

P023 Activation of mTOR complex 1 promotes adipogenesis
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Primarily through loss of function studies using rapamycin, mTOR complex 1 (mTORC1) has been suggested to be involved in mesenchymal cell differentiation into adipocytes (i.e., adipogenesis). To further define the role of mTORC1 in this process, we used a variety of cell lines lacking the TSC1-TSC2 complex as an mTORC1 gain of function model. Loss of *Tsc1* or *Tsc2* results in elevated and constitutive mTORC1 signaling concomitant with loss of PI3K-Akt signalling due, at least in part, to feedback inhibition of IRS1. Interestingly, despite severe insulin resistance throughout the differentiation process, TSC-deficient mouse embryo fibroblasts (MEFs) show a greater capacity to differentiate into adipocytes than their wild-type counterparts. Furthermore, stable shRNA-mediated knockdown of TSC2 in 3T3-L1 preadipocytes also leads to enhanced mTORC1-driven adipogenesis. The resulting adipocytes display mTORC1-dependent increases in intracellular triglycerides and higher expression levels of a variety of adipocyte markers. Unlike typical adipocytes, TSC-deficient adipocytes are completely insulin resistant and express low levels of IRS1, IRS2, and GLUT4, but high levels of GLUT1. Importantly, we find that the master regulator of adipogenesis, PPAR γ , is elevated in these cells in an mTORC1-dependent manner. These findings provide mechanistic insights into the role of mTORC1 in both obesity and the unusual adiposity of the renal angiomyolipomas common to TSC and LAM patients.