

## Identification of an IRES element in the human mTOR transcript: its structural and functional features

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Mammalian target of rapamycin (mTOR) is a conserved serine/threonine kinase that integrates signals from the cellular nutrient- and energy-status, acting namely on the protein synthesis machinery. Deregulation of mTOR signaling is implicated in major diseases, such as cancer, mainly due to its role in regulating protein synthesis. The main mTOR targets are proteins responsible for ribosome recruitment to the mRNA, thus, a specific inhibitor of mTOR, for example rapamycin, leads to global inhibition of translation. Major advances are emerging regarding the regulators and effects of mTOR signaling pathway, however, regulation of mTOR gene expression, is not well known. Knowing that in stress conditions such as hypoxia, overall protein synthesis is reduced, but synthesis of mTOR protein is not inhibited, we hypothesized that mTOR 5'UTR harbors an IRES allowing cap-independent synthesis of mTOR protein in stress conditions. By using dicistronic reporter plasmids we have tested and confirmed this hypothesis. In addition, we have shown that IRES-dependent translation of mTOR is stimulated by hypoxia with associated eIF2 $\alpha$  phosphorylation, in a manner that is independent of HIF1 $\alpha$  induction *per se*. The anti- and pro-apoptotic outcomes of the unfolded protein response induced by endoplasmic reticulum stress also stimulates mTOR IRES activity, with a more pronounced effect in the pro-apoptotic phase with associated eIF2 $\alpha$  phosphorylation. Furthermore, we have demonstrated that mTOR IRES activity is potentiated by mTORC1 inactivation, suggesting a feedback loop in order to maintain mTOR expression. Our data point out a novel regulatory mechanism

of mTOR gene expression that integrates the protein profile rearrangement triggered by global translational inhibitory conditions.