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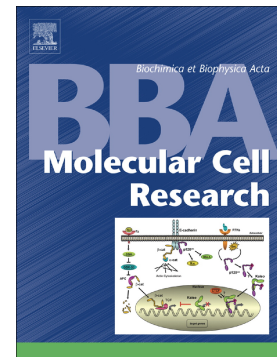
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**The intracellular domain of the leptin receptor prevents mitochondrial depolarization and mitophagy****Wauman Joris<sup>1,2</sup> & Tavernier Jan<sup>1,2,\*</sup>**

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**Abstract**

Hypothalamic leptin receptor (LR) signaling regulates body weight by balancing food intake and energy expenditure. It is well established that the human LR undergoes ectodomain shedding, but little is known about the fate of the remaining cytosolic domain. This study demonstrates that regulated intramembrane proteolysis (RIP) releases the LR intracellular domain (LR ICD), which translocates to the mitochondria where it binds to SOCS6. This LR ICD-SOCS6 interaction stabilizes both proteins on the mitochondrial outer membrane and requires a functional BC box in SOCS6 for mitochondrial association and a central motif in the LR ICD for SOCS6 binding. The LR ICD prevents CCCP-induced mitochondrial depolarization and mitophagy as shown by lowered Parkin translocation and p62 accumulation. Strict regulation of mitochondrial dynamics in the hypothalamus is known to be essential for body weight homeostasis. This is the first study showing that the LR can directly modulate mitochondrial biology.

Keywords: Regulated Intramembrane Proteolysis – Leptin Receptor –SOCS6 – Parkin - Mitophagy

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