LIMNA

Lausanne Integrative Metabolism & Nutrition Alliance

SEMINAR

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Conference room SV 1717 - EPFL - Lausanne

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"TIP60-mediated lipin 1 acetylation links fatty acid sensing to adiposity"

Host: Prof. Kristina Schoonjans & Prof. Johan Auwerx

Abstract:

Obesity is characterized by excessive fatty acid (FA) conversion to triacylglycerol (TAG) and fat accumulation in adipose tissues, afflicting a large population worldwide. However, how signaling networks sense FAs and connect to the stimulation of lipid synthesis is poorly understood. Here, we show that homozygous knock-in mice carrying a single point mutation of acetyltransferase Tip60 at the Ser^{86} phosphorylation site ($Tip60^{S86A}$) display 40-60% reductions of body fat mass. In addition, the $Tip60^{S86A}$ mice are virtually immune to high-fat diet (HFD)-induced obesity and metabolic disorders such as hepatosteatosis and insulin resistance. Mechanistically, upon HFD or FA treatment, TIP60 is hyperphosphorylated at Ser^{86}, as a result of the inherent inhibition of AKT signaling by FA, enhancing the acetyltransferase activity of TIP60. Activated TIP60 then directly interacts and acetylates the phosphatidic acid (PA) phosphatase lipin 1, which catalyzes the dephosphorylation of PA to diacylglycerol (DAG), the penultimate step in TAG biosynthesis. We have also identified Lys^{425} and Lys^{595} residues in lipin 1 as the TIP60-dependent acetylation sites. After acetylation, lipin 1 translocates from cytosol to endoplasmic reticulum (ER)-associated membranes, allowing for the production of neutral lipids therein. An acetylation-defective K425/595R mutant of lipin 1 failed to rescue lipin 1-dependent TAG synthesis in CRISPR/Cas9-mediated LPIN1 knockout cells. These results highlight a gate-keeping role of TIP60 as well as lipin 1 acetylation in lipid synthesis, and proper modulation of TIP60 activity might be a promising strategy for the alleviation of obesity.

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