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Sirt7 promotes adipogenesis by binding to and inhibiting Sirt1

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Background

Members of the mammalian sirtuin family, Sirt1 – Sirt7, are known to regulate metabolic processes especially carbohydrate and fat metabolism [1,2]. Sirt1 and Sirt2 inhibit adipocyte differentiation [3,4] while Sirt1 and Sirt6 prevent liver steatosis [5]. These examples illustrate a synergistic action of different sirtuins in promoting lean, "healthy" phenotypes. We have previously shown that Sirt7 knockout mice display signs of premature aging, suffer from progressive cardiomyopathy and have a reduced lifespan [6]. Here, we investigate the biological function of Sirt7 in the regulation of metabolism in white adipose tissue (WAT) and liver.

Results

To discover new regulators of Sirt1 activity we performed an unbiased screen for molecules that might interact with Sirt1 using a label free quantitative mass spectrometry based co-immunoprecipitation strategy. We identified Sirt7 as a novel Sirt1 binding protein. The interaction between Sirt1 and Sirt7 was confirmed by immunoprecipitation of endogenous proteins and GST pull-down assays. Sirt1 protein expression and enzymatic activity was increased in WAT of Sirt7 knockout mice leading to age-dependent lipodystrophic phenotype. Increased Sirt1 activity might account for resistance of Sirt7 knockout mice fed high fat diet against liver steatosis. In vitro experiments demonstrated a diminished ability of Sirt7 deficient MEFs and primary preadipocytes to undergo adipogenesis. These defects were rescued by knock-down of Sirt1 or in cells deficient for one Sirt1 allele (Sirt1+/-; Sirt7-/-).

Conclusions

Our results highlight the importance of cross-regulatory circuits among individual members of the sirtuin family in organismal homeostasis. Lack of Sirt7 leads to a sustained activation of Sirt1. Apparently, such un-physiologically exaggerated, persistent Sirt1 activation results in metabolic dysfunction and nullifies its principally beneficial effects such as fat mobilization and inhibition of adipogenesis.

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