disorders such as Leigh Syndrome. This session explores the similarities and differences between normative aging and mitochondrial disease and the potential for interventions to positively impact both conditions.

AGING AND MITOCHONDRIAL DISEASE: SHARED MECHANISMS AND THERAPIES?

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Mitochondrial disease describes multiple pathologies characterized by a wide array of disease symptoms and severity, caused by mitochondrial dysfunction in one or multiple organs. Aging organisms display a similar variety of disease phenotypes, which are often characterized by mitochondrial impairment. Despite the heterogeneity of aging phenotypes, several interventions have been identified which can increase lifespan and delay the onset of age-related diseases in multiple organisms. Two age-delaying interventions, rapamycin and acarbose, dramatically suppress pathology in a mouse model of mitochondrial disease caused by depletion of the NADH-Ubiquinone Oxidoreductase Complex (Ndufs4-/-). This model recapitulates human Leigh syndrome, a childhood mitochondrial disease. Upon treatment with either drug, disease suppression is accompanied by a remodeling of nutrient metabolism and restoration of the NAD+/NADH ratio in the brain without affecting the electron transport chain. Thus, we propose that metabolic derangements induced by mitochondrial dysfunction may be a shared mechanism of aging and mitochondrial disease.

TURNING THE OXYGEN DIAL AS A THERAPY: HYPOXIA TREATMENT FOR MITOCHONDRIAL DYSFUNCTION

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Mitochondrial disease affects 1 in 4800 live births, with little in the way of therapies. We found that chronic hypoxia extends the life of a Complex 1 disease model by 5-fold. Starting hypoxia therapy at a late-stage of disease can even reverse the MRI-detectable lesions. At the other extreme, mild hyperoxia greatly exacerbates disease and leads to death within several days. These findings have now led to a phase 1 clinical trial in healthy volunteers, with the ultimate goal of human translation. We believe we have identified a new mode of treatment that will be broadly applicable to different forms of mitochondrial dysfunction, ranging from rare inborn errors of metabolism to more common, age-associated pathologies. We believe that "turning the oxygen dial" to low or high oxygen will serve as a novel therapeutic for a range of conditions in the coming years.

MITOCHONDRIA AS REVERSIBLE REGULATORS OF AGING ASSOCIATED SKIN WRINKLES AND HAIR LOSS IN MICE

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To evaluate the consequences of the decline in mtDNA content associated with aging we have created an inducible mouse model expressing, in the polymerase domain of POLG1, a dominant-negative mutation that induces depletion of mtDNA. We utilized this inducible mouse model to modulate mitochondrial function by depleting and repleting the mtDNA content. We demonstrate that, in mice, ubiquitous expression of dominant-negative mutant POLG1 leads to 1) reduction of mtDNA content in skin, 2) skin wrinkles, and 3) hair loss. By turning off the mutant POLG1 transgene expression in the whole animal, the skin and hair phenotypes revert to normal after repletion of mtDNA. Thus, we have developed whole-animal mtDNA depleter-repleter mice. These mice present evidence that mtDNA homeostasis is involved in skin aging phenotype and loss of hair and provide an unprecedented opportunity to create tissue-specific mitochondrial modulation to determine the role of the mitochondria in a particular tissue.

DOES AUGMENTATION OF MITOCHONDRIAL THIOREDOXIN REDUCTASE 2 IMPROVE METABOLIC FITNESS?

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Mitochondrial Thioredoxin Reductase (TrxR2) is a rate limiting enzyme in the mitochondrial thioredoxin system which serves as one of the major mitochondrial ROS scavenging pathways. Txnrd2 is also a repressor of the ASK-1 oxidative stress induced apoptotic pathway. Our group previously identified a correlation with the expression of this protein and long-lived species and its overexpression prolonged lifespan in Drosophila. We have generated a TrxR2 transgenic (T-tg) mouse which has ubiquitously heighted (two-fold) TrxR2 expression. We found that overexpression of TrxR2 leads to enhanced mitochondrial metabolism and increased resistance to mitochondrial oxidative damage in MEFs (data not shown). We also found that female T-tg mice showed a leaner trend and reduced food consumption, with improved glucose tolerance but no difference in insulin sensitivity. These mice showed a lower Oxygen consumption and CO2 production with lower energy expenditure in individual metabolic cages. We further tested their exercise capacity where T-tg mice had a similar performance to control mice. These results suggest that TrxR2 overexpression can lead to some beneficial metabolic changes that need to be further understood. (Acknowledgments to Nathan Shock Lifespan assessment Core for the help developing all these assays in mice).