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# PAPER OF THE MONTH • APRIL 2012


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Molecular Cell


Article

Cell PRESS

# The Sam68 STAR RNA-Binding Protein Regulates mTOR Alternative Splicing during Adipogenesis


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SUMMARY

We report that mice ablated for the Sam68 RNA-binding protein exhibit a lean phenotype as a result of increased energy expenditure, decreased commitment to early adipocyte progenitors, and defects in adipogenic differentiation. The Sam68$^{-/-}$ mice were protected from obesity, insulin resistance, and glucose intolerance induced with a high-fat diet. To identify the alternative splice events regulated by Sam68, genome-wide exon usage profiling in white adipose tissue was performed. Adipocytes from Sam68$^{-/-}$ mice retained intron 5 within the mTOR transcript introducing a premature termination codon, leading to an unstable mRNA. Consequently, Sam68-depleted cells had reduced mTOR levels resulting in lower levels of insulin-stimulated S6 and Akt phosphorylation leading to defects in adipogenesis, and this defect was rescued by the exogenous expression of full-length mTOR. Sam68 bound intronic splice elements within mTOR intron 5 required for the usage of the 50 splice site. We propose that Sam68 regulates alternative splicing during adipogenesis.



DOI 10.1016/j.molcel.2012.02.007