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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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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].

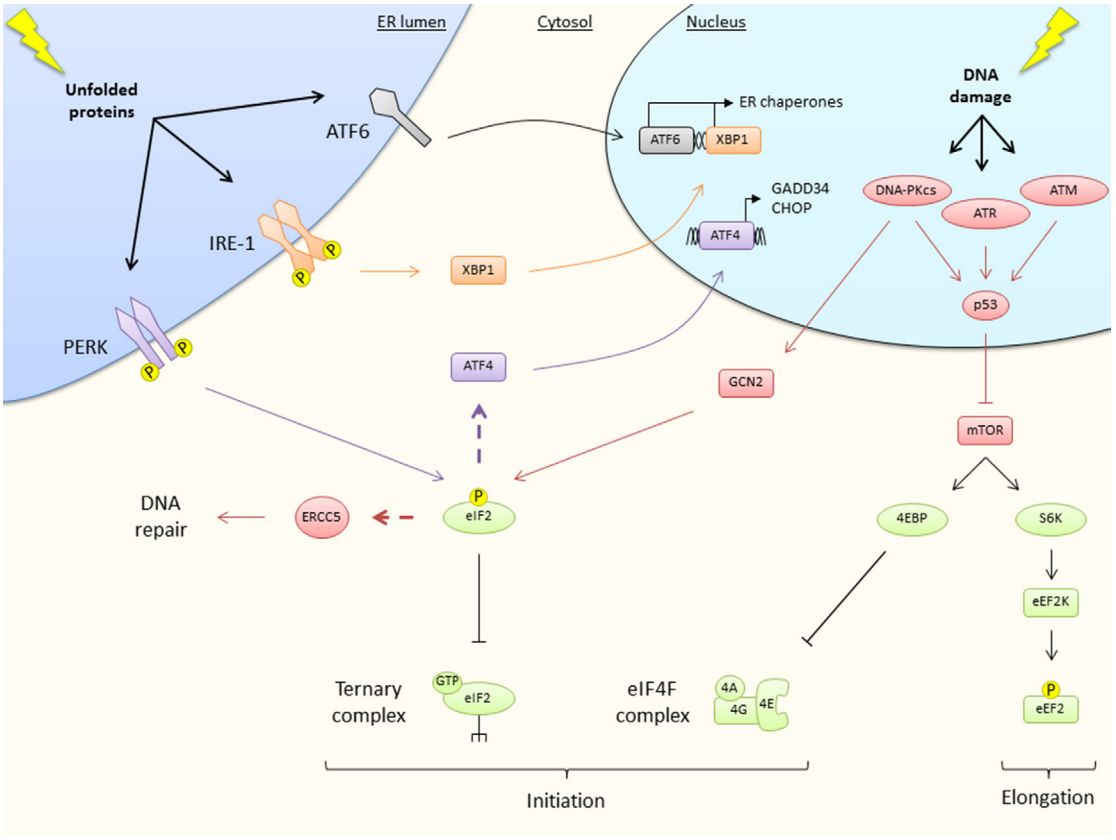
Elongation is controlled by regulating tRNA levels, in addition to the phosphorylation of eEF2 by eEF2K, which prevents ribosome translocation along the mRNA [3]. Interestingly, eEF2K is activated by Ca^{2+}/CaM and signalling downstream of AMPK, whereas it is inactivated by signalling through mTORC1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

cell survival to allow these cells to overcome the stresses associated with the tumour-microenvironment. Thus, it has been shown in cell lines where the UPR is inactivated by mutations in PERK and eIF2α, or alternatively by expressing dominant-negative PERK, there is reduced cell survival under conditions of extreme hypoxia [16]. In nude mice, tumours derived from these cells are smaller and exhibit higher levels of apoptosis in hypoxic areas compared those with intact stress signalling [16]. In agreement with these data, components of the UPR have been found to be overexpressed in many solid tumours including breast, gastric, liver, lung and prostate cancers (reviewed in [11]), and high levels of GRP78, IRE1α, PERK and ATP6 in prostate cancer patients are associated with poor prognosis [17•,18]. In addition to tumour progression driven by internal changes in the cell, recent data also show that induction of the UPR triggers the release of soluble factors that transmit ER stress to surrounding cells, a process termed transmissible ER stress (TERS) [19•]. It was shown that in TERS primed cells there was a reduction in PERK activity and eIF2α phosphorylation, and as a consequence, decreased ATF4 translation and CHOP expression, which protected the cells from CHOP-mediated apoptotic signalling [19•]. Cells exposed to TERS were also resistant to the effects of cytotoxic agents, in agreement with data which show that reduced translation of ATF4 is cytoprotective [20].

It is also possible to exploit ER stress to treat cancers with elevated protein production, for example in multiple myeloma (MM), where malignant plasma cells produce very high levels of immunoglobulin. This cancer is routinely treated with bortezomib, which induces ER stress and tumour cell killing by inhibiting the proteasome. A role for an active UPR and PERK/eIF2α axis in MM-cell cytotoxicity is supported by data which showed that low expression of ATF4 correlated with shorter progression-free survival of patients [21], and that genetic knockdown of IRE1α or XBP1 in human myeloma cell lines enhanced resistance to bortezomib [22].

DNA damage response

Double-strand or single-strand DNA breaks (DSB and SSB respectively), are induced by both endogenous (consequence of normal metabolism, such as ROS) and exogenous (UV, IR, chemotherapeutics) sources. DNA damage poses a significant risk to the genome as strand breaks interfere with DNA transcription and replication. Subsequently, cells have developed intricate mechanisms to maintain genomic stability, namely the DDR. The DDR is a collection of interlinked signalling pathways that coordinate DNA damage recognition, cell cycle arrest and DNA repair pathways [23]. Furthermore, if the damage cannot be adequately repaired, cell death pathways are induced to prevent compromised DNA being passed on to daughter cells.

The DDR is primarily mediated by three functionally similar PI3K serine/threonine protein kinases, ATM, ATR and DNA-PKcs, which are recruited to DNA breaks [23]. Importantly, all three kinases directly or indirectly stabilise the tumour suppressor p53, inducing a cascade of p53-dependent transcription pathways culminating in cell cycle arrest or cell death [24]. Moreover, it is becoming apparent that DDR genes are extensively regulated by post-transcriptional mechanisms [25].

A hallmark of cancer is genomic instability, and intriguingly, cancerous cells often show compromised activity of one or more DDR kinase, placing emphasis on the remaining pathways [26]. This is important considering many chemotherapeutic agents induce DNA damage or target the DDR and repair pathways, in an attempt to selectively kill cancerous cells [26].

UV-radiation and platinum-based chemotherapeutics, such as cisplatin, induce bulky adduct DNA damage and distort the DNA helix. Energy consuming protein synthesis is down-regulated via the phosphorylation of eIF2α [27], however, the expression of proteins involved in DNA repair pathways are enhanced via post-transcriptional regulatory mechanisms, including the presence of upstream open reading frames (uORFs) [28]. One such example is ERCC5, an indispensable endonuclease functioning within the nucleotide excision repair (NER) pathway [29]. A common polymorphic variant has been identified within the 5′UTR of ERCC5, generating an additional uORF, which enhances its translation following UV-and cisplatin-induced DNA damage [30••]. Importantly, this polymorphism was shown to confer resistance to platinum-based chemotherapeutics in paediatric patients with brain tumours (ependymoma) [30••], indicating the presence of this polymorphism could be used as a prognostic marker to determine the suitability of chemotherapeutics for an individual patient.

Post-transcriptional control of the DDR is also regulated by RNA binding proteins (RBPs). In response to IR-induced and UV-induced DNA damage, the RBP HuR promotes the selective translation of target mRNAs during global protein synthesis inhibition, including MDM2, p53, p21 and Bax, regulating cell cycle arrest and cell death pathways [31,32]. Moreover, many chemotherapeutics induce DNA damage through similar mechanisms to IR and UV, suggesting that dual targeting RBPs may aid chemotherapeutic efficacy.

Translational reprogramming within tumours

As discussed above, in the tumour environment cells are exposed to a range of external stresses, with limited blood supply contributing to hypoxia and nutrient deprivation, down-regulating protein synthesis [33]. Subsequently, adenocarcinoma tumour cells have been shown to adapt to stress by reprogramming translation and enhancing

ATF4 translation via activation of GCN2 and phosphorylation of eIF2α, in a mechanism essential for survival [34]. Moreover, translational reprogramming enhancing ATF4 expression in response to tumour stress also drives invasion and metastasis in melanoma, and more importantly is implicated in therapeutic resistance [35••]. These studies show how tumours can hijack a conserved stress response to promote cell survival, and implicate ATF4 as a mediator of tumour survival. Interestingly, relieving eIF2B inhibition with ISRIB (integrated stress response inhibitor) blocks tumour cell invasion [35••], highlighting how therapeutic targeting upstream of ATF4 may be beneficial.

mTOR is found within two alternative complexes, mTORC1 and mTORC2, distinguished by the presence of Raptor or Rictor respectively. As discussed above, mTORC1 regulates translation initiation and elongation through the phosphorylation of 4EBPs and p-70 S6K [4], as well as regulating the translation of specific subsets of mRNAs [36]. mTOR signalling is deregulated in tumours and promotes tumour growth [37], making mTOR an attractive chemotherapeutic target. The inhibition of mTOR in response to DNA damage and chemotherapeutic agents has been well studied [38–40], and this mechanism is likely to be dependent on p53 stabilisation [41]. Interestingly, mTORC1 and mTORC2 are both required for tumour cell survival in response to IR, by promoting the translation of protective mRNAs [42]. However, combined therapy of IR with dual mTORC1/2 inhibition overcomes resistance to DNA damage and promotes cancer cell death [42]. Additionally, mTOR inhibitors are effective when used singly to treat tumours. For example, upon depletion of the tumour suppressor, adenomatous polyposis coli (APC), the growth of the tumour is dependent on mTORC1 activity. Importantly, inhibition of mTORC1 with rapamycin selectively targets cancerous cells, reducing proliferation and tumour growth [43•]. Furthermore, proliferation of APC deficient tumour cells was dependent on mTORC1 inactivation of eEF2K, highlighting a mechanism where cancer cells drive tumorigenesis via the up-regulation of translation elongation [43•].

Interestingly, mTORC1 has also been shown to regulate the translation of ATF4 mRNA. Although ATF4 translation is regulated by a delayed re-initiation mechanism dependent on the phosphorylation of eIF2α [44], mTOR inhibition represses ATF4 translation by inhibiting cap-dependent translation and increasing the concentration of free TC that is no longer required for initiation, mimicking a decrease in eIF2α phosphorylation [45]. Although this mechanism may be transient, it indicates that targeting mTOR therapeutically could also relieve tumour reprogramming through ATF4.

Conclusions and future perspectives

Cancer cells take advantage of evolutionary conserved stress response pathways and post-transcriptional regulatory mechanisms to promote tumourigenesis and therapeutic resistance. Subsequently, these pathways have emerged as important therapeutic targets.

It has been proposed that targeting the UPR may be a promising method to treat cancers, however as discussed above, the effects of this stress response pathway on tumour development and maintenance are more complicated than originally anticipated, and dependent on both tumour stage and grade [12]. Therefore, extreme caution would be necessary when considering such targeting to ensure that pro-survival and pro-apoptotic roles of this pathway in individual tumour cells were fully explored [20,46]. Moreover, the phosphorylation of eIF2α generally promotes cell survival in response to stress [47], therefore, therapeutic targeting of eIF2α phosphorylation in conjunction with standard chemotherapy offers a unique opportunity to target tumours [35••]. However, treatment of cancer cell lines with an inhibitor of eIF2α phosphatases, subsequently enhancing eIF2α phosphorylation, sensitised cells to the chemotherapeutic doxorubicin [48], suggesting that these mechanisms, as with those observed in the UPR, could be tumour, cell line or therapeutic agent specific. Furthermore, the application of mTOR inhibitors individually, or in combination with alternative therapies, remains a crucial tool in the treatment of cancer, but as with platinum-based chemotherapy [30••], their effectiveness may be tumour type specific.

These studies underscore the importance of tumour and patient genotyping to determine the most effective way to target tumours that are utilising stress response pathways to proliferate and evade death, and should be considered for the development of future therapy.

Conflict of interest statement

Nothing declared.

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