**Sirtuins as regulators of mitochondrial fitness and EVOLUTION of heart failure**

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Siurtuins are emerging as key regulators of many biological functions, spanning from cell growth, metabolism to longevity. Members of the sirtuin family need NAD for their catalytic activity. The mammalian genome encodes seven sirtuin isoforms (SIRT1-SIRT7), which are localized in different subcellular compartments. Among them SIRT3 is primarily localized in mitochondria and possesses robust deacetylase activity. Increased expression of SIRT3 has been shown to be associated with increased lifespan of humans. In mitochondria SIRT3 regulates the activity of many metabolic enzymes involved in free-fatty acid oxidation, ROS production and ATP biosynthesis. Because the function of mitochondria also depends on the fusion-fission dynamics of the organelle, this study was undertaken to study the effect of SIRT3 in regulating fitness of mitochondrial population. We found that OPA1, an inner mitochondrial fusion protein is highly acetylated in hearts undergoing pathological stress, including pressure overload hypertrophy, doxorubicin-induced cardiac toxicity and diabetic cardiomyopathy. In SIRTKO hearts mitochondrial population was generally fragmented, where OPA1 was found to be acetylated. In vitro studies showed that lysine (K) acetylation reduced the GTPase activity of OPA1. SIRT3 was capable of deacetylating and preserving the enzymatic activity of OPA1. By mass-spectrometry and mutagenesis analyses we identified K926 and K931 as acetylated sites of OPA1. Furthermore, SIRT3 overexpression prevented doxorubicin-mediated mitochondrial fragmentation and myocyte cell death by deacetylating and activating OPA1. In vivo studies conducted with SIRT3 overexpressing transgenic mice showed that SIRT3 protects the heart from developing cardiac hypertrophy, fibrosis and heart failure by preserving health of mitochondrial population. In summary, our data showed that SIRT3 promotes mitochondrial function not only by regulating activity of metabolic enzymes, but also by regulating mitochondrial dynamics by targeting OPA1. Based on this and other published data I believe that SIRT3 could be a therapeutic target for the treatment of heart failure.