SCIENTIFIC SEMINAR

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Paradoxical activation of mTORC2 during fasting regulates mitochondrial fission and fat metabolism

Aging associates with a decline in mitochondrial function which, in turn, predisposes to diverse age-related diseases. Mitochondria adapt to changes in nutrient availability and lack thereof through changes in dynamics and respiration. However, we do not completely understand the mechanisms driving these mitochondrial adaptations when nutrients are scarce. We have found that fasting paradoxically reactivates the nutrient-sensitive mTORC2 pathway in liver. This mTORC2 reactivation supports fasting-induced increases in mitochondrial fission and respiration. Accordingly, inactivation of mTORC2 in liver by knocking-out its regulatory protein, RICTOR (RictorKO), impairs fasting-induced increases in fission and mitochondrial respiration. Consequently, fasted RictorKO livers exhibit marked accumulation of triglycerides due to failure to mobilize these lipids. Using quantitative phosphoproteomics, we identified a new role for mTORC2 in driving mitochondrial fission in liver by regulating the recruitment of a cascade of novel downstream targets at MAMs (mitochondria-associated membranes), which are contact sites for ER-mediated mitochondrial fission. Interestingly, we have also found that this fasting-induced mTORC2 reactivation and mitochondrial fission are each markedly suppressed with age. Nutrients activate mTOR signaling for anabolic functions; however, fasting-induced reactivation of mTORC2 plays an unexpected role in mitochondrial division and respiration, a response that is suppressed with age. Since loss of RICTOR associates with decreases lifespan, stimulating mTORC2 to restore mitochondrial fission and respiration may be a novel strategy to extend healthspan and lifespan.

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EXCELENCIA SEVERO OCHOA

Friday September 8
Atrio 800
12.00H

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