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The integral role of mTOR in lipid metabolism

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The mammalian Target of Rapamycin (mTOR) is comprised of two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), that have shared as well as distinct partners (reviewed in ref. 1). mTOR serves as a controller of both anabolic and catabolic pathways. *Anabolic processes* of lipid metabolism include lipogenesis (fatty acid synthesis), adipogenesis and esterification. Fatty acid synthesis is mediated by Acetyl CoA Carboxylase (ACC) and Fatty Acid Synthase (FAS) enzymes. Subsequent desaturation by steroyl CoA desaturase (SCD) and chain elongation yields polyunsaturated fatty acids. Consequently, esterification of free fatty acids (FFA) forms triacylglycerol (TAG). The *catabolic processes* of lipid metabolism include hydrolysis of TAG (lipolysis) to yield glycerol and FFA, followed by β-oxidation of FFA to yield Acetyl CoA (**Fig. 1**). While the roles of mTOR in lipid biosynthesis have been addressed,[2-7] the effects of mTOR on TAG lipolysis and FFA breakdown via β-oxidation are not understood.[6,8-12]

mTOR and de novo Fatty Acid Synthesis

mTOR has been shown to activate the transcription factor, SREBP (Sterol Regulatory Element Binding Protein) in rat hepatocytes,[5] which in turn activates ACC,[5] FAS,[6] and SCD[7] enzymes involved in lipogenesis (**Fig. 1**). Additionally, rapamycin, a specific mTORC1 inhibitor, has been shown to block the expression of SREBP1 target genes ACC, FAS and SCD, indicating a role for mTORC1 in fatty acid biosynthesis.[2,5,6] Rapamycin also inhibited the transactivation of transcription factors PPARγ (Peroxisome Proliferator-Activated Receptor-gamma, an adipocyte specific nuclear receptor) and C/EBP (CCAAT-enhancer-binding proteins).[4] C/EBPβ and C/EBPγ induce the expression of C/EBPα that in turn stimulates PPARγ transactivation driving the process of adipogenesis. Subsequently, PPARγ activates fatty acid uptake, synthesis, esterification and storage in the newly synthesized adipocytes. Using the S6K1 knockout mouse model, a recent study documented the role of S6K1, an mTOR downstream target, in de novo adipogenesis and affirmed that S6K1 is involved in the commitment of multipotent stem cells to the adipocyte lineage.[13]

mTOR and Triacylglycerol Synthesis

FFA are esterified by glycerol to generate TAG, which are the major storage fuels in the adipose tissue. By promoting both lipogenesis and adipogenesis, mTOR is well poised to enhance FFA esterification to yield TAG. Indeed, studies have shown that mTOR increases TAG synthesis via phosphorylation of Lipin 1.[3] Lipin 1, a phosphatidic acid phosphatase involved in the cleavage of phosphatidic acid, an integral step in TAG synthesis, has been shown to be phosphorylated by mTOR in an insulin sensitive manner.[3] In *C. elegans,* a rictor (TORC2 partner) mutant phenotype exhibited increased fat accumulation, implying that TORC2 serves as a negative regulator of fatty acid esterification and TAG formation.[14] Taken together, it appears that there is a balance between mTORC1 and mTORC2 activities that functions to maintain energy homeostasis.

mTOR and β-Oxidation

FFA are transferred to the inner mitochondrial membrane by Carnitine Acyl Transferase (CAT) and are subsequently oxidized to yield acetyl CoA, which enters the citric acid cycle to generate energy. Using human BJAB B-lymphoma cell lines and murine CTLL-2 T lymphocytes, Peng et al. (2002) reported that rapamycin treatment (12 and 24 hours) increases VLACD (Very Long Acetyl CoA Dehydrogenase) enzyme gene expression, as well as CAT expression, indicating that inhibition of mTOR leads to accelerated β-oxidation and increased catabolism of FFA.[6] Similarly, Um et al. (2004) found that mice deficient in S6K1, an mTOR downstream target, showed enhanced β-oxidation, which led to a lean mouse phenotype.[15]

mTOR and Lipolysis

Mobilization of stored TAG via the lipolytic pathway is necessary to provide FFA to be used as an energy source. Studies of Adipose Triglyceride Lipase (ATGL) deficient mice documented the role of ATGL in initiating lipolysis.[16] Knockdown of 4E-BP1 and 4E-BP2 genes, which lie downstream of mTOR, led to decreased lipolysis and increased TAG accumulation.[12] While in S6K1 knockout mice, increased lipolysis was observed, which contributed to a lean phenotype and resistance to obesity.[15] We showed that rapamycin treatment of 3T3-L1 adipocytes led to increased β-adrenergic agonist induced lipolysis without altering basal lipolysis,[9] an effect that is partially attributed to increased phosphorylation of Hormone

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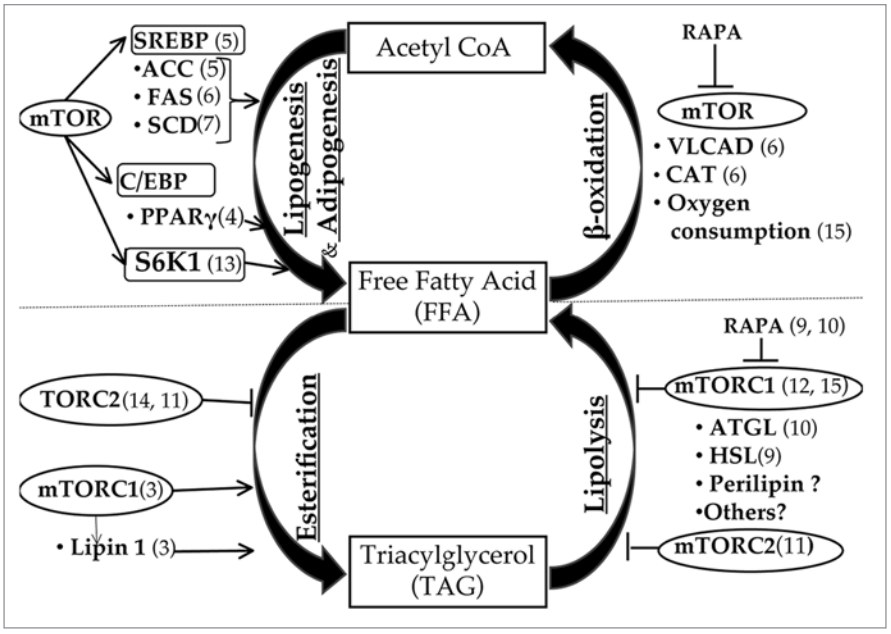

Figure 1. mTOR and lipid metabolism.

Sensitive Lipase (HSL) at serine-563. Additionally, Charabati et al. reported that overexpression of the mTOR activator Rheb in 3T3-L1 cells led to decreased ATGL (Adipose Triacylglycerol lipase) expression, increased de novo lipogenesis and suppressed lipolysis. Using western blot analysis, we did not find changes in ATGL expression after rapamycin treatment.[9] The apparent discrepancy may be explained by different experimental conditions and possible increase in ATGL enzymatic activity that may have contributed to increased rates of lipolysis. We observed that rapamycin augments the PKA-mediated phosphorylation of HSL on Serine 563, which suggests a cooperative role of mTORC1 inhibition with a β-adrenergic PKA-activated response. Whether mTORC1 inhibition and PKA activation converge on the same lipolytic targets or via parallel pathways, remains to be elucidated. Polak et al.[8] reported that adipose tissue specific raptor (mTORC1 partner) knockout mice showed a lean phenotype, which was related to increased energy expenditure and increased mitochondrial uncoupling proteins. Further, adipose tissue-specific rictor knockout mice showed a phenotype of increased FFA and glycerol, which implies that mTORC2, also plays a role in suppressing lipolysis.[11]

Taken together, mTOR signaling plays an integral role in lipid metabolism including *anabolic* pathways, which encompass lipogenesis, adipogenesis and fatty acid esterification, and *catabolic* pathways, which include lipolysis and β-oxidation (**Fig. 1**). These findings implicate mTOR as an attractive target for intervention in chronic diseases with deregulation of lipid homeostasis such as obesity and diabetes. Further research is warranted to understand the impact of mTOR signaling on lipolysis, β-oxidation and energy homeostasis.

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