

# Translation initiation in cancer at a glance

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## ABSTRACT

Cell division, differentiation and function are largely dependent on accurate proteome composition and regulated gene expression. To control this, protein synthesis is an intricate process governed by upstream signalling pathways. Eukaryotic translation is a multistep process and can be separated into four distinct phases: initiation, elongation, termination and recycling of ribosomal subunits. Translation initiation, the focus of this article, is highly regulated to control the activity and/or function of eukaryotic initiation factors (eIFs)

and permit recruitment of mRNAs to the ribosomes. In this Cell Science at a Glance and accompanying poster, we outline the mechanisms by which tumour cells alter the process of translation initiation and discuss how this benefits tumour formation, proliferation and metastasis.

**KEY WORDS:** Cancer, Cell signalling, Translation

## Introduction

In healthy cells, control of translation initiation is required for homeostasis, which is mediated through the production of key proteins that underpin essential cellular processes. In contrast, malignant cells ‘hijack’ the canonical translation machinery, leading to aberrant modulation of protein synthesis (Bhat et al., 2015; Hershey et al., 2012). This, in turn, presents cancer cells with many survival benefits, such as unregulated cellular divisions or dysregulated metabolism, which allow – if not promote – disease progression and metastasis.

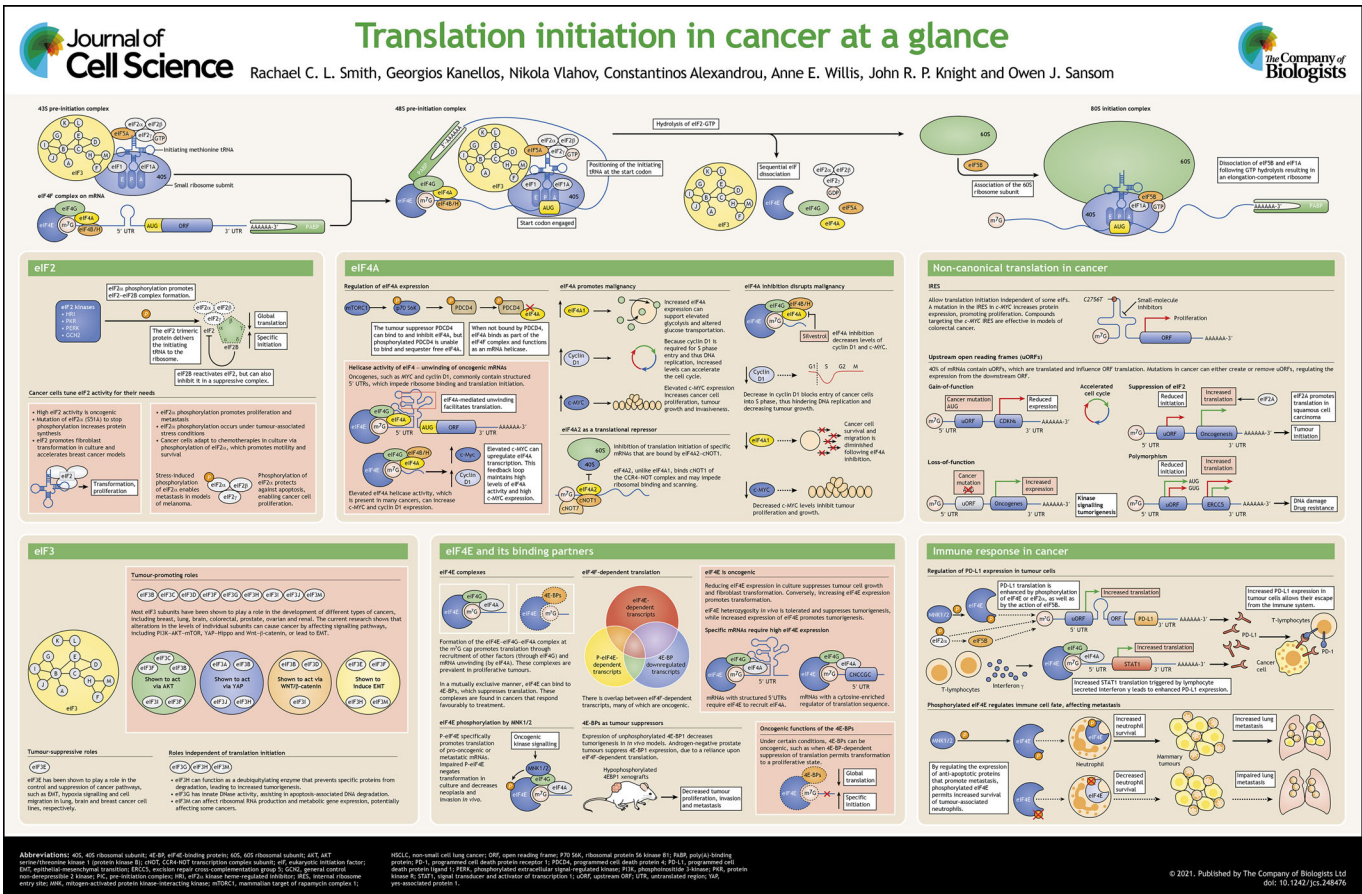
In the canonical pathway of translation initiation, eukaryotic initiation factors (eIFs) are recruited in a cap-dependent manner to mRNAs (reviewed in Hershey et al., 2012). However, under stress

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conditions, particularly those associated with the tumour cell microenvironment, including nutrient deprivation and hypoxia, the canonical initiation pathway is shut down (reviewed in Bhat et al., 2015). Cancer cells circumnavigate the shutdown of cap-dependent translation by upregulating expression of oncogenes and exploiting alternative methods of translation initiation (see Box 1). Furthermore, translational control has recently been implicated in the regulation of immune evasion (discussed in Box 2). This Cell Science at a Glance describes the diverse roles eIFs have in the progression and maintenance of the malignant phenotype. Owing to space limitations, it is not possible to discuss every eIF at length and instead we focus on the most studied factors. We direct the reader to related in-depth reviews addressing the role of translation in cancer (Bhat et al., 2015; Knight et al., 2020; Robichaud et al., 2019). Here, we guide the reader through the canonical translation initiation pathway, highlighting eIF2 and its regulators, the eIF2A and eIF5B family, the multi-protein eIF3 complex, the mRNA cap-binding protein eIF4E and its suppressor 4E-BP1 (also known as eIF4EBP1), and finally the RNA helicase eIF4A, and focussing on the oncogenic roles and expression patterns of each factor and pathway.

### Box 1. Non-canonical translation in cancer

Translation can be initiated by non-canonical pathways. Here, we detail how cancers exploit two of these, internal ribosome entry sites (IRESs) and upstream open reading frames (uORFs). mRNAs can initiate translation independently of some or all of the canonical eIFs using IRESs (Spriggs et al., 2009). Many oncogenes exploit IRESs to increase expression under conditions where cap-dependent translation is compromised. The IRES present within the 5'UTR of the *MYC* transcript is one of the most highly studied, and interestingly a mutation was identified in the IRES in cells derived from patients with multiple myeloma, which contributed to increased c-MYC expression (Chappell et al., 2000). This IRES is also required for c-MYC induction in colorectal cancer models (Schmidt et al., 2019). Small-molecule inhibitors of the c-MYC IRES have been developed, which may allow direct targeting in cancer (Didiot et al., 2012; Vaklavas et al., 2015).

Over 40% of mammalian mRNAs contain uORFs, and these are generally permissive for translation of the downstream coding region. However, certain uORFs are known to decrease the translation of the downstream cistron since re-initiation of translation following uORFs can be inefficient (Somers et al., 2013). In some cases, it has been shown that mutations in uORFs are associated with tumorigenesis through aberrant regulation of gene expression (Orr et al., 2019). For example, point mutations within uORFs of two cyclin-dependent kinase inhibitors (*CDKN2A* and *CDKN1B*) were shown to suppress their expression, accelerating cell cycle progression and contributing to hereditary cancers (Liu et al., 1999; Occhi et al., 2013). Mutations in uORFs can also increase protein expression. High-throughput screens found uORF loss-of-function mutations to be common in cancer, allowing increased expression of oncogenic proteins (Schulz et al., 2018; Wethmar et al., 2016).

uORFs can allow increased expression from downstream coding sequences following stress. Thus, under conditions where ternary complex levels are reduced, uORFs can be bypassed, increasing the number of 40S subunits that reach the coding sequence (Orr et al., 2019). For example, expression of the immune regulator programmed cell death ligand-1 (PD-L1; also known as CD274) is regulated by uORF read-through following cell stress, and this requires eIF5B (Suresh et al., 2020; Xu et al., 2019). In some cases, eIF2A is required for translation of uORF-containing transcripts, including those essential for tumour initiation in squamous cell carcinoma (Sendoel et al., 2017). uORFs can also affect drug responses. A polymorphism in the excision repair cross-complementation group 5 (*ERCC5*) gene generates an additional uORF that increases protein expression from the *ERCC5* coding region following DNA damage, providing resistance to DNA-damaging therapies *in vitro* and the clinic (Somers et al., 2015).

### eIF2

The trimeric protein eIF2 (eIF2 $\alpha$ , eIF2 $\beta$  and eIF2 $\gamma$ ; encoded by *EIF2S1*, *EIF2S2* and *EIF2S3*, respectively) is required to recruit the initiating methionine-tRNA to the 40S subunit, with initiation occurring following GTP hydrolysis by eIF2 $\gamma$  (see poster). eIF2 binds the 40S subunit as part of the 43S pre-initiation complex (43S PIC). After initiation, eIF2 is recycled by the guanine-nucleotide exchange factor eIF2B. This process is negatively regulated by phosphorylation of eIF2 $\alpha$  (P-eIF2 $\alpha$ ), which promotes formation of an inhibitory eIF2–eIF2B complex. eIF2 $\alpha$  is phosphorylated by four stress-responsive kinases, HRI (haem-regulated inducible kinase; *EIF2AK1*), PKR (protein kinase R; *EIF2AK2*), PERK (PKR-like endoplasmic reticulum kinase; *EIF2AK3*) and GCN2 (general control nonderepressible 2; *EIF2AK4*) resulting in reduced global translation, but increased translation of selected mRNAs by a number of mechanisms (see Box 1) (Leprivier et al., 2015; McConkey, 2017). This allows the stress to be resolved without continued protein synthesis.

Interestingly, mutant cell lines generated to have non-phosphorylatable eIF2 $\alpha$  were found to have oncogenic capacity (Donzé et al., 1995), as supported by more recent data, which show that in animal models of human epidermal growth factor receptor 2

### Box 2. Translation control of the immune response in cancer

Many aspects of immunity are governed by translation (Herdy et al., 2012; Piccirillo et al., 2014; Salerno et al., 2018, 2020); however, here we focus on recent reports of translational regulation of PD-L1 and the role of P-eIF4E in immune cells.

The interaction between PD-L1 on tumour cells and programmed cell death protein-1 (PD-1; also known as PDCD1) on T-cells allows tumours to escape immune surveillance. In a liver cancer mouse model, it was shown that altered translation of the *PD-L1* message facilitates tumour progression and metastasis (Xu et al., 2019). The presence of uORFs on the *PD-L1* mRNA facilitates increased PD-L1 synthesis following stress induced P-eIF2 $\alpha$ , a mechanism that lung cancer cells were also shown to employ in order to evade immune attack (Suresh et al., 2020). In the latter study, the presence of P-eIF2 $\alpha$  allows eIF5B to direct translation and enhance the selective engagement with the canonical *PD-L1* ORF for increased PD-L1 expression. In both cases, P-eIF2 $\alpha$  inhibition in cultured cells using ISRIB blocked PD-L1 upregulation (Xu et al., 2019; Suresh et al., 2020).

P-eIF2 $\alpha$  is not only required for upregulation of PD-L1, but is also critical for eliciting immunogenic cell death, a term describing the immune clearance of cancer cells presenting new antigens following stress (Bezu et al., 2018; Galluzzi et al., 2017; Senovilla et al., 2012) – so it is conceivable that cancer cells exploit the uORF-mediated PD-L1 expression to evade this immune attack. As various oncogenic drivers, as well as chemotherapy, increase the expression of PD-L1, carefully balanced combination treatments may offer significant advances in cancer therapy (Gilad et al., 2019; Pfirschke et al., 2016).

Interestingly, melanoma cells use another translation control mechanism to increase surface PD-L1 levels (Cerezo et al., 2018). In this case, increased eIF4F complex activity drives STAT1 translation, which in turn increases *PD-L1* transcription. PD-L1 upregulation can be successfully targeted by reducing the constituents of the eIF4F complex or by pharmacological inhibition of eIF4A (Cerezo et al., 2018).

Translation control mechanisms that affect tumour progression are not confined to cancer cells. Neutrophil activation by a range of stimuli requires P-eIF4E (Fortin et al., 2013). P-eIF4E promotes survival of prometastatic neutrophils by increasing expression of anti-apoptotic proteins, leading to greater metastasis (Robichaud et al., 2018). Importantly, inhibition of P-eIF4E reduces neutrophil survival and suppresses metastasis, while it was also shown to reduce PD-L1 expression in tumour cells (Xu et al., 2019).

positive (HER2<sup>+</sup>) breast cancer, non-phosphorylatable eIF2 $\alpha$  hastens tumorigenesis, whereas increasing P-eIF2 $\alpha$  assists targeted therapy (Darini et al., 2019). Moreover, low levels of P-eIF2 $\alpha$  in resected tumours correlate with worse survival in HER2<sup>+</sup> breast cancers. However, there are also reports of increased levels of P-eIF2 $\alpha$  in cancer tissues, for example, in gastrointestinal tumours (Lobo et al., 2000), Burkitt's lymphoma (Hart et al., 2012) and triple-negative breast cancer (TNBC) (Guo et al., 2017). Furthermore, high P-eIF2 $\alpha$  correlates with worse survival in pancreatic cancer (Wang et al., 2019) and prostate cancer (Nguyen et al., 2018). A key question is what is the advantage to the cancer cells of suppressing protein synthesis by increasing P-eIF2 $\alpha$ ?

Cancer cells use P-eIF2 $\alpha$  to respond to stresses that are concomitant with transformation, such as nutrient deprivation (via GCN2) and increased unfolded proteins (via PERK). HRI and PKR respond to heavy metals, and viral RNA and metabolic stress, respectively, with their roles in cancer summarised elsewhere (Burwick and Aktas, 2017; Marchal et al., 2014). P-eIF2 $\alpha$  increases following MYC proto-oncogene (c-MYC) expression in lymphoma models (Hart et al., 2012) and during progression of aggressive prostate cancers in mice (Nguyen et al., 2018). In both of these animal models, PERK is essential for P-eIF2 $\alpha$ , with *Eif2ak3* deletion in either model suppressing tumorigenesis. What drives PERK activation remains to be elucidated, although it is known it can be activated by hypoxia in addition to proteotoxic stress (Bi et al., 2005). Elevated c-MYC in colorectal cancer (CRC) cell and organoid models leads to depletion of amino acids and P-eIF2 $\alpha$  via GCN2 (Schmidt et al., 2019). The same study showed that interfering with P-eIF2 $\alpha$  results in tumour-cell-specific MYC-dependent apoptosis due to an inadequate amino acid supply. Tumour cytotoxicity is attractive therapeutically and was also seen in the PERK-dependent models of prostate cancer and lymphoma described above (Hart et al., 2012; Nguyen et al., 2018), highlighting both the importance of P-eIF2 $\alpha$  in responding to stress and its potential as a therapeutic target.

While induction of P-eIF2 $\alpha$  is a crucial adaptation to stress in cancer growth, it can also be a driver of metastasis (García-Jiménez and Goding, 2019). P-eIF2 $\alpha$  has been shown to be required for cell migration (Falletta et al., 2017), with this cross-species, cell-intrinsic mechanism co-opted for metastasis; melanoma cells pre-treated with salubrinal to increase P-eIF2 $\alpha$  colonise mouse lungs an order of magnitude more readily than untreated cells. This has prompted a comparison of cancer cells to starved cells, which also increase P-eIF2 $\alpha$  to enable migration (García-Jiménez and Goding, 2019). Consistent with these data, xenographs derived from prostate cancer patients are less metastatic when treated with integrated stress response inhibitor (ISRIB), a compound that increases eIF2 activity by targeting eIF2B (Nguyen et al., 2018). Mechanistically, metastasis may be driven by PERK due to increased protein secretion during epithelial to mesenchymal transition (EMT; the changing of epithelial cells into more motile mesenchymal cells) (Feng et al., 2014).

Various chemotherapies are used to treat cancer, which generally target important processes involved in cell proliferation. However, drug resistance can develop to these chemotherapies via the signalling changes they induce, with P-eIF2 $\alpha$  one such signal induced by cancer treatments. Doxorubicin suppresses proliferation, but, in parallel, inhibition of mTORC1 induces P-eIF2 $\alpha$ -dependent cell migration in culture (Harvey et al., 2019). Treatment with bortezomib or gemcitabine induces P-eIF2 $\alpha$  in drug-resistant pancreatic cancer cells, which are then re-sensitised by co-targeting P-eIF2 $\alpha$  (Palam et al., 2015; White et al., 2018). How these compounds induce P-

eIF2 $\alpha$  is unclear, although bortezomib does so via induction of HRI (White et al., 2018). Therefore, inhibiting P-eIF2 $\alpha$  may provide a means to induce tumour cell apoptosis and limit metastasis, but it could also be explored to improve current therapies.

### eIF2A and eIF5B

Initiation codon selection can occur independently of eIF2, such as through the action of eIF2A and eIF5B (Hinnebusch, 2014) (see poster). In doing so, both eIF2A, which is distinct from the eIF2 trimeric complex discussed above, and eIF5B direct translation of specific mRNAs. An elegant *in vivo* shRNA screen found a negative role for eIF2 members but a pro-tumorigenic effect of eIF2A in a model of squamous cell carcinoma (Sendoel et al., 2017). This same study identified oncogenic proteins that required eIF2A for synthesis, via non-canonical translation initiation (see also Box 1).

Following cellular stress and P-eIF2 $\alpha$ , the IRES-mediated translation of X-linked inhibitor of apoptosis (*XIAP*) mRNA is dependent on eIF5B (Thakor and Holcik, 2012). IRESs are structured elements within mRNAs that promote their translation through interaction with translation factors and/or the ribosome (see Box 1). Moreover, eIF5B has been shown to promote the translation of several additional IRES-containing mRNAs that encode anti-apoptotic proteins, including cellular inhibitor of apoptosis protein 1 (cIAP1, also known as *BIRC2*) and B-cell lymphoma extra-large (Bcl-xL; a splice variant of *BCL2L1*) (Ross et al., 2019). eIF5B was also shown to increase the translation of p21 and regulate the activation of the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway, thereby promoting resistance and survival in glioblastoma multiforme (GBM) cells (Ross et al., 2019). Increased eIF5B expression has been associated with poor prognosis in patients with hepatocellular carcinoma (HCC); this is partly based on the observation of eIF5B-mediated increases in ARF GTPase-activating protein 1 (ASAP1) expression, which promoted HCC cell proliferation and migration *in vitro* and *in vivo* (Wang et al., 2016). The GTPase enzymatic activity of eIF5B provides a potential mode of inhibition. As such, a compound targeting eIF5B would significantly aid future studies of eIF5B function in cancer.

### eIF3

eIF3 is a ~800 kDa complex containing 13 subunits denoted eIF3A to eIF3M, (Browning et al., 2001; Marchione et al., 2013) (see poster). eIF3 has two major roles in canonical initiation, recruiting eIF2 to form the 43S PIC and stimulating binding of the 43S PIC to mRNA (Hershey, 2015; Valášek et al., 2017; Yin et al., 2018). By binding to IRESs, eIF3 also plays an important role in cap-independent translation (see Box 1). The role of each eIF3 subunit in cancer development remains poorly understood, with studies showing reliance upon and upregulation of specific eIF3 subunits (eIF3A–eIF3D and eIF3G–eIF3M), whereas other studies point to specific downregulation (eIF3E and eIF3F) (reviewed in Gomes-Duarte et al., 2018; Hershey, 2015; Yin et al., 2018).

Data also suggest that certain subunits have roles in translation that are independent of the eIF3 complex. For example, direct interaction between eIF3D and the 7-methylguanosine (m<sup>7</sup>G) mRNA cap results in the increased translation of the proto-oncogene *Jun* (Lee et al., 2016). eIF3E (also called INT6) can act as a negative regulator of translation, as loss of eIF3E in breast and lung cancer cells has been linked to increased translation of EMT genes and overproduction of the cytokine transforming growth factor  $\beta$  (TGF $\beta$ ) (Desnoyers et al., 2015; Gillis and Lewis, 2013). Overexpression of eIF3I drives CRC by direct translational

upregulation of cyclooxygenase-2 (COX-2, also known as PTGS2), activating WNT signalling (Qi et al., 2014). Furthermore, in oestrogen-receptor-positive breast cancer cells, oestrogen regulates the levels of eIF3F expression, thus affecting the global translation rates and promoting the proliferation and survival of the cancer cells (Cuesta et al., 2019).

Recent reports show a link between eIF3 subunits and proteins that can write, erase and read the reversible N<sup>6</sup>-methyladenine (m<sup>6</sup>A) RNA modification, the most common post-transcriptional modifier of gene expression (reviewed in Roundtree et al., 2017; Wang et al., 2020b; Zaccara et al., 2019). For example, both eIF3A and eIF3B have been independently shown to directly bind to either the m<sup>6</sup>A reader YTH domain-containing family protein 1 (YTHDF1) or the m<sup>6</sup>A writer methyltransferase like 3 (METTL3) to promote Yes-associated protein 1 (*YAP1*) translation, which results in an increase in cell growth, invasion, drug resistance and metastasis *in vitro* and *in vivo* (Jin et al., 2019; Jin et al., 2020a). YTHDF1 can bind, and m<sup>6</sup>A modify, to increase translation of *eIF3C* mRNA, which has been linked to increased cell growth and migration of ovarian cancer cells (Liu et al., 2020). Furthermore, a recent study showed a novel mechanism for mRNA circularisation mediated by the direct interaction between METTL3 and eIF3H (which is elevated in most solid tumours), promoting transformation and specific translation of oncogenic mRNAs (Choe et al., 2018).

Finally, eIF3 subunits also have roles that are distinct from translation initiation. For example, two pools of eIF3H exist, one binding to the eIF3 complex and another functioning as a deubiquitylating enzyme that stabilizes *YAP1*, promoting tumour invasion and metastasis both *in vitro* and *in vivo* (Zhou et al., 2020). In bladder carcinoma cells, eIF3G is cleaved during apoptotic cell death, resulting in translocation to the nucleus, where cleaved eIF3G promotes both caspase activation and has innate DNase activity, assisting in apoptosis-associated DNA degradation (Kim et al., 2013). In addition, alterations in the levels of some subunits have a transcriptional, rather than a translational effect. In the liver, *in vivo* reduction of eIF3M expression has little effect on translation but reduces ribosomal RNA production and the transcription of genes whose products are associated with metabolism, although the exact mechanism behind this is unclear (Smekalova et al., 2020). While it is not known whether overexpression of eIF3M has the opposite effect, its overexpression is associated with poor prognosis for patients with CRC and TNBC (Han et al., 2020; Hershey, 2015; Wang et al., 2020a), which would be consistent with increased ribosome biogenesis and dysregulated metabolism.

### eIF4E

eIF4E binds to mRNAs via the m<sup>7</sup>G cap structure at the 5' end of most mRNAs. This protein is part of the eIF4F complex, also comprising the scaffold protein eIF4G and the RNA helicase eIF4A (see below). Cap-bound eIF4F recruits the 43S PIC through an interaction between eIF4G and eIF3 (see poster).

Elevated eIF4E expression has been reported in many cancers and, in general, is not associated with gene amplification (Haydon et al., 2000; Sorrells et al., 1998). Both gain-of-function and loss-of-function studies in cells and animal models have revealed a clear role for eIF4E in tumorigenesis. In fibroblasts, eIF4E overexpression promotes malignant transformation (Lazaris-Karatzas et al., 1990), and depletion of eIF4E reduces RAS-driven transformation (Rinker-Schaeffer et al., 1993). *In vivo* overexpression of eIF4E from the  $\beta$ -actin promoter increases tumour formation and accelerates the

E $\mu$ -MYC lymphoma model (Ruggero et al., 2004; Wendel et al., 2004). Complete ablation of eIF4E is embryonic lethal, but eIF4E heterozygosity sustains global protein synthesis and provides resistance to tumour formation (Truitt et al., 2015).

Two classes of mRNAs are particularly sensitive to eIF4E expression. mRNAs with long 5' untranslated regions (UTRs) are more readily translated following eIF4E overexpression (Koromilas et al., 1992), including key proliferation genes such as cyclin D1 and MYC (reviewed by Bhat et al., 2015; Rosenwald et al., 1993). This family of eIF4E-sensitive mRNAs require eIF4E to recruit the helicase eIF4A for 5'UTR unwinding (see section on eIF4A below). The second class of mRNAs is enriched for proteins involved in managing oxidative stress and are sensitive to the level of eIF4E due to a specific 5'UTR regulatory motif (Truitt et al., 2015). As such, eIF4E heterozygosity leads to tumour-specific oxidative damage, limiting tumour growth. There seems little overlap between these two mRNA classes, suggesting that there are context-dependent determinants of eIF4E sensitivity. Furthermore, mRNAs containing the 5'UTR regulatory motif that encode proteins not involved in the oxidative stress response may show dependency on eIF4E expression in different contexts to the tumour models used by Truitt et al. (2015).

A variety of therapeutic agents have been developed against eIF4E (reviewed by Siddiqui and Sonenberg, 2015). The most promising of these is the repurposed anti-viral ribavirin, which targets eIF4E by disrupting its interaction with the m<sup>7</sup>G-cap, although its exact mechanism of action remains controversial (Westman et al., 2005; Yan et al., 2005; Kentsis et al., 2005). This compound has been used in over 10 cancer trials, displaying few side-effects and high efficacy (reviewed by Casaos et al., 2019).

eIF4E serine 209 can be phosphorylated by the homologous kinases MAP kinase-interacting serine/threonine-protein kinase 1 and 2 (MNK1 and MNK2; also known as MKNK1 and MKNK2) (Waskiewicz et al., 1997). Genetically deleting the MNKs or mutating eIF4E serine 209 to alanine is completely tolerated in mice (Furic et al., 2010; Ueda et al., 2004), despite P-eIF4E being the culmination of multiple proliferative signalling cascades, such as the ERK and p38 MAPK pathways (Proud, 2015). P-eIF4E is not required for initiation, but regulates translation of specific mRNAs, a role which is commonly dysregulated in cancer. Cells expressing an engineered non-phosphorylatable eIF4E evade malignant transformation both *in vitro* (Topisirovic et al., 2004) and *in vivo* (Wendel et al., 2007). Similarly, in a mouse model of prostate cancer, non-phosphorylatable eIF4E reduces neoplasia and invasive carcinoma (Furic et al., 2010). Furthermore, MNK inhibition reduces lung colonisation by melanoma cells by 50% (Konicek et al., 2011). How P-eIF4E drives specific translation is unclear, but there is overlap between the eIF4E-sensitive transcripts and the P-eIF4E sensitive mRNAs. For example, we recently showed a requirement for P-eIF4E to maintain MYC expression in colorectal cancers (Knight et al., 2020). A formal comparison within the same model system is needed to delineate the mechanisms regulating specific oncogenic translation controlled by overall eIF4E expression and/or its phosphorylation.

### eIF4E-binding proteins

eIF4E can be bound by the eIF4E-binding proteins (4E-BPs) in an interaction that is mutually exclusive with that of eIF4G, the scaffold protein that binds many eIFs that are essential for initiation (Pause et al., 1994). The three 4E-BP homologues are phosphorylated downstream of the growth-promoting mTOR complex 1 (mTORC1), with only hypo-phosphorylated 4E-BPs able to bind

eIF4E (Gingras et al., 1999). The eIF4E–4E-BP interaction suppresses protein synthesis, meaning that 4E-BP expression is generally reduced, or its phosphorylation increased in malignancies (reviewed by Musa et al., 2016). Reducing 4E-BP increases eIF4F formation, as well as the translation of a subset of mRNAs similar to those sensitive to eIF4E expression.

In a mouse model of prostate cancer, tumours in androgen-negative animals have reduced 4E-BP1 expression and a reliance upon eIF4F formation for the translation of proliferative mRNAs (Liu et al., 2019). Targeting the eIF4F complex, by expression of hypo-phosphorylated 4E-BP1, reduced tumour proliferation and extended survival in xenograft models. Increased eIF4F formation augmented translation of mRNAs with structured 5'UTRs (Liu et al., 2019). Previous work in the same prostate cancer model found that hypo-phosphorylated 4E-BP1 decreases the expression of mRNAs involved in cell migration, independently of 5'UTR structure or length, thereby reducing invasion and metastasis (Hsieh et al., 2012). This study instead defined a specific motif that resulted in 4E-BP1-dependent suppression. This motif appears to be conserved across species as it was also found in an RNA-binding screen using the *Drosophila* 4E-BP homologue (Jin et al., 2020b). The same hypo-phosphorylated 4E-BP1 expression system was shown to extend survival in a mouse model of lymphoma (Hsieh et al., 2010).

Consistent with a role in inhibiting translation, 4E-BPs suppress transformation in the absence of p53 (also known as TP53) *in vitro* and *in vivo* (Petroulakis et al., 2009). However, the same study showed that in MEFs expressing p53, 4E-BP expression permits greater transformation by inhibiting p53-dependent senescence, thus revealing an oncogenic function of the 4E-BPs (Petroulakis et al., 2009). 4E-BPs can also promote tumorigenesis under conditions of hypoxia through an upregulation of non-canonical translation (Braunstein et al., 2007). In hypoxic breast cancer cell lines, overexpression of 4E-BP1 promotes tumorigenesis by increasing angiogenesis. This relies upon eIF4G expression to promote the translation of pro-angiogenic vascular endothelial growth factor (*VEGF*) via its IRES (Braunstein et al., 2007) (see Box 1). Furthermore, a recent study has shown that 4E-BP expression maintains proliferation under hypoxia and, although 4E-BP deletion accelerated tumorigenesis in a mouse model of prostate cancer, the resulting tumours had smaller areas of hypoxia (Ding et al., 2018).

The interplay between eIF4E, eIF4G and 4E-BPs has been studied in *BRAF* mutant cancers that develop resistance to *BRAF* inhibition. Point mutations in *BRAF* are common across many tumour types, resulting in hyperactivation of downstream signalling. *BRAF* mutant tumours respond well to specific inhibitors of the mutant protein, but acquired resistance to these inhibitors is common, making mechanisms of re-sensitisation a priority (Poulikakos and Rosen, 2011). Longitudinal analysis of patient tissue found persistent eIF4F complex formation as a marker of resistance (Boussemaert et al., 2014). Importantly, the eIF4F complex provides more than just a marker, allowing re-sensitisation to mutant *BRAF* inhibition by co-targeting the eIF4E–eIF4G interaction or eIF4A activity.

### eIF4A

Structured 5'UTRs impede the scanning ribosome and require unwinding by ATP-dependant RNA helicase activity exerted by eIF4F-bound eIF4A (eIF4A<sub>c</sub>). Binding of eIF4B or eIF4H further stimulates helicase activity, while eIF4A availability is controlled by programmed cell death 4 (PDCD4), which sequesters free eIF4A (see poster). PDCD4 is inhibited downstream of mTORC1, allowing increased eIF4A<sub>c</sub> formation. Mammals express two

eIF4A paralogues, eIF4A1, which has been most studied in cancer, and eIF4A2. Both paralogues are structurally similar and can bind as eIF4A<sub>c</sub> (Conroy et al., 1990), yet recent data suggest that eIF4A1 and eIF4A2 are functionally distinct (Lu et al., 2014; Meijer et al., 2013; Galicia-Vázquez et al., 2012).

Dysregulation of eIF4A, PDCD4, eIF4B or eIF4H is observed in many malignancies. Ectopic eIF4A expression decreases survival in T-cell acute lymphoblastic leukaemia (T-ALL) (Wolfe et al., 2014), while targeting eIF4A in pancreatic cancer bypasses drug resistance (Müller et al., 2019). Increased levels of eIF4B and eIF4H in lung and colorectal cancer correspond with increased proliferation, invasion and drug resistance (Vaysse et al., 2015; Wu et al., 2011), whereas decreased PDCD4 expression – increased eIF4A<sub>c</sub> – in breast (Meric-Bernstam et al., 2012), colon (Mudduluru et al., 2007) and ovarian cancer (Wei et al., 2009) is associated with poor prognosis. Furthermore, eIF4B is required for translation of cancer-promoting mRNAs with long structured 5'UTRs in diffuse large B-cell lymphoma, where high eIF4B expression correlates with poor prognosis (Horvilleur et al., 2014).

How does eIF4A activity promote and maintain malignancy at the molecular level? The mRNAs encoding many oncogenic proteins, including pro-proliferative *MYC* and the cell cycle regulator *CCND3*, contain highly structured 5'UTRs that rely upon eIF4A helicase activity (Modelska et al., 2015; Rubio et al., 2014; Wolfe et al., 2014). Increased c-MYC expression is observed in CRC where eIF4A inhibition using silvestrol, a small molecule inhibitor of both eIF4A1 and eIF4A2, decreases c-MYC expression and tumour growth (Wiegering et al., 2015). In the same study, mTORC1 inhibition, which also suppresses protein synthesis, had no effect on c-MYC or growth, showing this to be a specific requirement for eIF4A activity rather than a requirement for maintained protein synthesis rates. Similarly, silvestrol derivatives reduce DNA replication and tumour growth in pancreatic cancer, despite its resistance to mTOR inhibition (Müller et al., 2019). c-MYC protein also upregulates *EIF4A1* transcription (Lin et al., 2008), a feedforward loop likely to reinforce elevated c-MYC expression and underpin sensitivity following eIF4A targeting. Progressive PDCD4 loss marks adenoma to colorectal tumour transition (Mudduluru et al., 2007), highlighting that eIF4A perhaps regulates tumour progression and invasiveness. eIF4A promotes translation of cyclin D1, which is required for progression into the DNA synthesis phase of the cell cycle. Inhibition of eIF4A in TNBC blocks this progression, diminishes cell survival and may mitigate cell migration (Rubio et al., 2014). In pancreatic cancer, an accelerated cell cycle is supported by elevated glycolysis and dysregulation of glucose transportation, allowing effective dual targeting of eIF4A and glutamine catabolism (Chan et al., 2019).

eIF4A2 has been shown to mediate miRNA repression through binding CCR4-NOT transcription complex subunit 1 (cNOT1) (Meijer et al., 2013; Wilczynska et al., 2019). It is suggested that eIF4A2 may 'clamp' specific mRNAs, impeding translation and repressing gene expression, activities which may or may not prove beneficial for tumour cells. There is no consensus in the role of eIF4A2 in cancer; high eIF4A2 expression predicts good prognosis in breast (Yan et al., 2011) and lung cancer (Shaoyan et al., 2013), but increases invasion and migration in CRC (Chen et al., 2019). These differences may be due to distinct tumour microenvironments. Interestingly, eIF4A2 downregulation in CRC causes decreased transcription of *MYC*, signifying possible overlap between the targets of eIF4A1 and eIF4A2. Furthermore, eIF4A2 loss in CRC increases sensitivity to oxaliplatin therapy, extending overall survival (Chen et al., 2019).

## Concluding remarks

Translation initiation is extensively regulated to control both bulk protein output and specific synthesis of cancer related proteins. Cancers exploit the mechanisms by which translation is regulated in order to generate a proteome that is conducive with proliferation, invasion or migration. This can result from an increase in total protein synthesis rates by elevated expression of specific eIFs, but additionally from the effects of signalling to translation by pathways that converge on, for example, eIF2 $\alpha$  and the 4E-BPs. Specific translation of proto-oncogenes has been reported to result from dysregulated expression of all initiation factors, increasing the synthesis of numerous proteins that promote proliferation, immune evasion and cell motility. Insights into how translational control within the tumour microenvironment contributes towards cancer progression and permits metastasis, demonstrate the possibility of targeting non-tumour cells via translation regulators.

Given the recent insights into the differences in translation between normal and cancer cells, many eIFs are now being reassessed as bona fide therapeutic targets for cancer, with clinical trials already underway investigating inhibitors of eIF4E and eIF4A (Xie et al., 2019; Cunningham et al., 2018). The field eagerly awaits the results of these trials, which may provide the first proof-of-concept that translation can be targeted in the clinic. As we have discussed, advances in our understanding of the eIFs in cell and animal models of cancer, coupled with disease-positioning studies and the development of potent inhibitors, means that future clinical trials targeting further components of the translation initiation machinery are very much in sight.

## Competing interests

The authors declare no competing or financial interests.

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## Cell science at a glance

A high-resolution version of the poster and individual poster panels are available for downloading at <http://jcs.biologists.org/lookup/doi/10.1242/jcs.248476.supplemental>

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