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SEMINAR

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“Mitochondrial mediated aging is modulated by CEP-1, the C. elegans homolog of p53”

Hosts: Kristina Schoonjans and Johan Auwerx
Conference Room: SV 1717A
EPFL - Lausanne

Abstract
In this study we investigated how mitochondrial electron transport chain (ETC) dysfunction modulates longevity by engaging CEP-1, the C. elegans homolog of mammalian p53. Previous findings indicated that ETC complex III mutant isp-1(qm150) is long-lived due to a mild elevation of mitochondrial superoxide (O2-) levels (1). This mechanism is distinct from that of the long-lived coenzyme Q biosynthesis enzyme mutant clk-1(e2519), which is thought to have a general increase in antioxidant response. Our double mutant analysis showed that cep-1 is required to mediate the longevity of isp-1 but not that of clk-1, suggesting that CEP-1 might sense a slight increase in mitochondrial ROS in order to promote longevity. Also, inactivation of cep-1 by RNAi suppressed the longevity of mitochondrial superoxide dismutase mutant sod-2(ok1030) and ETC complex I mutants nuo-6(qm200). Both sod-2 and nuo-6 mutants have been shown to be long-lived due to increased mitochondrial O2- levels (1,2). While a slight increase in mitochondrial O2- is thought to promote longevity, a large elevation of mitochondrial stress is detrimental. The complex I missense mutant gas-1(fc21) and the complex II missense mutant mev-1(kn1) are both thought to be short lived because of a severe block in ETC leading to a high increase in O2- levels. Double mutant analysis showed that inactivation of cep-1 is able to rescue short-lived mev-1 and gas-1 mutants, suggesting that CEP-1/p53 is able to respond to a high elevation in mitochondrial ROS to shorten lifespan. In addition to lifespan modulation CEP-1/p53 is also involved in mitochondrial mediated growth and reproduction in worm.

To dissect the transcriptional response of CEP-1/p53 to different mitochondrial dysfunctions, we compared the expression profiles of isp-1 and mev-1 mutants with or without cep-1. Despite the opposite effect of cep-1 inactivation on the longevity of isp-1 and mev-1 mutants, the transcriptional outcomes of cep-1 inactivation in these mutants were quite similar. We further compared CEP-1 regulated genes in response to mitochondrial dysfunction to CEP-1 regulated genes in response to UV irradiation (3). Results show that CEP-1 regulates a similar set of genes upon mitochondrial dysfunction and UV irradiation. Since UV irradiation is known to induce ROS production, this finding is consistent with our model that elevation of mitochondrial ROS engages CEP-1/p53.

An intriguing observation from the expression profiling was the differential regulation of ftm-1 (ferritin-1) in mitochondrial ETC mutants. A quantitative PCR analysis confirmed that ftm-1 is induced both in isp-1 and mev-1 in a cep-1 dependent manner. Similar results were observed using Pftn-1::GFP. Ferritin regulates iron availability important in the context of mitochondrial dysfunction. Functional studies are underway to demonstrate the importance of ftm-1 in affecting longevity of mitochondrial ETC mutants.