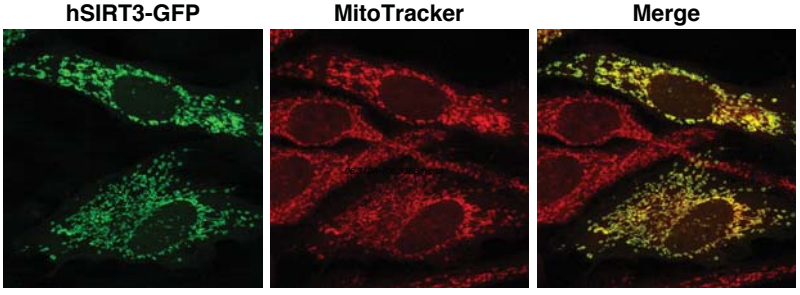
Eric Verdin, MD

Aging and Age-Associated Diseases: SIRT3 in Mitochondria

UNIQUE GENES HAVE BEEN IDENTIFIED that regulate life span. Sirtuins are protein deacetylases that regulate life span in yeast, worms, flies, and mice. Another way to increase life span is by calorie restriction. Mice consistently fed 30% fewer calories than normal live about 30% longer. Importantly, calorie restriction fails to increase life span when sirtuin genes are lacking. Short-term studies in humans indicate that calorie restriction is likely to afford the same advantages, including increased life span and decreased diabetes, cancer, atherosclerosis, and neurodegeneration with aging. Resveratrol, a polyphenolic compound in red wine, is a direct activator of a sirtuin called SIRT1. Treating mice with resveratrol increases life span and protects mice from the deleterious effects of a high-fat diet.

Our laboratory focuses on SIRT3, one of seven human sirtuin proteins. SIRT3 is located in mitochondria in mammalian cells. Mitochondria are critical in aging: they are the metabolic center of the cell and the site of production of radical oxygen species, byproducts of the respiration system that contribute to aging. We hypothesized that SIRT3 regulates acetylation levels of key mitochondrial proteins. We recently observed that SIRT3 expression is upregulated in liver and brown adipose tissues during fasting. Livers from mice lacking SIRT3 show higher levels of intermediate products of fatty acid oxidation and triglycerides during fasting associated with decreased levels of fatty acid oxidation than wildtype mice. Mass spectrometry analysis of mitochondrial proteins shows a critical enzyme in fatty acid oxidation, long-chain acyl CoA dehydrogenase (LCAD), is hyperacetylated at lysine 42 in the absence of SIRT3. LCAD is deacetylated by SIRT3 in wildtype mice under fasting conditions. Decreases in acetylation levels of LCAD by overexpression of SIRT3, incubation of recombinant LCAD with SIRT3 in vitro, or mutation of LCAD lysine 42 into arginine enhance its enzymatic activity. Mice lacking SIRT3 exhibit other hallmarks of fatty acid oxidation disorders: reduced ATP levels during fasting and intolerance to cold exposure upon fasting. These findings identify acetylation as a novel regulatory mechanism for mitochondrial fatty acid oxidation and show SIRT3 modulates mitochondrial intermediary metabolism and fatty acid utilization during fasting.

We continue our characterization of mice lacking SIRT3 by measuring their life span and sensitivity to metabolic disturbances, such as obesity and diabetes. Our working model is that SIRT3, like SIRT1, is an important link between calorie restriction and its beneficial effects in mammals.



A fluorescent version of SIRT3 was introduced into cells (green-hSIRT3-GFP, left) and shows a unique distribution around the nucleus of the cells and throughout the cytoplasm of two cells. Staining of the same cells to highlight mitochondria (red-MitoTracker, middle) reveals the same staining distribution, indicating that SIRT3 is located in mitochondria. This is further confirmed by the perfect overlap (yellow) of the two merged pictures (right).

RECENT PUBLICATIONS

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Verdin Laboratory Members

Leonard Chavez
Amy Collins
Liang Guo
Shweta Hakre
Matt Hirschey
Linh Ho
Jing-Yi Huang
Glen Adams Huynh
Herbert Kasler
Steven Kauder
Wiebe Kruijer
Hyungwook Lim
Dennis Mottet
Laura Saunders
Tadahiro Shimazu
Kotaro Shirakawa
Jamie Tawney
Eric Verdin