Mitochondrial ROS Produced via Reverse Electron Transport Extend Animal Lifespan

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Summary

Increased production of reactive oxygen species (ROS) has long been considered a cause of aging. However, recent studies have implicated ROS as essential secondary

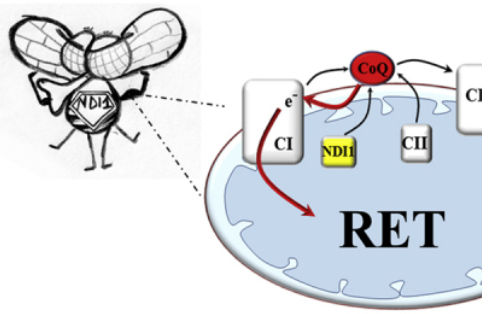
messengers. Here we show that the site of ROS production significantly contributes to their apparent dual nature. We report that ROS increase with age as mitochondrial function deteriorates. However, we also demonstrate that increasing ROS production specifically through respiratory complex I reverse electron transport extends *Drosophila* lifespan. Reverse electron transport rescued pathogenesis induced

by severe oxidative stress, highlighting the importance of the site of ROS production in signaling. Furthermore, preventing ubiquinone reduction, through knockdown of PINK1, shortens lifespan and accelerates aging; phenotypes that are rescued by increasing reverse electron transport. These results illustrate that the source of a ROS signal is vital in determining its effects on cellular physiology and establish that

manipulation of ubiquinone redox state is a valid strategy to delay aging.

Keywords: aging, coenzyme Q, electron transport chain, mitochondria, reactive oxygen species

Graphical Abstract



Introduction

Historically, mitochondrial ROS (mtROS) production and oxidative damage have been associated with aging and age-related diseases such as Parkinson's disease

(Morais et al., 2014). In fact, the age-related increase in ROS has been viewed as a cause of the aging process (Forster et al., 1996) while mitochondrial dysfunction is considered a hallmark of aging (López-Otín et al., 2013), as a consequence of ROS accumulation. However, pioneering work in *Caenorhabidits elegans* has shown that mutations in genes encoding subunits of the electron transport chain (ETC) (Dillin

et al., 2002) or genes required for biosynthesis of ubiquinone (Asencio et al., 2003, Wong et al., 1995) extend lifespan despite reducing mitochondrial function. The lifespan extension conferred by many of these alterations is ROS dependent, as reduction of ROS abolishes this effect (Lee et al., 2010, Yang and Hekimi, 2010b). Moreover, chemical inhibition of glycolysis or exposure to metabolic poisons that

block respiratory complex I (CI) (rotenone, paraquat, or piericidin A) or complex III (CIII) (e.g., antimycin A) also prolong lifespan in *C. elegans* in a ROS-dependent manner (Dillin et al., 2002, Schmeisser et al., 2013, Schulz et al., 2007, Yang and Hekimi, 2010a). Various studies have shown that ROS act as secondary messengers in many cellular pathways, including those which protect against or repair damage (Ristow and