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Lausanne Integrative Metabolism and Nutrition Alliance (LIMNA) SEMINAR

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2.00pm

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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 (0_2^-) 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 0_2^- [1,2]. While a slight increase in mitochondrial 0_2^- is thought to promote longevity, a large elevation of mitochondrial 0_2^-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 0_2^- 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 *ftn-1* (ferritin-1) in mitochondrial ETC mutants. A quantitative PCR analysis confirmed that *ftn-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 *ftn-1* in affecting longevity of mitochondrial ETC mutants.

1. Yang W, Hekimi S. A mitochondrial superoxide signal triggers increased longevity in C. elegans. PLoS Biol. 2010 Dec 7;8(12):e1000556.
2. Van Raamsdonk JM, Hekimi S. Superoxide dismutase is dispensable for normal animal lifespan. Proc Natl Acad Sci U S A. 2012 Apr 10;109(15):5785-90.
3. Derry WB, Bierings R, van Iersel M, Satkunendran T, Reinke V, Rothman JH. Regulation of developmental rate and germ cell proliferation in C. elegans by the p53 gene network. Cell Death Differ. 2007 Apr;14(4):662-70.

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