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Editorial

Editorial Note on Mitochondrial Dysfunction

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EDITORIAL

Reduced expression of mitochondrial genes appears to be a highly conserved characteristic of ageing in species ranging from C. elegans to humans, according to gene expression studies. In mice, rhesus macaques, and humans, organ-specific analyses of brain ageing have shown a gradual decrease in mitochondrial gene expression. Mitochondrial role appears to be a significant modulating factor on the ageing process in all organisms studied, with either positive or negative effects on lifespan depending on the context.

Mitochondrial dysfunction is particularly common in the brain and muscle. Human mitochondrial encephalomyopathies are inherited diseases caused by mitochondrial DNA deletions or mutations. Depending on the amount of mitochondria affected per cell, these mitochondrial defects cause a variety of neurological and muscle-related problems. This reliance on the number of infected mitochondria also influences the age at which clinical symptoms appear. As a result, it's been proposed that age-related functional deficits in neurons and myocytes could be caused by a natural decline in mitochondrial function. Drosophila studies show that the orthologue of the mammalian brain-specific mitochondrial uncoupling protein UCP5 regulates metabolism and lifespan specifically in neurons. Declining mitochondrial function in the human brain can target neuronal populations with high bioenergy demands, such as the large pyramidal neurons that degenerate in Alzheimer's disease. This decreasing mitochondrial function can play a role in brain ageing and make neurons more susceptible to age-related pathology.

surprisingly, extend lifespan in some cases reduced mitochondrial function. The study of clk-1 mutant worms was one of the first to suggest this. CLK-1 is needed for ubiquinone synthesis, which is necessary for mitochondrial respiration, and clk-1 mutant worms have lower respiratory rates. These worms are also known for their long lifespans and sluggish developmental and behavioural speeds. Following that, RNA interference screens revealed that reducing the role of several genes involved in the electron transport chain would extend life. This effect appears to be dose based, as a small reduction in electron transport chain activity will lengthen lifespan while a larger reduction shortens it. Recent evidence indicates that the retrograde response, a nuclear transcriptional response to mitochondrial defects that involves the activation of oxidative stress resistance and xenobiotic detoxification genes, may be involved in this lifespan extension.

Reduced expression of electron transport chain components in adult neurons is adequate to extend lifespan in Drosophila. While Coq7 heterozygous mutant mice (the mouse orthologue of clk-1) live for a long time, this phenomenon may also occur in mammals. In fact, a mouse model with reduced activity of the cytochrome c oxidase complex, an electron transport chain portion, has a longer lifespan. Fortunately, this mouse also seems to be resistant to neuronal excitotoxicity throughout the brain. Although the signalling mechanisms mediating increased longevity in this context are unknown, one possibility is that ROS in a slightly higher concentration mediates increased longevity. In Drosophila, reduced expression of electron transport chain components specifically in adult neurons is sufficient to extend lifespan. This phenomenon may also occur in mammals, because Coq7 heterozygous mutant mice (Coq7 being the mouse orthologue of clk-1) are long lived. Furthermore, a mouse model with reduced activity of the cytochrome c oxidase complex, a component of the electron transport chain, shows increased lifespan. Intriguingly, this mouse also exhibits protection against neuronal excitotoxicity in the brain. Although the signalling mechanisms affecting increased longevity in this context are unknown, one possibility is that ROS in slightly higher concentrations act as signalling molecules, activating survival pathways and increasing lifespan.

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