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Review

The role of IRES trans-acting factors in carcinogenesis ☆

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ABSTRACT

Regulation of protein expression through RNA metabolism is a key aspect of cellular homeostasis. Upon specific cellular stresses, distinct transcripts are selectively controlled to modify protein output in order to quickly and appropriately respond to stress. Reprogramming of the translation machinery is one node of this strict control that typically consists of an attenuation of the global, cap-dependent translation and accompanying switch to alternative mechanisms of translation initiation, such as internal ribosome entry site (IRES)-mediated initiation. In cancer, many aspects of the RNA metabolism are frequently misregulated to provide cancer cells with a growth and survival advantage. This includes changes in the expression and function of RNA binding proteins termed IRES trans-acting factors (ITAFs) that are central to IRES translation. In this review, we will examine select emerging, as well as established, ITAFs with important roles in cancer initiation and progression, and in particular their role in IRES-mediated translation. This article is part of a Special Issue entitled: Translation and Cancer.

1. Introduction

Protein synthesis is a critical regulatory process for maintaining cellular homeostasis as it can rapidly and reversibly modify the protein output in response to different cues [1]. Therefore, and also because translation is energetically very demanding (consuming in excess of 50% of the cell's energy), it is tightly regulated. In fact, misregulation of the translation machinery can lead to several disease states, including carcinogenesis. Regulation of translation occurs at all steps of the process, namely initiation, elongation and termination; however, it is generally accepted that translation initiation is the rate limiting step, and the most tightly regulated one [2]. Mammalian translation initiation starts with the recognition of mRNA by the translation machinery through binding of the m7G cap by the cap-binding protein, eukaryotic initiation factor 4E (eIF4E). In turn, eIF4E is bound by the scaffolding protein eIF4G and the RNA helicase eIF4A to form the eIF4F complex. This complex is subsequently bound by additional initiation factors, including eIF3 which recruits the small ribosomal subunit associated with Met-tRNA-bound eIF2 (43S ribosome complex) to the 5′ end of the mRNA. It is believed that the resultant 48S ribosomal complex scans along the mRNA until the correct initiation codon (most often AUG) in the proper context is recognized and it is then joined by the 60S ribosomal subunit to form the 80S translating ribosome that proceeds with polypeptide chain elongation.

Carcinogenesis has traditionally been linked to genetic alterations and defects in the transcription program of cells. However, it is now becoming apparent that alterations in the rate of protein synthesis, or in the composition of the translation machinery are also strongly linked to cancer cell properties. For instance, it is now well established that increased protein synthesis and ribosome biogenesis is required to maintain increased cancer cell proliferation [3]. In contrast, induction of apoptosis (such as that triggered by the use of chemotherapeutic drugs) is accompanied by substantial and rapid down-regulation of protein synthesis [4]. These changes in global translation rates are mainly due to changes in the activity or abundance of the canonical translation initiation factors mentioned above, although some evidence suggests that degradation of mRNAs also plays an important role in this process [5]. Modifications of the translation initiation factors and of ribosomes in cancer have been extensively reviewed ([6–8] and in this issue), hence they will not be covered in much detail in this article. Nonetheless, it is important to note that the cells' ability to regulate translation is frequently focused on two key control points which are shared by virtually all mRNAs – components of the eIF4F complex and eIF2α (Fig. 1). Indeed, stress-induced phosphorylation of eIF2α is one way by which global protein synthesis is inhibited and decreased eIF2α phosphorylation is often linked to carcinogenesis [9]; however, some studies suggest that increased eIF2α phosphorylation might be associated with tumour progression [10,11]. To reconcile these differences, it was proposed that the role of eIF2α in cancer probably depends on the stage of the disease where stress-induced eIF2α phosphorylation in the first stages of cancer

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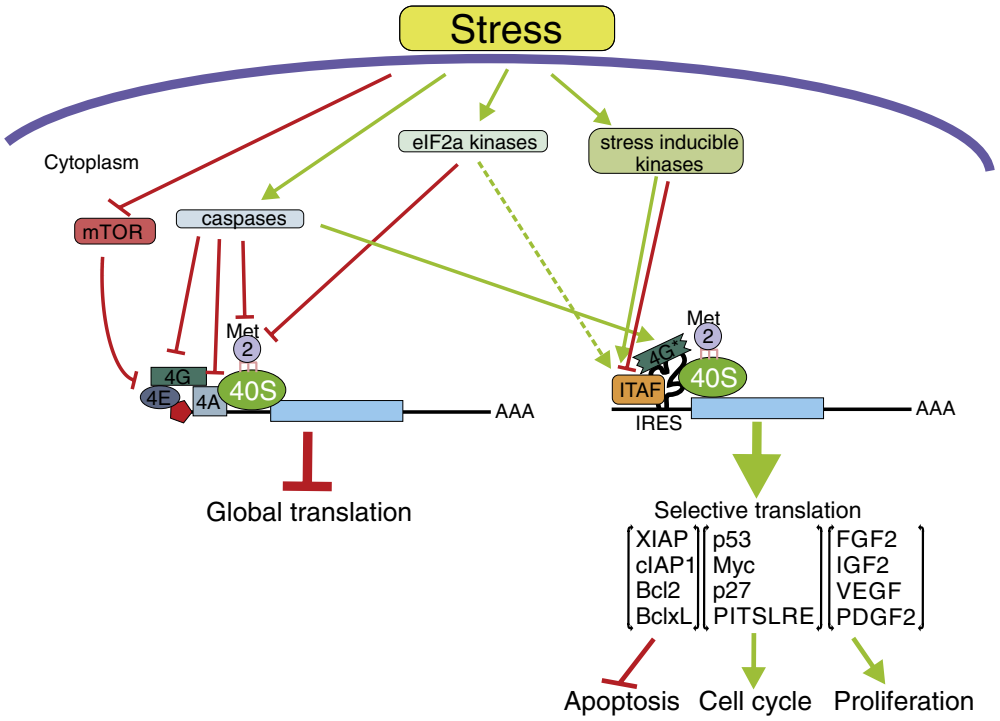

Fig. 1. A schematic diagram illustrating regulation of translation during stress. The left side of the model depicts regulation of general (cap-dependent) translation; the right side depicts selective (IRES-mediated) translation. Green lines indicate positive, while red lines negative impact. Dotted line depicts indirect effect. For simplicity, not all factors are shown. (Adapted from [8]).

leads to decreased translation rates and facilitate selective tumour cell survival whereas in later stages, there is an uncoupling of eIF2α kinases activity with translation repression, thus favouring tumour progression (reviewed in [6]). Overexpression of the cap-binding protein eIF4E is observed in several cancers and is often associated with worse clinical outcome and decreased survival [12]. Concomitantly, increased eIF4E binding proteins (4E-BPs) phosphorylation, which leads to increased eIF4E availability, is also observed in several cancers and is associated with tumour progression as well as decreased survival [13]. Caspase activity during stress-induced apoptosis can also lead to the proteolytic cleavage of initiation factors and general inhibition of translation, although tumour cells frequently find other ways to survive these conditions (reviewed in [8]).

Although inactivation of translation initiation factors by means of phosphorylation or proteolytic cleavage generally leads to translation inhibition, it can also promote assembly of modified or alternative initiation complexes that are believed to promote selective translation of mRNAs required during carcinogenesis and tumour progression. For instance, eIF4E overexpression is thought to preferentially activate the translation of mRNAs with highly structured 5′UTRs, some of which are involved in cancer progression, such as c-Myc, VEGF-A and FGF2 [14]. Existence of an alternative translation initiation was also suspected by the fact that under conditions when cap-dependent translation is severely compromised (e.g. nutrient deprivation, hypoxia, irradiation and viral infection), a subset of mRNAs is still efficiently translated [e.g. 15] and this alternative mode of translation control is required for effective stress response [16,17]. It was therefore proposed that selective translation by alternative modes of translation initiation is a key mechanism which is required for cellular survival under stress and is used by cells to fine-tune their stress response, including during carcinogenesis [2,6,7]. One such alternative mode of translation initiation is the Internal Ribosome Site Entry (IRES)-mediated translation. IRESes are discrete regulatory elements present in the 5′UTR of select cellular mRNAs that can recruit the ribosome independently of the 5′cap [18]. It is estimated that about 3% of mRNAs in the cell could be translated by an IRES-dependent mechanism [15,19]. Interestingly, many proteins encoded by mRNAs with an IRES play important roles in cell survival (cIAP1, XIAP, Bcl-2, Bcl-xL, Apaf-1, Bag1), proliferation (Myc, FGF2, IGF2, PDGF2), cell cycle (p53, p27, PITSLRE) and angiogenesis (VEGF-A, HIF-1α), all processes that are important in cancer initiation and progression and that will be discussed herein. However, it needs to be emphasized that not all cellular IRES have been validated and that the existence of cellular IRESes is still hotly debated [20]. Notwithstanding this criticism, many cellular IRESes were shown to be *bona fide* regulatory elements that drive translation of their respective proteins during cellular stress when global protein synthesis is compromised (Fig. 1).

Precisely how IRES-mediated translation initiation operates and is regulated is still not fully understood; however, it is known that most cellular IRESes require binding of some canonical initiation factors to initiate translation [21], but also interaction with other protein factors that have been termed IRES trans-acting factors (ITAFs) [2]. ITAFs are RNA-binding proteins that act to facilitate or block ribosome recruitment to the IRES, thus enhancing or inhibiting translation of these mRNAs [22,23]. Interestingly, apart from their regulation of translation, many ITAFS are involved in other aspects of RNA metabolism that are important in carcinogenesis such as mRNA splicing, export and stability. In the following review we will describe the emerging as well as established ITAFs with important roles in cancer initiation and progression, and in particular their role in IRES-mediated translation.

2. Insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1)

IGF2BP1 is a member of the VICKZ family of proteins named after its founding members from different organisms (Vg1RBP/Vera, IMP1-3, CRD-BP, KOC and ZBP1) [24]. IGF2BP1 and its human paralogs, IGF2BP2 and IGF2BP3 (or IMP1-3), were first identified as RNA binding proteins that interact with the human IGF2-leader 3 5′UTR and negatively regulate its translation in mouse 3 T3 fibroblasts [25]. IGF2BP1 also regulates the translation and stability of several other transcripts