Editorial

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Bigger than Expected: IRES-Dependent mRNA Translation Initiation Enlarges the Eukaryotic Proteome

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Until recently it was believed that in eukaryotic cells, mRNA translation initiates entirely by binding of the mRNA 5'- m7G cap-structure to the cap-binding complex E1F4F. Anyway, new evidences pointed out that eukaryotic cells have evolved also alternative translation initiation strategies from one single mRNA, i.e., IRES-dependent mRNA translation initiation, that can increase the size and function of a given cell proteome. Here we briefly discuss the emerging role of protein isoforms deriving from IRES-dependent translation initiation in mammalian cells, at the light of more recent findings.

Only a few years before the completion of the Human Genome Project, popular predictions stated that humans had up to 100,000 genes. But the emerging evidences following extensive genome sequencing and analysis lowered that number to a more modest range of about 19,000 genes [1].

Anyway, the composition of the cellular proteome is controlled by multiple processes that can increase protein number, especially in eukaryotes, as more proteins can be produced from a single gene, due to alternative splicing. Recently, the discovery in eukaryotic cell of alternative translation initiation strategies from a single mRNA raised new questions about the real size of a specific given proteome [2]. Until recently, it was believed that in eukaryotic cells, mRNA translation initiates entirely by binding of the mRNA 5 - m7G cap-structure to the cap-binding complex E1F4F. Cap-independent mechanisms of translation initiation were first discovered in viruses infecting eukaryotic cells. This alternative way to initiate viral mRNA translation, occurs through internal ribosome entry site (IRES)s elements in their 5'UTRs, that are able to recruit the ribosome independently of the 5'-cap. IRES elements have complex secondary structures, and IRES-mediated translation is often dependent on specific IRES trans-acting factors (ITAFs). As eukaryotic viruses utilize factors of the host cell to carry on their molecular pathways, it is pretty surprising the recent discovery that IRES elements have been found in mRNAs expressed in animal cells, plants, and yeasts. Expression of genes bearing IRES elements in their mRNAs is controlled by multiple molecular mechanisms, with IRES-mediated translation favored under conditions where 5'cap-dependent translation is compromised. Translation initiation on such mRNAs results in the synthesis of proteins harboring different amino terminal domains potentially conferring to these isoforms distinct functions. It is striking that alternative mechanisms of translation initiation are most active during mitosis, cell stress, or viral infection, when canonical cap-dependent mechanisms of translation are inhibited. Therefore, it is currently believed that cellular IRES-mediated translation plays an important role in cell-fate decisions under a variety of conditions.

Fibroblast growth factor-2 (FGF-2) is a member of a large family of proteins that bind heparin and heparin sulfate and modulate the function of a wide range of cell types. An alternative translational process gives rise to five FGF2 isoforms with specific localization and functions: a low molecular weight (LMW, 18 KDa) and four high molecular weight (HMWs, 22, 22.5, 24, 34 KDa) isoforms. IRES control the expression of all the isoforms except for the 34 KDa HMW, which depends instead on the canonical cap-dependent mechanism.

In our lab, we evaluated the differential roles of 5'cap-dependent and IRES-dependent Fibroblasts Growth Factor 2 (FGF2) isoforms in stress conditions in mammalian cell cultures

Our results demonstrate that the induced expression of the LMW FGF-2 and/or HMW FGF-2 isoforms differently modulates drug resistance and gene amplification properties in the NIH 3T3 and A31 murine fibroblastic cell lines by differential amplification of the CAD gene [3].

Moreover, FGF2 expression is correlated with different types of human cancer, included melanoma, where it is thought to contribute to its development and progression. We demonstrated in a human metastatic melanoma cell line that, while LMW FGF2 expression confers stem-like traits and a pro-angiogenic profile to melanoma cells, HMWs isoforms are involved in the migratory processes and in the maintenance of tumor perfusion, when endothelial cell-driven angiogenesis is lacking, by promoting vasculogenic mimicry [4].

This comparative study shows the differential contribution of FGF2 isoforms in melanoma progression, pointing out that, even behaving in specific/antithetical manners, they cooperate in different steps of metastatic cascade, providing melanoma cells with higher malignancy and aggressiveness.

As eukaryotic mRNA IRES are difficult to identify, research efforts are mainly directed to IRESs which have been at least to some extent experimentally proven

We can conclude that experimental demonstration of IRES in 5' UTR remains a challenging task, masking the real contribute of this translation initiation mechanism to the size and the functions of a eukaryotic cell proteome.

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