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Current Opinion in Genetics & Development

Post-transcriptional control of stress responses in cancer

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The processes by which the canonical protein synthesis machinery is modified by environmental stresses to allow healthy cells to respond to external conditions to maintain homeostasis, are frequently hijacked by tumour cells to enhance their survival. Two major stress response pathways that play a major role in this regard are the unfolded protein response (UPR) and the DNA damage response (DDR). Recent data have shown that key proteins which coordinate post-transcriptional control, and which are regulated by signalling through the UPR and DDR, are upregulated in cancers and that targeting these proteins/pathways will provide new therapeutic avenues for cancer treatments.

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Current Opinion in Genetics & Development 2018, **48**:30–35

This review comes from a themed issue on **Cancer genomics**

Edited by **Fatima Gebauer-Hernandez** and **Omar Abdel-Wahib**

http://dx.doi.org/10.1016/j.gde.2017.10.006

Introduction

Regulation of protein synthesis makes a major contribution to post-transcriptional control, and during disease or following cell stress, reprogramming of the translatome is essential to orchestrate the appropriate cellular response [1]. Protein synthesis is a three-stage process of initiation (where eukaryotic initiation factors (eIFs) bind to the RNA and recruit the ribosome), elongation (when tRNA-dependent and eEF1A-dependent codon decoding, and eEF2-dependent ribosome translocation occurs to produce the polypeptide chain) and termination (where upon reaching a stop codon, the polypeptide chain is released from the ribosome) [2]. Both initiation and elongation phases are highly regulated by changes in the phosphorylation status of eIFs or eEFs, and these processes combine to determine the overall rate of translation [2,3].

Initiation is for the most part controlled by changes in the phosphorylation status of 4EBPs and eIF2α. 4EBPs are regulated by mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that is inhibited in response to cellular stress such as DNA damage, low energy levels and hypoxia [4]. Upon mTOR inhibition 4EBPs are dephosphorylated and sequester the cap-binding protein eIF4E, reducing protein synthesis rates [5]. However, following stimulation with growth factors and amino acids, upstream signalling pathways including PI3K/AKT and MAPK, activate mTOR to enhance phosphorylation of 4EBPs and the release of eIF4E, stimulating protein synthesis.

EIF2 is required for the formation of ternary complex (TC) with GTP and $tRNA_{imet}$, which is necessary to recruit the initiator methionine to the start codon. When phosphorylated on the alpha subunit, eIF2 binds to its GEF eIF2B, inhibiting its activity and reducing the amount of TC available. There are four mammalian kinases that control the phosphorylation of eIF2: PERK, PRK, GCN2 and HRI [6,7]. Each kinase is activated by specific stress stimuli, however many stresses activate more than one kinase. For example, both hyperosmotic stress and double-stranded RNA, activate PKR [8,9].

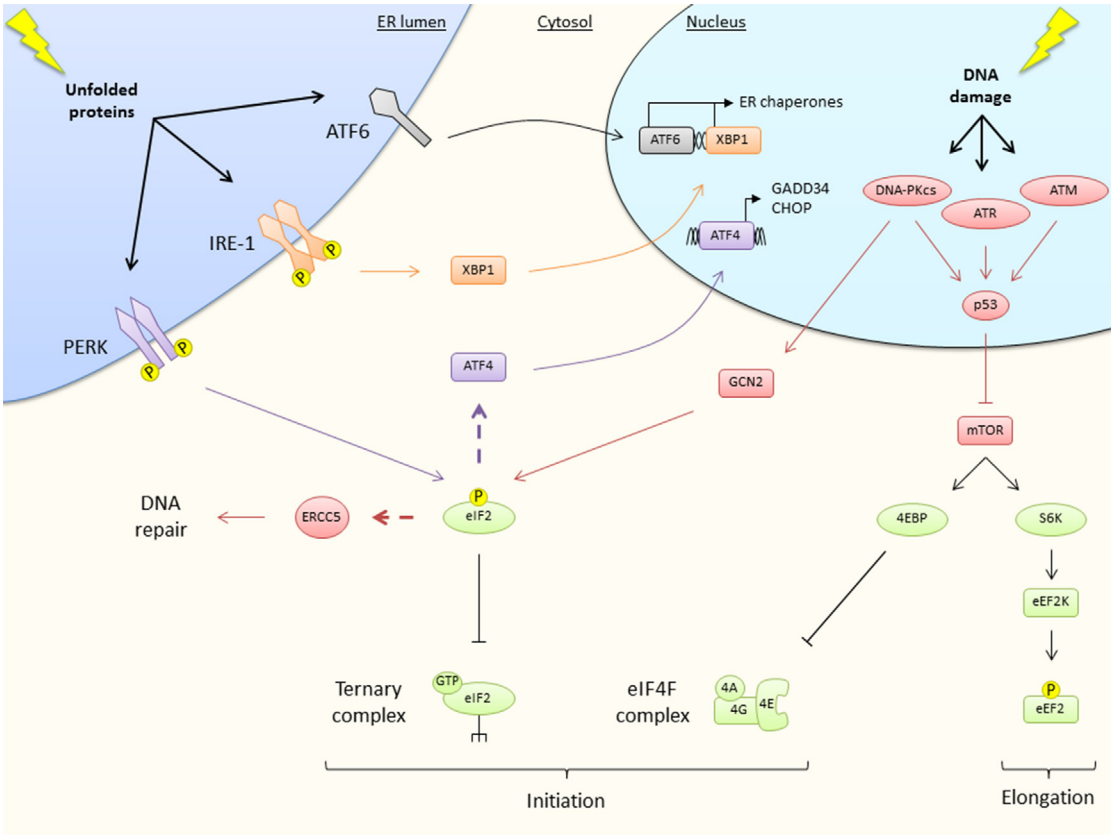
Elongation is controlled by regulating tRNA levels, in addition to the phosphorylation of eEF2 by eEF2K, which prevents ribosome translocation along the mRNA [3]. Interestingly, eEF2K is activated by Ca^{2+}/CaM and signalling downstream of AMPK, whereas it is inactivated by signalling through mTORC1 [10], enabling mTOR to regulate both initiation and elongation.

Many of the environmental stresses that modify the canonical protein synthesis machinery in response to external stress are also important for survival of a tumour cell. Two major stress response pathways that are modulated in tumours are the unfolded protein response (UPR) and the DNA damage response (DDR) (summarised in Figure 1). Here, we will discuss the recent findings identifying how post-transcriptional control pathways downstream of the UPR/DDR are modulated in cancer, and discuss translational reprogramming within tumours and its implication for future therapy.

Unfolded protein response

Endoplasmic reticulum (ER) stress in tumours can result from aberrant increases in protein synthesis, accumulation of unfolded proteins, disrupted calcium homeostasis,

Figure 1



Post-transcriptional regulation initiated by the unfolded protein response and DNA damage response. Schematic representation of post-transcriptional regulation of the unfolded protein response (UPR) and DNA damage response (DDR). Unfolded proteins activate signalling from three ER transmembrane receptors: PERK (purple), IRE-1 (orange), and ATF6 (grey); whereas DNA damage activates signalling from three DDR kinases: DNA-PKcs, ATR, and ATM (red). The UPR and DDR both phosphorylate eIF2α and post-transcriptionally regulate the expression of ATF4 and ERCC5 respectively (indicated by broken arrows), restoring homeostasis while simultaneously inhibiting ternary complex (TC) formation and translation initiation. Additionally, the DDR regulates mTOR signalling to inhibit translation initiation and elongation by regulating eIF4F complex formation and ribosome translocation respectively.

nutrient deprivation, hypoxia and oxidative stress [11]. To manage this stress, tumour cells initiate the evolutionary conserved stress response pathway, the UPR. This response is coordinated by three ER *trans*-membrane bound receptors, inositol-requiring *trans*-membrane kinase endoribonuclease 1α (IRE1α), PERK, and activating transcription factor 6 (ATF6) [12]. In unstressed cells, these receptors are maintained in an inactive state through association with the glucose-regulated protein GRP78 (also known as BiP) within the ER lumen. In the presence of unfolded/misfolded proteins, GRP78 dissociates from the three sensor proteins enabling them to activate downstream signalling pathways: IRE1α cleaves XBP-1 mRNA, which leads to the production of XBP-1 protein and ultimately ER chaperones; ATF6 translocates to the golgi where it is cleaved into its functional form and works in concert with XBP-1; PERK dimerises, autophosphorylates and phosphorylates eIF2α (eIF2α-P), reducing protein synthesis to restrict ER protein load [13]. In conjunction with the reduction in protein synthesis that follows activation of PERK, accumulation of eIF2α-P allows translation of selected mRNAs including ATF4 and ATF5 [13]. These transcription factors drive the expression of a number of proteins including growth arrest and DNA damage-inducible protein 34 (GADD34), which dephosphorylates eIF2α to restore protein synthesis, and C/EBP homologous protein (CHOP), a transcription factor which has a pro-apoptotic role following ER stress [13].

The major role of the UPR is to restore cell homeostasis and interestingly, it has been suggested that triggering of the UPR in early stages of tumourigenesis can hamper tumour progression [14]. For example, in HRAS-mutated melanocytes, UPR activation resulted in cell cycle arrest and premature senescence, which was associated with vacuolisation and expansion of the ER [15]. However, chronic induction of this pathway is required for tumour