Universität Basel

Research Project

mTOR signaling in growth and metabolism (BoE)

Third-party funded project

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TOR (target of rapamycin) is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, and cellular energy. TOR was originally discovered in budding yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals. The discovery of TOR led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR is found in two structurally and functionally distinct multi-protein complexes, TORC1 and TORC2, each regulating its own set of downstream effector pathways. The two TOR complexes, like TOR itself, are highly conserved. The two TORCs mediate cell growth and metabolism by activating and inhibiting several anabolic and catabolic processes, respectively. The processes regulated by TORC1 and TORC2 include ribosome biogenesis, translation, transcription, lipid and nucleotide synthesis, nutrient transport, and autophagy. Thus, the two TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. While the role of TOR in controlling growth of single cells is relatively well understood, a major challenge now is to understand the role of TOR signaling in coordinating and integrating overall body growth and metabolism in multi-cellular organisms. This will require elucidating the role of TOR signaling in individual tissues. As a continuation of our current SNSF grant and our longstanding interest in TOR, a goal of our research for the next three years is to continue the characterization of the non-cell autonomous function of mammalian TOR (mTOR) signaling in metabolic tissues in the mouse. More specifically, how does mTOR signaling in adipose tissue and the adrenal cortex control whole body physiology? The major specific aims are 1) to identify an mTORC2-regulated adipokine that improves â cell function, and 2) to investigate the role of mTORC1 signaling in adrenal steroid hormone production. In addition to these non-cell autonomous functions of mTOR signaling, will also continue to study cell autonomous function of mTOR. The major specific aims of this part of our proposed research are 3) to characterize oncogenic mTOR signaling in the liver, and 4) to study the role of mTOR in regulating RNA-binding proteins. As a central controller of cell growth and metabolism, mTOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes. Our findings may be of fundamental and medical importance.

Keywords mTOR, cell growth, signal transduction, rapamycin, liver, adipose tissue, nutrient sensing, insulin, adrenal cortex, ageing, metabolism, energy homeostasis, novel therapeutics
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Follow-up project of 3000670 mTOR signaling in growth and metabolism

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