be a weaker association. Interrogation of transcripts in the chromosome 13 region identified a genetic defect in the gene encoding nicotinamide nucleotide transhydrogenase (*Nnt*) in B6. The genetic defect is most likely due to a deletion at the genomic level, resulting in truncated mRNA and an extremely low level of NNT protein in B6 tissues. NNT is located in the inner membrane of mitochondria and maintains the reduction of NAD(P)H in a reaction that is coupled to transmembrane proton translocation. Based on the evidence for the chromosomal location and the genetic defect of the gene in B6 and the subcellular location and the function of the protein, *Nnt* is a strong candidate for the genetic modifier for lifespan extension in *Sod2*-/- mice.