Biological Benefit of mCAT

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Background

Aging is a natural pervasive process that is complex and multifactorial; therefore, controversy exists over the root cause(s) of aging. The free radical theory of aging (FTRA) posits that the toxic build-up of free radicals and reactive oxygen species (ROS), promotes oxidative stress therefore enhancing aging. Normal metabolic processes within cells produce free radicals and ROS. To detoxify these oxidants, cells also produce a variety of antioxidants. Extensive research links increased oxidants and reduced antioxidant buffering capacity with aging. Limiting the study of oxidative stress in naturally aged mice is the burdensome time and cost limitations. To alleviate these burdens, the Niedernhofer Lab routinely uses *Ercc1*$^{-/\Delta}$ mice. These progeroid mice are lacking a critical DNA repair enzyme and are thus unable to repair damaged DNA and that accumulates in an age-dependent manner. In hopes to better understand how free radicals and ROS limit mammalian lifespan, human catalase was targeted to the mitochondria (mCAT) of cells. The mCAT transgene was shown to reduce ROS and H_2O_2 production and associated with the longevity of mammals. The mCAT transgene was bred into the *Ercc1*$^{-/\Delta}$ background, to determine if the mCAT delays the accelerated aging phenotype observed in *Ercc1*$^{-/\Delta}$ mice. *I hypothesize that exogenous expression of the mCAT transgene will alleviate the age related symptoms progeroid Ercc1*$^{-/\Delta}$ *mice experience.*

ERCC1-XPF nuclease and aging

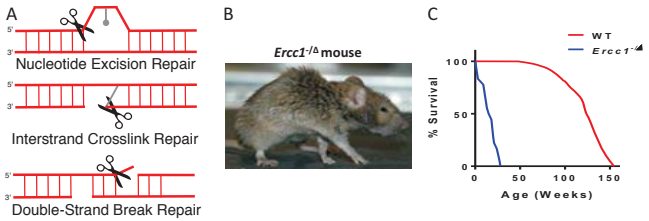

Figure 1. (A) DNA repair pathways that ERCC1-XPF nuclease complex participates in. (B) Reduced expression of ERCC-1-XPF results in the early appearance of many age-related phenotypes and (C) reduced lifespan.

Analysis of mCAT and senescence marker expression in progeroid mice

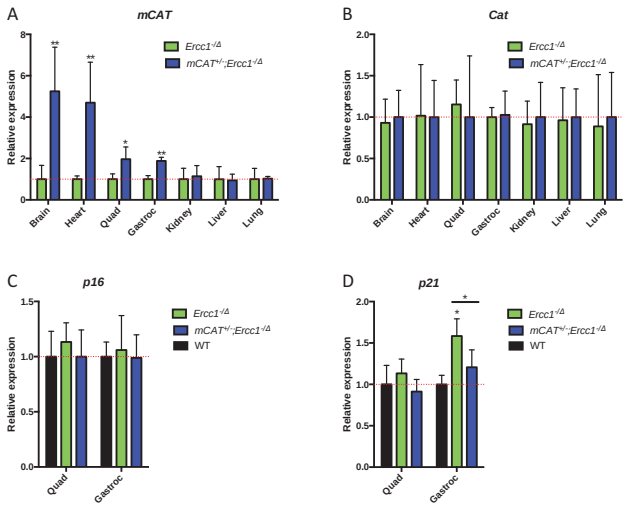

Figure 2. RNA isolated from 15-18 week old mice to measure expression of (A) human and (B) mouse catalase and (C-D) senescence markers *p16* and *p21* in tissues by qPCR. Expression was quantified and normalized to WT mice (red line) using *Gapdh* expression as a housekeeping control. Expression of mCAT was limited to brain and muscle tissues and senescence was not present in muscle of mice.

Body composition analysis

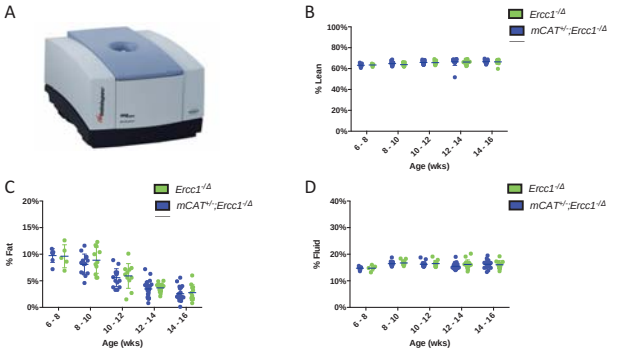

Figure 3. (A) Bruker minispec mq-one SFC analyzer used to collect nuclear magnetic resonance (NMR) data. (B-D) As *Ercc1*$^{-/\Delta}$ and *mCAT*$^{+/-}$*;Ercc1*$^{-/\Delta}$ mice age, (B) percent lean mass remains relatively constant, (C) percent fat decreases, and (D) percent fluid mass remains relatively constant except for slightly lower values in the 6-8 week cohort (which is expected since the mice are smaller).

Analysis of muscle performance and healthspan

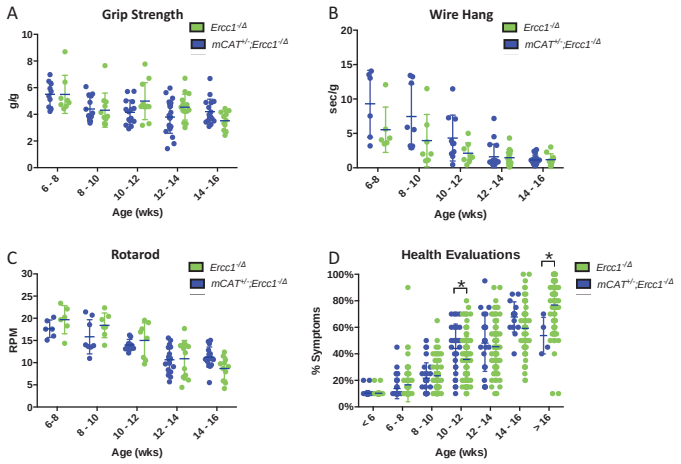

Figure 4. (A) Grip strength was similar between *Ercc1*$^{-/\Delta}$ mice and *mCAT*$^{+/-}$*;Ercc1*$^{-/\Delta}$ mice. (B-C) No significant rescue was seen in the wire hang or the rotarod; however, as both groups of the mice age, (B) the time the mice spend on the wire grid decreases and (C) the rotations per minute decrease. (D) *mCAT*$^{+/-}$*;Ercc1*$^{-/\Delta}$ mice show significant reduction of age-related symptoms compared to *Ercc1*$^{-/\Delta}$ mice once mice are older than 16 weeks.

Conclusion

- mCAT transgene expression was limited to the brain and muscle tissue.
- Senescence was not present in the muscle of progeroid mice.
- There were no significant differences within the physiology or the physical phenotypes of the mice.
- Overall, mCAT expression did not significantly alleviate the age related symptoms of progeroid *Ercc1*$^{-/\Delta}$ mice.

References

"Extension of Murine Life Span by Overexpression of Catalase Targeted to Mitochondria" PMID: 15879174

"A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis" PMID: 17183314

"Physiological Consequences of Defects in Ercc1$^{-/\Delta}$ XPF DNA Repair Endonuclease" PMID: 21612988