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Translational control of innate immune response

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Translation initiation is a highly regulated process. In eukaryotes the ribosome recruitment is facilitated by the 5´-cap structure (m7GpppN, where N is any nucleotide) present on all nuclear transcribed mRNAs (1). The cap structure is recognized by eukaryotic initiation factor 4F (eIF4F). It is well established that, activated downstream of PI3´K and Akt, mTOR modulates signal transduction pathways that play central roles in the initiation of mRNA translation. mTOR regulates protein synthesis through the phosphorylation and inactivation of the repressor eukaryotic initiation factor 4E-binding protein (4E-BP1/2), and through the phosphorylation and activation of S6 kinase (S6K1) (2). mTOR exists in two complexes: mTOR complex 1 (mTORC1), which is sensitive to the drug rapamycin and regulates mRNA translation, and mTORC2 which is rapamycin insensitive (3).

Type I interferon (IFN) is an essential component of the antiviral response and its production is controlled by transcription. Nevertheless, during last years it has being described that translational control is critical for induction of type-I IFN production (4). Several groups showed that mTORC1 stimulates type I IFN production trough phosphorylation of its target proteins 4E-BPs and S6K1/2 (5). Furthermore, the role of mTORC1 signaling pathway in innate immunity response was demonstrated using a inhibitor "rapamycin" that block mTORC1 and as consequence suppresses type I IFN production in plasmacytoid dendritic cells (pDCs)(6). Previously we describe that the lack of the translational repressors 4E-BP1/2 leads to enhanced type I IFN production, because the interferon regulatory factor 7 (IRF7) messenger RNA is more efficiently translated, resulting in elevated expression of IRF7 (7). In this work we demonstrate that in mouse embryonic fibroblasts cells and also in the mice lacking the translational repressors 4E-BP1 and 4E-BP2, the replication of vesicular stomatitis virus is suppressed almost totally. These findings showed the role of 4E-BPs as negative regulators of type-I IFN production, via translational repression of Irf7 mRNA.

In addition, genetic deletion of the mTOR downstream target S6K1/2 leads to impaired type I IFN response. In this work it was showed that mouse embryonic fibroblasts and mice lacking S6K1 and S6K2 are more susceptible to vesicular stomatitis virus (VSV) infection than their WT counterparts as a result of an impaired type I IFN response (8).

Finally, recently we showed that *Leishmania* down-regulates macrophage protein synthesis and affects its polysome distribution. The molecular mechanism involves the parasite protease GP63, which cleaves and disrupts the formation of mTORC1 and leads to the activation of the translational repressors 4E-BP1 and 2. Rapamycin treatment, which activates 4E-BPs, results in a dramatic increase in parasite survival. In contrast, a reduced parasite load is observed in 4E-BP1/2 double knockout (DKO) macrophages. Remarkably, 4E-BP1/2 DKO mice are significantly less susceptible to cutaneous leishmaniasis. This phenotype was explained by enhanced type-I IFN immune response (9).

All of these research were done in a mice model, now we are working with differents human cell lines, in order to corroborate these findings in our specie. In conclusion, these studies demonstrate the central role that "translational control" plays in modulating the innate immune response through the IFN production.