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REVIEW

Translation factors and ribosomal proteins control tumor onset and progression: how?

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Gene expression is shaped by translational control. The modalities and the extent by which translation factors modify gene expression have revealed therapeutic scenarios. For instance, eukaryotic initiation factor (eIF)4E activity is controlled by the signaling cascade of growth factors, and drives tumorigenesis by favoring the translation of specific mRNAs. Highly specific drugs target the activity of eIF4E. Indeed, the antitumor action of mTOR complex 1 (mTORc1) blockers like rapamycin relies on their capability to inhibit eIF4E assembly into functional eIF4F complexes. eIF4E biology, from its inception to recent pharmacological targeting, is proof-of-principle that translational control is druggable. The case for eIF4E is not isolated. The translational machinery is involved in the biology of cancer through many other mechanisms. First, untranslated sequences on mRNAs as well as noncoding RNAs regulate the translational efficiency of mRNAs that are central for tumor progression. Second, other initiation factors like eIF6 show a tumorigenic potential by acting downstream of oncogenic pathways. Third, genetic alterations in components of the translational apparatus underlie an entire class of inherited syndromes known as 'ribosomopathies' that are associated with increased cancer risk. Taken together, data suggest that in spite of their evolutionary conservation and ubiquitous nature, variations in the activity and levels of ribosomal proteins and translation factors generate highly specific effects. Beside, as the structures and biochemical activities of several noncoding RNAs and initiation factors are known, these factors may be amenable to rational pharmacological targeting. The future is to design highly specific drugs targeting the translational apparatus.

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INTRODUCTION

The nucleolus is the nuclear site of ribosomal production. Here, ribosomal RNA (rRNA) is transcribed and processed. In the meantime, most ribosomal proteins are assembled on the rRNA by the help of trans-acting factors of ribosome biogenesis.[1] Enlarged nucleoli, which are thought to reflect increased ribosome biogenesis, are often seen in cancer cells. Nucleolar staining by AgNors was consequently proposed as a prognostic malignancy marker in the 80's.[2] It is likely that nucleolar enlargement is a readout of malignancy due to specific genetic lesions because the loss of tumor suppressors like pRB and p53 causes an increase in ribosome biogenesis.[3] Surprisingly, 'loss of function' mutations in the ribosomal machinery can lead to syndromes with increased cancer risk, indicating an unexpected and additional role of the ribosomal apparatus in the control of gene expression.[4] More recently, ribosomal mutations have been found also in juvenile sporadic cancers.[5] Thus, tumorigenesis is linked both to an increased demand for ribosomal factors, as well to specific unexpected alterations of the ribosomal apparatus.

It is common knowledge that ribosomes are employed in the cytoplasm for translation, although controversial evidence for protein synthesis in the nucleus has been proposed.[6] This said, translational control commonly refers to the multiple mechanisms coordinating translation in the cytoplasm. Rapamycin derivatives (rapalogs) block mTORc1 kinase. Rapalogs inhibit several stages of ribosome production and translational control, and have been pivotal in showing that translation is a druggable aspect of the oncogenic process.[7–9] Rapalogs were first used for treating graft rejection and are now employed for the treatment of selected cancer types, renal cell carcinoma, giant cell astrocytoma, breast cancer and progressive neuroendocrine tumors.[10] The clinical use of rapalogs provides evidence to the concept that oncogenic signaling converges on the translational machinery.

In retrospective, it is not 'so' surprising that translational control is pivotal to cancer progression. The massive sequence data obtained in the last years show that mRNAs contain a plethora of untranslated regulatory elements (UTRs) in *cis*. In addition, hundreds of micro RNAs[11] and long noncoding RNAs[12] annealing on their target mRNAs and regulating translation have been described. The magnitude of regulatory information brought by nucleotide sequences correlates with experimental evidence, indicating that the mere existence of an mRNA into a cell does not necessarily predict the existence of its encoded protein. This was first shown in the simple *Saccharomyces cerevisiae* model long ago,[13] and more recently in mammalian fibroblasts.[14] Several aspects of translational control in cancer have been recently covered.[15–17] Here, we will provide a collection of evidence showing that translation is offering us

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several elements, which may help us to understand and defeat cancer.

THE GENERAL MECHANICS OF TRANSLATION AND THE IMPACT OF NEW TECHNOLOGIES

In simple terms, the translational landscape is shaped by three mechanistic factors: translation apparatus; RNA sequences and signaling pathways converging to the translational machinery.[16] The hardware of the translational machinery is composed by ribosomes and translation factors. Ribosomal components include ribosomal proteins and rRNA. Signaling pathways dynamically modulate translation in demand to specific needs, providing a rapid adaptation of the machinery to the cellular conditions. As genetic studies have shown that mutations of several ribosomal proteins lead to inherited disease and increased tumor formation,[18] as well as to specific syndromes, we conclude that the interplay between ribosomes and tissue-specific signals is a central factor in adapting an ubiquitous ribosomal machinery to local conditions.

Translation itself is divided into four phases: initiation, elongation, termination and recycling. Translation can be recapitulated by *in vitro* systems, thus providing us with an excellent knowledge of mechanistic steps.[19] Moreover, the recent addition of several ribosomal and translation factor structures provide us with unique snapshots of the translational machinery.[20] Last, the emergence of single-molecule analysis of ribosomal components is giving us an insight on the dynamics of translation.[21] The combination of *in vitro* systems allowing mechanistic studies, structural data and single-molecule analysis render translation uniquely amenable to modern and rationale drug design. This enormous advantage, in comparison with other biological processes, has not been fully exploited due to a severe misconception on the lack of value of targeting the translational machinery. Wrongly, for long time, the translational machinery has been seen as a passive 'translator' of the transcriptional landscape.

Concerns about targeting the translational machinery were based on the misconception of its 'lack of specificity', ignoring important facts. First, the efficiency of translation, *in vivo*, is incomparably higher than *in vitro*; second, initiation, held as the rate-limiting step of translation, is controlled by signaling pathways that converge to translation factors known as eukaryotic initiation factors (eIFs).[16] The consequence of these two facts is that, whereas inhibition of eIFs *in vitro* may lead to general effects, *in vivo* it achieves highly specific results. Genetic evidence proves this conclusion.

CONTROL OF TRANSLATION BY RNA SEQUENCES

RNA sequences regulate translational efficiency and RNA stability. The oncogenic property of a RNA regulatory sequence may depend from the cellular context, being active only upon the appropriate input (see IRES as an example below). Thus, one important concept is that the interplay among different components of the translational apparatus is critical to define the function of a single element, thus providing a layer of specificity poorly understood. Some mRNA regulatory sequences (Figure 1) will be discussed in function of specific processes.

Cytoplasmic decay of mRNA is obviously controlled by *cis*-acting sequences on the mRNAs and multiple proteins recognizing those sequences in *trans* that together control the recruitment of the degradation machinery.[22] Several recent reviews have addressed the mechanisms of cytoplasmic decay. The link between translational efficiency and degradation is particularly intriguing, that is, what comes first? Evidence shows that two mechanisms of translational repression associate with premature mRNA degradation: microRNA (miRNA)-driven repression[23] and nonsense-mediated decay.[24] The actual modalities by which miRNAs induce downregulation of protein levels by either translational repression or by inducing mRNA decay are complex and somewhat linked to the cellular models.[25] Further complexity is due to the fact that RNA-binding proteins and miRNAs coregulate mRNAs: AUF1 1 binds AU-rich elements in 3′-untranslated regions to regulate mRNA degradation and/or translation. For mRNAs in which AUF1 affects the decay rate, degradation requires the component of the miRNA machinery, AGO2.[26] Nonsense-mediated decay is caused by the presence of premature stop codons on mRNA. So far, limited evidence suggests that nonsense-mediated decay may act as a protection from tumorigenesis. The inhibition of nonsense-mediated decay

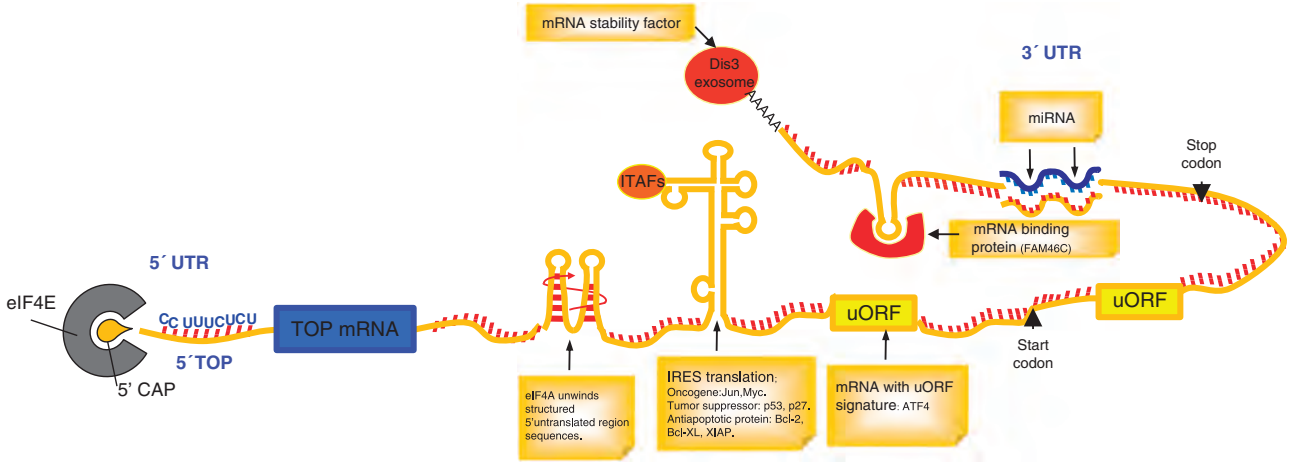

Figure 1. Multiple regulatory sequences on mRNAs. The 5′ UTR sequence with the 7-methyl-GTP cap is recognized by the tumorigenic eIF4E cap-binding protein, which assembles into the eIF4F complex containing eIF4G and eIF4A. Hairpin structures, inhibitory for translation, are opened by the eIF4A helicase. IRES sequences can allow translation in conditions of eIF4F inhibition. uORF sequences repress translation except upon stresses like the unfolded protein response. miRNAs act on target mRNAs by reducing translational efficiency and subsequently mRNA stability. A variety of exonucleases and RNA-binding proteins couple translation to mRNA stability. ITAFs, IRES *trans*-acting factors. 5′-terminal oligopyrimidines (5′-TOP) sequences regulate translation of several mRNAs of the translational machinery by conferring growth factor responsiveness.

promotes resistance to endoplasmic reticulum stress, and encourages tumor formation and survival *in vivo*.[27]

More generally, a number of proteins are involved in RNA stabilization binding either at the 3′-UTR or 5′-UTR and greatly contribute to the control of gene expression. The general picture is still confusing because most of the interactions are remarkably cell-specific.[28] In spite of confusion, cell specificity is not artifactual from cellular models, but rather the key issue for targeting these factors. Indeed, it was found that a number of RNA-binding proteins that affect translation and/or mRNA stability are mutated in specific subtypes of cancer cells: prominent cases are Fam46c and Dis3 in multiple myeloma.[29] The molecular mechanism, and the targets of Fam46 and Dis3 are yet unknown, but they may couple RNA translation with degradation. Whatever the mechanism, the significance is clear.

The bulk of translation is cap-dependent and relies on a complex of proteins that assemble at the 7-methyl-guanosine cap at the 5′ end of mRNAs. Oncogenic stimulation by growth factors increases cap-dependent translation and will be discussed in the next chapter. However, additional translational mechanisms explain how tumor cells adapt to growth factor deprivation and hypoxia, when cap-dependent translation is impaired. Internal ribosomal entry sites (IRESs) are structured elements in the 5′ region of mRNAs that allow translation in conditions of reduced cap-dependent translation. IRES sequences permit the binding of an mRNA to 40S ribosomes, with limited assistance of initiation factors. First described in picornaviruses,[30] IRES have emerged as a prominent way by which viral mRNAs are used in conditions of translational shut-off.[31] Later, cellular mRNAs containing IRES elements have been identified.[32] Some cellular IRES require specific IRES *trans*-acting factors, whereas others require few additional proteins and can bind ribosomes directly. It is estimated that in ~10% of eukaryotic mRNAs, translation is initiated via this cap-independent mechanism.[33,34] IRES-mediated translation is the preferred method of protein synthesis when cap-mediated translation is attenuated under conditions of stress, like hypoxia,[35,36] genotoxic shock and apoptosis,[37–39] or in specific physiological conditions such as mitosis.[40] IRES-containing mRNAs encode for oncogenes like jun,[41] and myc,[42,43] tumor suppressors as p53,[44] and p27,[45] or antiapoptotic factors as bcl2[46,47] and Xiap.[46] One word of caution about cellular IRES sequences: not all the described IRES sequences have received a full physiological validation encompassing multiple technologies.[48] Therefore, when the existence of IRES-dependent translation is suspected, rigorous experimentation is needed.

Another regulatory sequence that controls translation and response to therapy in cancer cells is represented by upstream open reading frame (uORF). uORFs are short reading frames upstream of the main ORF (Figure 2). The main regulatory mechanism of uORF is the inhibition of translation of the downstream ORF. This is due to the fact that reinitiation of the downstream ORF, following translation of a uORF is inefficient, therefore, uORFs typically function as translational barriers. Paradoxically, the translational barrier can be overcome in conditions of reduced translation driven by impaired ternary complex formation (ternary complex abbreviated as TC is formed by eIF2, GTP, Met-tRNA). Impairment of TC levels is seen in conditions of specific cellular stress, that is, viral infection, amino acid deprivation and unfolded protein response (UPR).[49] Reduced TC permits post-termination 40S subunits to resume scanning, and reinitiate downstream at the main ORF. By this elegant mechanism, uORF containing mRNAs have silent ORF in healthy

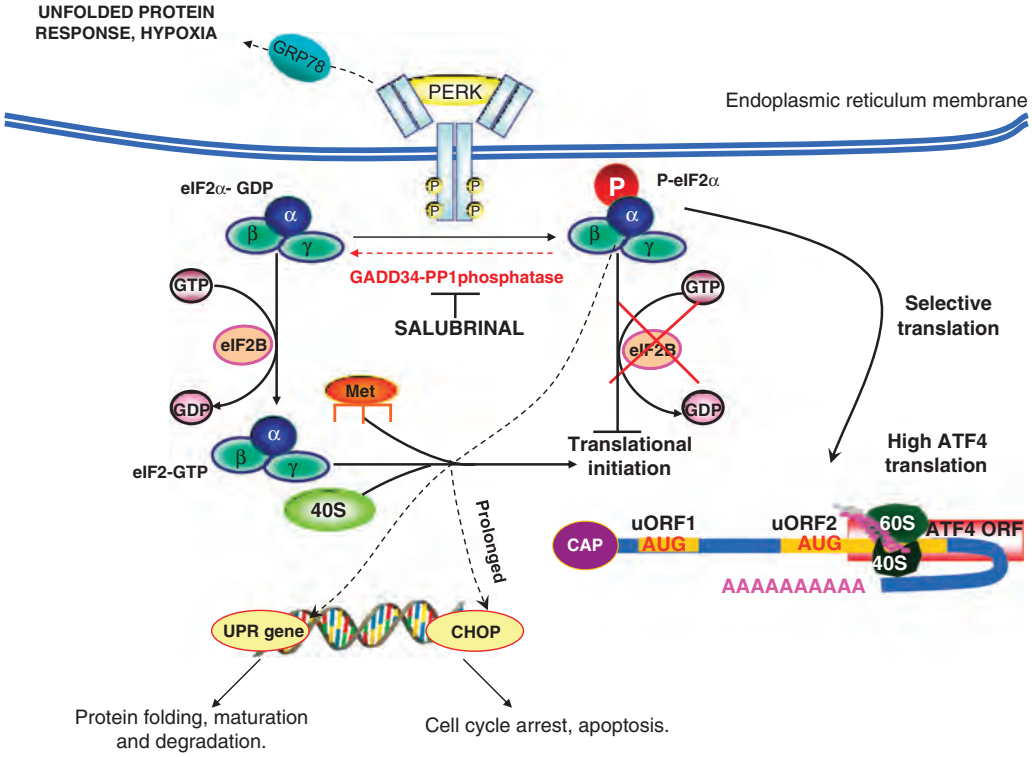

Figure 2. uORF response in stress. Four kinases (here PERK) phosphorylate eIF2α inhibiting eIF2 activity. Salubrinal blocks dephosphorylation of eIF2α. In conditions of eIF2α dephosphorylation, mRNAs with uORF are shut-off. In conditions of eIF2α phosphorylation, translation resumes in the main ORF of uORF containing mRNAs by reinitiation. For instance, accumulation of unfolded proteins causes translational shut-off accompanied by selective translation of mRNA for the transcription factor ATF4, which is a part of the UPR. C/EBP homology protein (CHOP) is a stress-induced transcription factor that acts downstream of ATF4 in response to DNA-damaging agents, amino acid deprivation and ER stress.

cells, but are translationally induced upon critical conditions. We will describe as an example the UPR that occurs when misfolded proteins accumulate in the endoplasmic reticulum. Accumulation of unfolded proteins results in a three-branched response.[50] One of these branches is the phosphorylation of eIF2α by the endoplasmic-reticulum-resident kinase PERK. eIF2α phosphorylation causes a reduction in TC formation and global translation, but favors reinitiation at the downstream ORF.[16,51] mRNAs with a clear uORF signature include transcription factors such as ATF4 that are important in the pro-survival stress response induced by unfolded proteins accumulating in the endoplasmic reticulum. A particularly important transcriptional target of ATF4 is GADD34, a substrate-specific subunit of a phosphatase that dephosphorylates eIF2α, restoring translation and suppressing ATF4 translation to basal levels.[52] Which is then the connection to cancer? Proteins of the UPR response are activated following administration of several anticancer drugs like the proteasome inhibitor Bortezomib, employed in multiple myeloma.[53–55] Attempts at blocking the pro-survival uORF-mediated response of cancer cells are in progress.[56] Recent evidence by the revolutionary technology of ribosome profiling[57,58] suggests that functional uORFs are more widespread than expected. As for IRES sequences, independent techniques must be employed to validate the physiological relevance of putative uORFs, as the simple existence of a 5′-ATG is not sufficient to generate an efficient uORF.

miRNA biology has been widely studied in the last years. The evidence by which miRNAs affect translation, and RNA stability, as well as cancer progression has been addressed in several reviews and will not be further discussed.[23,59,60] Briefly, miRNAs anneal to their complementary 3′-UTR sequences recruiting the RISC complex. There is a general consensus on the concept that miRNAs first act by repressing translation of a target mRNA, and only later they recruit the decapping/deadenylating machinery, inducing mRNA destabilization and degradation. Most studies converge on the idea that miRNAs act at initiation of translation. However, some cases have described alternative mechanisms of miRNA action at termination or elongation. As for their functional consequence, miRNAs may act either as a tumor suppressor or accelerating factor, depending on the context. One of the most powerful tumor suppressors is represented by miRNA 21 that targets the PI3K and the apoptotic pathways.[61] Intriguingly, we do not yet know whether the oncogenic signaling apparatus dynamically affects the efficiency of miRNA-regulated repression or not.[23,59] As far as we know, the activity of the RISC complex is constitutive. Last but not least, the repertoire of miRNA can lead to diagnostic tools.[62]

Other RNAs acting in *trans* (long noncoding RNAs), able to affect cancer progression without acting on translation, have been described.[63] Recently, long noncoding antisense RNAs bearing SINE2 sequences complementary to the 5′ of mRNAs have been identified. SINE2 may stimulate either RNA transport or directly RNA translation.[64]

ONCOGENIC SIGNALING TO INITIATION FACTORS: FROM 43S TO 80S FORMATION

Initiation of translation is attractive to pharmacological inhibition because it is made by specific mechanistic steps regulated by eIFs under the control of oncogenic signaling (Figure 3). Two pathways, activated by growth factors have a prominent role in nutrient sensing and translational control, the PI3K-mTOR cascade and the Ras-Erk-Mnk.[65] Since RNA sequences interplay with initiation factors, we observe that the pharmacological inhibition of initiation *in vivo* results in effects far more specific than expected. At initiation, three steps occur, 43S, 48S and 80S formation, explained below. Growth factors affect all steps.[66]

43S formation occurs when the small 40S subunit is loaded with the ternary complex (eIF2, Met-tRNA and GTP), that is, when the active initiator Met-tRNA binds 40S subunits. eIF2B promotes the exchange of GDP for GTP on eIF2 to regenerate active eIF2. Phosphorylation of eIF2B catalyzed by glycogen synthase kinase-3 (GSK3) inhibits its activity. GSK3 is inhibited by growth factors and insulin, leading to the dephosphorylation and activation of eIF2B.[67] Furthermore, amino acid deprivation also results in eIF2B phosphorylation and inactivation.[68] Inhibition of eIF2B activity leads to the regression of a transformed phenotype.[69] eIF2 activity is essential for loading Met-tRNA on the 40S and 43S formation. eIF2 is an heterotrimer consisting of an alpha, a beta and a gamma subunit. Specific stress signals (amino acid deficiency, unfolded proteins, viral infections, heme lack and hypoxia) activate eIF2α kinases phosphorylating eIF2α subunit. Importantly, eIF2α phosphorylation blocks 43S formation and global translation (Figure 2). However, as mentioned before, specific mRNAs containing a short uORF in front of a main ORF are de-repressed when eIF2α is phosphorylated, and are translated through a mechanism known as reinitiation.[70] Four kinases can phosphorylate eIF2α: PERK, activated by the UPR,[71] gcn2, activated (mainly) by amino acid deprivation,[72] PKR, activated by ds RNA[73] and HRI, activated by heme.[70] The role of eIF2α phosphorylation in cancer cells is dual and context-dependent, possibly due to the multiple mechanisms ending in eIF2α phosphorylation.[15] A common idea is that eIF2α-induced stress responses lead to increased survival in the short term and, if prolonged, to cell death. Salubrinal is a specific inhibitor of eIF2α dephosphorylation.[74] Its use in cancer has been proposed in the treatment of myeloma, where the widely employed proteasome inhibitor Bortezomib supposedly kills cells by accumulation of undegraded proteins, induction of eIF2α phosphorylation, triggering of the UPR and subsequent apoptosis.[75,76] One way to envisage eIF2-based therapy in cancer cells is to exploit their maladaptive properties due to increased endogenous levels of stress compared with normal cells.

48S formation occurs when the 43S subunit is loaded with mRNA. Several reviews have described this aspect.[17,77] We will focus on some points. In general, mRNAs bind the 43S, aided by the cap complex eIF4F. eIF4F formation is stimulated by the PI3K-mTOR cascade downstream of growth factors. eIF4F is composed by the cap-binding protein eIF4E, an helicase eIF4A and the scaffold eIF4G (Figure 3). Different mRNAs have different requirement for eIF4F, thus growth factor stimulation changes the pool of mRNAs that are translated by favoring the mRNAs that depend on eIF4F complex.[16] 48S formation has attracted a major interest in cancer biology[15] and has become a spectacular example of how translational control can become a therapeutic target in cancer cells. The central concept is that several mRNAs involved in cell cycle progression have structured 5′-UTRs and depends on eIF4F complex. In turn, eIF4F activity is regulated by mTOR kinase. Specifically, the cap-binding protein eIF4E in the eIF4F complex is inhibited by 4E-BPs, which is inactivated by phosphorylation through mTOR complex 1 (mTORc1) kinase activity. Rapamycin is a specific mTORc1 inhibitor that causes dephosphorylation of 4E-BPs. Dephosphorylated 4E-BPs bind and sequester the cap-binding protein eIF4E.[16] The net result is the impairment of eIF4F formation and an inhibition of translation of specific mRNAs.[78] In general, rapamycin acts as a cytostatic rather than a proapoptotic. For this reason, soluble rapamycin derivatives are used as drugs in limited cancer therapy settings. Furthermore, rapamycin leads to feedback activation of Akt by mTOR complex 2, inducing tumor survival. For this reason, novel mTOR competitive inhibitors that also inhibit Akt phosphorylation have been introduced.[77,79,80] The remarkable development of the eIF4F field in biology, from basic mechanisms to a prognostic factor and therapeutic target in cancer, is proof-of-principle that translational

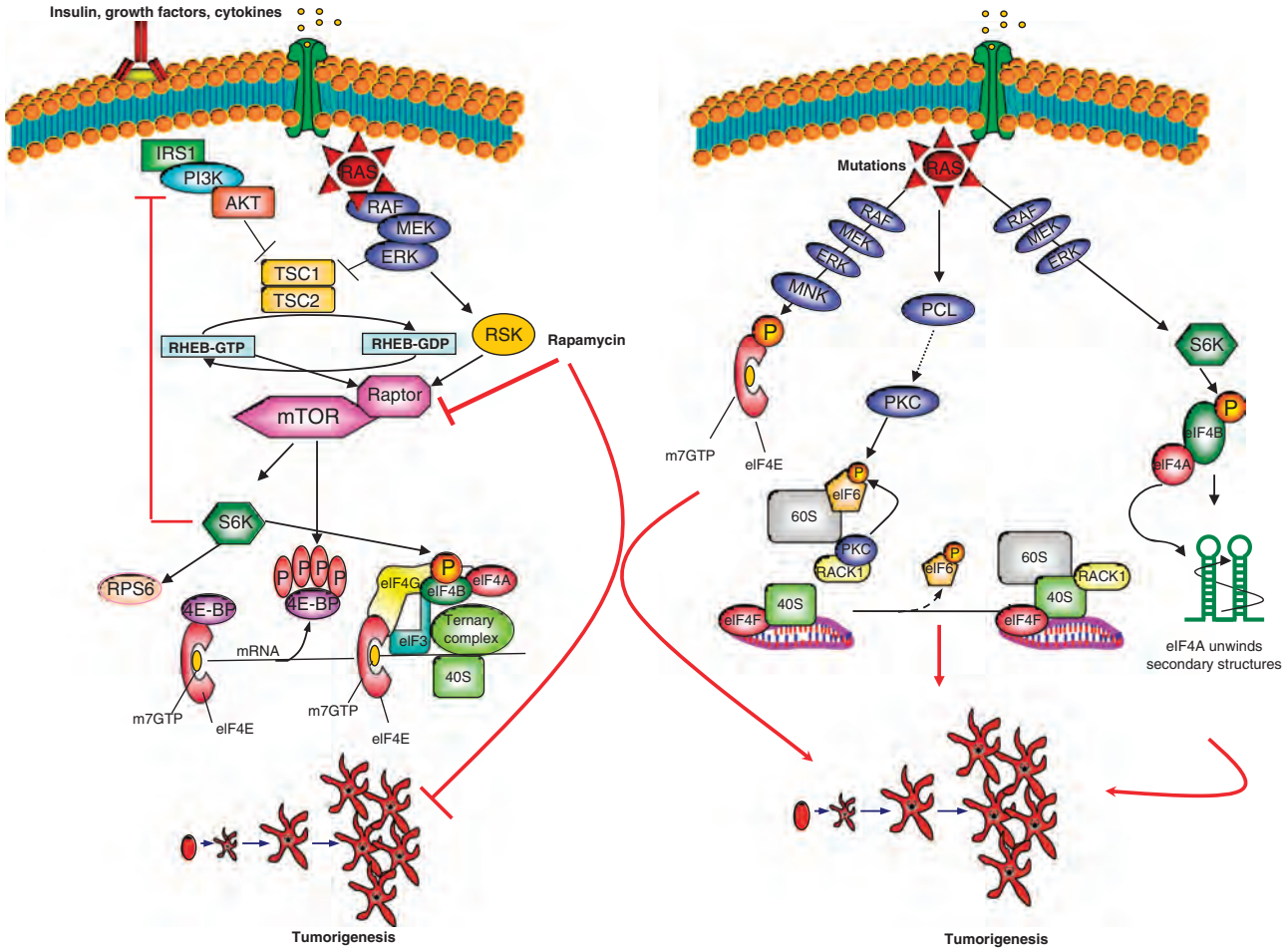

Figure 3. PI3K/mTORc1 and RAS/PKC cascade to initiation. mTORc1 downstream of PI3K phosphorylates 4E-BPs, allowing the assembly of eIF4E in the eIF4F complex. This highly known step is targeted by rapamycin. The role of S6 phosphorylation is less understood. The RAS pathway acts on Mnk kinases that phosphorylate eIF4E, increasing its tumorigenicity; PKC signaling converges on eIF6 whose activity is rate-limiting for tumor onset and tumor growth. Finally, the branch of RS6 kinases downstream of RAS phosphorylates also S6 and eIF4B. This at last turns on eIF4A.

control of cancer cells may be targeted. Last, it should be mentioned that although 4E-BP1 over expression is able to revert rapamycin resistance in mouse cancer models[80] and mTOR targeting therapies seem to depend on the ratio between eIF4E and 4E-BPs,[81,82] several other mTOR targets have been described. Among them, mTORc1-dependent activation of S6K1 and S6K2 leads to phosphorylation of eIF4B[83] and rpS6.[84] mTORc1 can also regulate elongation by phosphorylation of eukaryotic elongation factor 2 kinase,[85] or ribosome biogenesis by activating RNA polymerase I transcription.[86] The role of these components has received minor attention, but deserves more studies. Moreover, phosphorylation of 4E-BP in some cells and conditions is insensitive to rapamycin, suggesting a mechanism for resistance to mTORc1 inhibition.[87]

80S formation occurs when free 60S is recruited and elongation begins. 60S availability is rate-limiting for tumor growth. This can happen with at least two mechanisms: downregulation of rpL24 reduces tumorigenesis by impairing IRES-mediated translation.[40] Alternatively, eIF6 is the initiation factor that controls 60S availability. eIF6 is necessary for ribosome biogenesis of 60S subunits[88,89] and for high levels of translation.[90] Thus, eIF6 translation activity is dispensable for translation *in vitro*, but is required for maximal stimulation of mitogens *in vivo*. eIF6 involvement in tumorigenesis is described below.

THE CASE FOR RAPAMYCIN-INSENSITIVE TRANSLATION

Perhaps more visionary is to discuss the oncogenic role of 'rapamycin-insensitive' translation (Figure 3, right panel). The starting point is the observation that effective blockade of the mTOR pathway results in residual translation and tumor growth. Indeed, several cancer cells and patients do not respond to rapalogues (clinically exploitable and soluble rapamycin analogs). One mechanism that accounts for resistance to rapamycin is the ratio between 4E-BPs and eIF4E.[82] However, this cannot be the only explanation because in some cells, 4E-BP phosphorylation is resistant to rapamycin treatment.[91] Recently, it was found that mutations in the ras pathway induce rapamycin-resistant translation and tumor growth.[92] In line with this, some data suggest the presence of rapamycin-insensitive translation pathways stimulated by PKC and ras activators,[93] or by adhesion to extracellular matrix.[94] Obviously, the presence of rapamycin insensitivity in conditions of ras mutations can be interpreted with the idea that alternative oncogenic pathways, acting on translation, rely on independent signaling of ras.

First, eIF4E is phosphorylated by Mnk kinases downstream of the ras-Mapk cascade.[95] The mechanistic role of eIF4E phosphorylation is pretty unclear. However, mouse cancer models have shown that eIF4E phosphorylation greatly affects cancer development.[96,97] Second, eIF4B is an activator of eIF4A

helicase in the eIF4F complex. Stimulation of ras/Mapk leads to activation of ribosomal S6 kinases (RSK1/2). RSK1/2 have overlapping substrates with S6 kinases (S6K1/29), downstream of mTORc1. These substrates include rpS6, as well as eIF4B. The relevance of RSK1/2 in eIF4B phosphorylation is shown by pharmacological, biochemical and genetic approaches. eIF4B phosphorylation results in an increase of its eIF4A-stimulating activity. Helicase activity can be critical for translating mRNAs with highly structured 5′ regions.[98]

A third case is represented by eIF6 and the ras–PKC cascade.[99] The role of eIF6 in tumor progression is remarkable. eIF6 is highly overexpressed in cancer cells[88,100] and is rate-limiting in fibroblast transformation.[90] eIF6 haploinsufficiency or mutations of PKC consensus Ser235 of eIF6 reduce translation and lymphomagenesis in mice models.[101] eIF6 cytoplasmic activity is controlled by phosphorylation by RACK1–PKC complex,[102] in a pathway independent from mTORc1. Briefly, *in vitro* studies have suggested that PKC-mediated phosphorylation of serine 235 in the eIF6 tail reduces its affinity for the 60S ribosomal subunit and correlates with increased translation.[102] However, the tail of eIF6 is heavily phosphorylated in cycling cells,[103] thus suggesting that other signaling pathways may converge on eIF6. The crucial role of eIF6 in binding free 60S subunits and regulating translation suggests that antagonists of eIF6 binding to the 60S may have a role in cancer therapy. In addition, an alternative model predicts that efl1p/SBDS are responsible for the release of eIF6 from the 60S subunit[104] and, intriguingly, SBDS mutations result in increased leukemia.[105] Moreover, in this case, it has been postulated that the affinity of binding of eIF6 to the 60S is the critical step for ribosomal activation, increasing the need for eIF6 antagonists.

The adapter role of RACK1 on the ribosomal machinery is especially intriguing, as it may bring signaling molecules to the ribosomal platform. Indeed, RACK1 is a structural ribosomal protein of the 40S subunit, which may bring activated PKC to the ribosomal apparatus.[106,107] RACK1 binds active PKC, helping to stabilize its active conformation. Among PKCs, the most affine PKC-isoform-binding RACK1 is PKC beta II, reportedly at nM affinity.[108] It has also been reported that ribosomal RACK1 promotes chemoresistance and growth in human hepatocellular carcinoma, independently from eIF6 and affecting 4E-BP1 phosphorylation.[109] Currently, clinical trials employing PKC beta inhibitor enzastaurin as an anticancer molecule are under way.[110] Toxicity of enzastaurin has been attributed, partly, to 4E-BP dephosphorylation.[111] PKC phosphorylation has been also proposed for another member of the eIF4F complex, eIF4G1,[112] which in principle can bind 40S subunits fairly close to RACK1. This said, although there is scattered evidence that a PKC pathway may converge on translation factors and be important in tumor growth, the complexity of signaling pathways is still not understood and requires better genetic models for validation. RACK1 role on the translational machinery may not be limited, however, to the function of bringing PKC isoforms '*in situ*'. A recent hypomorphic model for RACK1 shows a pretty unique phenotype, characterized by reduced translation and a white bellyspot.[113] These data suggest that RACK1 affects the specific translation of mRNAs, as recently suggested by its binding to the β-actin mRNA/ZBP1 complex,[114] and its essential role in miRNA-regulated translation.[115,116]

A powerful oncogenic pathway converging on translation is driven by Myc oncogene. c-Myc regulates translation via transcriptional control of genes coding for translation initiation factors, such as eIF4E, and up to 30% of protein-coding genes. The complexity of Myc-induced synthesis of the translational machinery has been already reviewed.[117,118] A few central aspects will be stressed. First, Myc acts as a general inducer of protein synthesis, as it increases transcription of rDNA in the nucleolus by directing the assembly of the Pol I preinitiation complex or by enhancing the expression of rDNA transcription factors such as UBF.[117,118] Second, genetic strategies that reduce translation to normal levels in Myc transgenic mice by either downregulation of eIF6[101] or rpL24,[40] reveal that the oncogenic potential of Myc fully relies on the translational machinery. In addition, deregulation of mitotic translational control as a consequence of Myc hyperactivation leads to genome instability by modulating the translation of specific mRNAs.[40] Myc-dependent control of the translational machinery has thus a pleiotropic role in distinct steps of cancer initiation and progression. It should be, however, stressed that we do not have a full knowledge of which genes of the translational machinery are direct Myc targets, and which are indirect. Recently, it was reported that Akt signaling is essential for propagating the signal of Myc to the translational machinery, thus showing that some Myc-induced changes are likely indirect.[119]

eIF3 is a multisubunit complex involved in several steps of initiation of translation, including binding of mRNA to ribosomes and keeping a free pool of ribosomal subunits. Several of its subunits are overexpressed in cancer, and their downregulation by antisense RNA reverses the malignant phenotype in cultured cells. For instance, eIF3h phosphorylation or overexpression malignantly transform NIH-3T3 cells.[120] However, eIF3f subunit can ultimately act as a tumor-suppressor-like molecule.[121] Moreover, these data demonstrate that ubiquitous factors of the translational machinery are highly specific for their tumorigenic potential *in vivo*. It has not been yet demonstrated that changes in eIF3 subunit levels alter the spectrum of the translated mRNAs. Intriguing data showing that eIF3h modulates epigenetic changes would suggest that, at least partially, these changes may be mRNA-specific and result in reprogramming of cells.[122]

Another remarkable case is eIF4G1. eIF4G1 is an essential part of the eIF4F complex, where it acts by stimulating cap-dependent translation.[16] In adverse conditions for eIF4F formation, eIF4GI acts by reprogramming the protein synthetic machinery for increased translation of mRNAs with IRESs. By this action, eIF4GI overexpression promotes translation of survival, growth arrest and DNA-damage-response mRNAs that elicit cell survival after genotoxic DNA damage.[36,123]

Among surprising new tumor suppressors, there are adenosylmethionine decarboxylase 1 and eIF5A. eIF5A is hypusinylated, that is, modified by a unique amino acid produced from polyamine metabolism through a highly conserved pathway. Unexpectedly, heterozygous deletions encompassing adenosylmethionine decarboxylase 1 and eIF5A often occur together in human lymphomas and cosuppression of both genes promotes lymphomagenesis in mice.[124] Recently, it has been proposed that the bacterial homolog of eIF5A, EF-P has a specific function in the rapid synthesis of proteins containing consecutive prolins.[125,126] It will be interesting to see if this relates to its role in tumorigenesis. It should be added that eIF5A is upregulated in several malignancies, raising the question on whether, upon the cellular context, eIF5A can act both as a tumor suppressor or as a pro-oncogenic factor.[9]

RIBOSOMES AND CANCER

It is unarguable that cell growth requires adequate amount of ribosomes to synthesize cellular components. This is especially true for a cancer cell that at some point of its development towards unrestricted growth will require the support of the translation apparatus. Indeed, in the previous paragraphs we have summarized the experimental evidence that sustains the possible causal role of translation alteration in carcinogenesis. However, a number of studies pointed to additional questions on the relationship between translation and cancer, such as: (1) can an alteration of a ribosomal structural component be (part of) the driving force for carcinogenesis? (2) Can a ribosome alteration affect the quality and/or quantity of translation products

Table 1. Summary of ribosomopathies

Disease	*Altered gene*	*Clinical features*	*Cancer association*	*Reference*
Diamond Blackfan anemia	*RPS 7, 10, 17, 19, 24, 26, RPL5, 11, 35A*	Macrocytic anemia, reticulocytopenia, physical abnormalities	MDS, AML, colon adenocarcinoma, osteogenic sarcoma, genital cancer	4,137,172
X-linked dyskeratosis congenita	*DKC1*	Skin hyperpigmentation, nail dystrophy and mucosal leucoplakia bone marrow failure	AML, head and neck tumors	173
5q- syndrome	*RPS14*	Macrocytic anemia	AML	169
Shwachman–Diamond syndrome	*SBDS*	Pancreatic insufficiency, impaired hemopoiesis, physical abnormalities	MDS, AML	174–176
Cartilage hair hypoplasia	*RMRP*	Skeletal dysplasia, hypoplastic hair, immune dysfunction, macrocytic anemia and lymphopenia	Non-Hodgkin lymphoma, basal cell carcinoma	177,178
Treacher Collins syndrome	*TCOF1*	Craniofacial defects		179

Abbreviations: AML, acute myeloid lymphoma; MDS, myelodysplastic syndrome.

and induce cell transformation? (3) Can a ribosomal defect induce compensatory alteration that contribute to cancer development?

These questions emerged from the analysis of a group of genetic diseases named ribosomopathies that share, as a causative factor, alteration of either a structural component of the ribosome or a protein involved in ribosome biogenesis.[127] The study of these diseases, listed in Table 1, revealed the intriguing and unexpected finding that alteration in a biogenesis factor or a structural component of the ribosome (defined as ribosomal stress) can cause a tissue-specific defect.[4] There is a clear prevalence of hematopoietic cell defects, but other specific alterations are also present (for example, pancreatic insufficiency in X-linked dyskeratosis congenital (DC)). Besides the tissue-specific effect (discussed in Narla and Ebert[4]), the other interesting observation is the association of the ribosomopathies with different hematological and solid tumors. Here, we will review published data and working hypotheses on the relationship between ribosomopathies and tumorigenesis.

Among the first researchers to propose the implication of ribosome-driven oncogenic changes, Ruggero's[128,129] group observed a specific change of translation pattern in a mouse model for the ribosomopathy DC. The most common form of this genetic disease (X-linked DC) is associated to mutations in the gene-encoding dyskerin (DKC1) that is the enzyme responsible for the modification of about 100 uridine residues of rRNA into pseudouridine.[130] The role of these post-transcriptional modifications in the function of ribosome is not yet fully understood. The main pathological features of X-DC include skin abnormalities and bone marrow failure, but a variety of solid tumors and hematological malignancies are also observed in patients. The interesting finding of Ruggero's[39,44,45,131] group and other researchers was that both in X-DC patient cells and in experimental models, the defect in rRNA modification affects translation efficiency of only a subset of mRNA. These mRNAs share the presence of an IRES in the 5′ UTR and are presumably translated in a cap-independent way. As the list of inefficiently translated mRNA includes important tumor suppressors such as p53 and p27, the hypothesis is that cancer development would be favored by the inhibition of their synthesis. What is the role of rRNA modifications in IRES-dependent translation is not clear. One possibility is that rRNA modifications are necessary for the interaction with IRES-specific factors, but this remains to be shown. The importance of rRNA modifications is also supported by the finding that rRNA methylation is important for IRES-dependent translation of specific mRNAs.[132,133] The more general model proposed by Ruggero[17], therefore, is that altered ribosomes can induce tumorigenesis because of specific changes in the translation pattern.

Other studies indicate that in the definition of 'altered ribosomes', we can probably include ribosomes lacking a structural component, that is, a ribosomal protein. For instance, the report by Barna and colleagues[134] shows that RPL38 +/− mice exhibit homeotic transformations of the axial skeleton due to translational alteration of a subset of Hox mRNAs. The authors hypothesize that RPL38 has a specialized role in translation and that the presence of RPL38-defective ribosome could affect the translation pattern. Similarly, it has been shown that in yeast, the absence of RPS25 affects the translation of only specific IRES-containing mRNAs.[135] The possibility that ribosomes lacking a ribosomal protein could have selective effects on translation emerges also from studies on the canonical ribosomopathy Diamond Blackfan Anemia (DBA). This disease is caused by mutations in any of the 10 ribosomal protein genes (reviewed in[4,136]). The molecular mechanism of the pathology is not understood and its discussion is outside the aims of this review. However, very recently, a careful quantitative evaluation of cancer risk in DBA patients confirmed the notion that DBA is indeed a cancer predisposition syndrome.[137]

The identification of several DBA genes and the evaluation of the genotype–phenotype correlation led to a second unexpected feature of DBA (the first being the tissue specificity). In addition to the common hematological defect, DBA patients show some gene-specific clinical features. For instance, there is a clear association between oral cleft abnormalities and mutations of RPL5,[138] whereas this phenotype has not been reported in more than 120 RPS19-mutated patients analyzed in another study.[139] Although other explanations are possible (see below), these findings could indicate that ribosomes lacking specific ribosomal proteins (RPs) can have different translation specificity. A similar conclusion is proposed by Horos *et al.*[140] in the analysis of an *in vitro* DBA experimental model. They found that the depletion of RPS19 or RPL11 in mouse erythroblast causes translation alteration of specific IRES-containing transcripts (Bag1 and Csde1), suggesting the possibility of defective ribosomes with modified translation specificity. A correlation of these studies with cancer predisposition of DBA patients would suggest that the altered translation pattern of the defective ribosomes (that is, without an RP) increases the risk of cancer (model 1 of Figure 4).

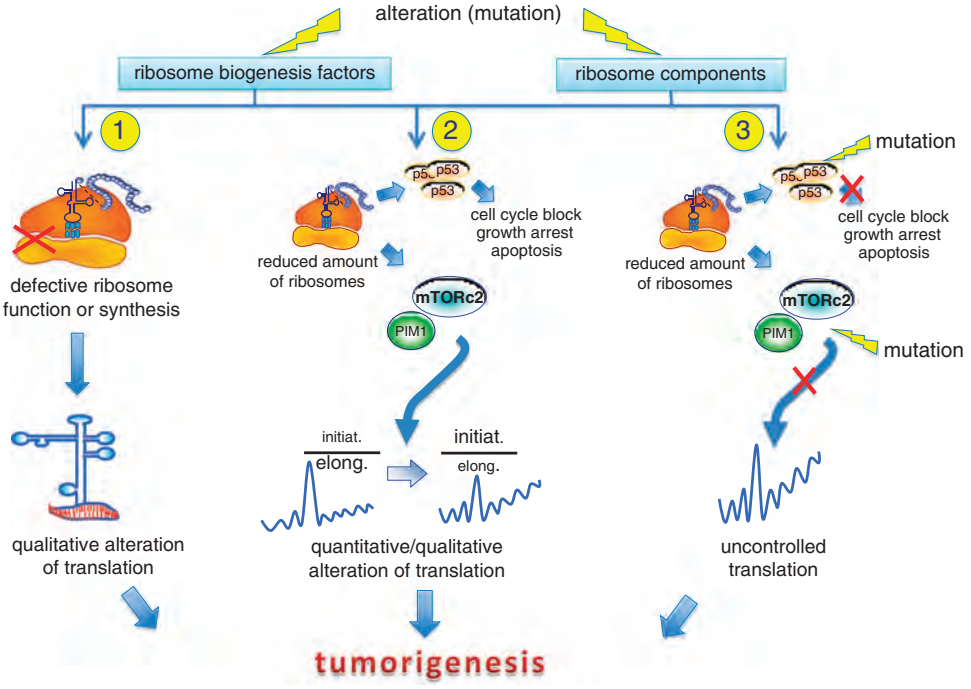

Figure 4. Hypotheses on the tumorigenic effect of ribosome alterations. Model 1: structural alteration of ribosome, such as lack of rRNA modifications or lack of an RP, causes qualitative changes in the pattern of translation. These include inhibition of IRES-containing tumor-suppressor mRNAs. Model 2: mutations in ribosome biogenesis factors or structural components causes a decrease in the amount of available ribosomes. This generates a response (ribosomal stress) through signaling molecules such as p53, mTORc2 and PIM1. Some of the signals could affect the quality of translation by changing, for instance, the ratio between initiation and elongation. Model 3: the response to ribosomal stress causes growth inhibition in cells with defective ribosome biogenesis or function. Accidental mutations in the pathways (red crosses) will allow unrestricted growth of cells with defective ribosome biogenesis, possibly leading to cell transformation.

However, although there is experimental evidence of ribosomes lacking an RP,[135,141,142] the model of ribosome heterogeneity caused by alteration of RP quantity or quality does not seem coherent with the general picture of ribosome biogenesis. In fact, the synthesis of ribosomes is a process that appears to be regulated at multiple levels. It has been shown that RPs are generally produced in excess and that the unassembled proteins are degraded in the nucleus.[143] Depletion of an RP in cultured cells induces a decrease in the level of the other RP of the same ribosomal subunit, causing an unbalanced production of the two subunits[144] and a block in rRNA maturation, observed also in cells from DBA patients.[145–147] In addition, mutated RPs appear to be assembled very poorly (if at all) into ribosomal subunits.[148] These studies suggest that the assembly of the ribosomal subunits is tightly controlled and the synthesis of defective ribosomes is not very likely to occur.

Another possibility to explain how defect in the synthesis or function of the ribosomes could affect the pattern of translated mRNAs and possibly lead to cell transformation is more speculative. It has been known for a long time that changes in the ratio between translation initiation and elongation can affect differently the various mRNAs according to their relative affinity for the translation apparatus (that is, translation factors).[149,150] More recently, a large-scale analysis of mTOR signaling targets identified a specific subgroup of mRNAs involved in cell proliferation, metabolism and invasion that includes terminal oligopyrimidine mRNAs.[151] These mRNAs appear to be particularly sensitive to translation initiation inhibition induced by mTOR inhibitors. It could be hypothesized that the same mRNAs would be less sensitive to inhibition of translation elongation.[66,152] Indeed, it has been recently observed that RP depletion in HeLa cells causes downregulation of mTOR complex 2.[153] This, in turn, causes an increase of the phosphorylated form of eEF2, with a consequent inhibition of translation elongation.[154] A possible involvement of the mTORC1 signaling in the response to RP depletion has been recently shown in zebrafish. Payne *et al.*[155] showed that leucine-mediated mTORC1 activation could rescue the phenotype caused by RPS19 or RPS14 depletion. Therefore, the model is that a quantitative inhibition of ribosome synthesis or function could induce a cellular response that, by altering the ratio between initiation and elongation, could affect the translation pattern favoring the synthesis of oncogenic products (model 2, Figure 4). Similar effects could be mediated by the kinase PIM1, recently shown to be involved in the response to ribosomal stress.[156] Although considerably speculative, this hypothesis could apply to all the ribosomopathies, including those involving ribosome biogenesis factors such as Schwachman–Diamond syndrome, cartilage hair hypoplasia, Treacher Collins syndrome.

A third model on the tumorigenic potential of ribosome defects is based on possible indirect effects, including selection of mutations, on other cellular components. It is now accepted, as shown by an abundant number of studies, that the pathological mechanism of ribosomopathies includes the activation of checkpoints for quality control of ribosome biogenesis. The most characterized response to ribosomal stress involves the activation of tumor suppressor p53, with a consequent cell cycle arrest, senescence or apoptosis.[141,157–163] However, in addition to the p53-dependent mechanisms, other possible signaling molecules are thought to mediate growth inhibitory effects of ribosomal stress independently of p53.[156,164,165] The best evidence of p53 involvement in the response to ribosomal stress is that p53 suppression by genetical or biochemical means in experimental model systems can rescue at least part of the defects caused by ribosome alteration.[141,157,162,166] To explain the relationship

between ribosomal stress and tumorigenesis, it could be hypothesized that a prolonged growth inhibition caused by either p53 activation or by other signaling molecules could select for mutations or gene expression alterations that promote unrestricted growth. This phenomenon has been observed in zebrafish, in which mutations in a number of RP genes have been shown to favor the development of malignant peripheral nerve sheath tumors.[167] Further investigation showed that cells derived from tumors were not able to produce p53 protein, although mutations in p53 gene were not detected and p53 mRNA was present.[168] Other observations, consistent with the same model, came from the studies on the ribosomopathy 5q- syndrome. This disease is one of the myelodysplastic syndromes, a group of hematopoietic stem cell disorders that have a risk of progression to acute myeloid leukemia. It has been shown by Ebert *et al.*[169] that haploinsufficiency of RPS14 has a critical role in the development of the anemia that characterizes 5q- syndrome. Similar to other ribosomopathies, bone marrow cells from a mouse model of 5q- syndrome shows elevated level of p53. Moreover, intercross with a p53-null mouse could rescue the macrocytic anemia and dysplasia phenotypes of the 5q- mouse.[170] Recent data suggest that mutation of p53 may be one of the molecular events necessary for progression of the 5q- syndrome to acute myeloid leukemia.[171] The authors of the study showed that mutations in p53 were present years before disease progression and were associated with an increased risk of leukemic evolution.[171] One possibility is that following the activation of p53 at an early stage of 5q- syndrome, some cell clones harboring a mutated form of p53 would expand, leading to leukemic transformation. The same model could apply to other activities whose function is to restrict the growth of cells with defect in ribosome biogenesis or function. Counteracting growth impairment by altering gene expression or by selecting inactivating mutation can be a way for the cell to survive, but at the same time could lead to cell transformation (model 3, Figure 4). As a final remark we would like to mention the possibility that more than one mechanism could be activated at the same time in the cell, and that different circumstances (mutations, cell types) could induce different mechanisms.

CONCLUSIONS

Ribosomal alterations in cancer are not a byproduct, but a driving force. The case of eIF4F in cancer, from early studies showing its transformation capability to current pharmacological targeting, is a beautiful 'proof-of principle' that the translational machinery is a suitable target in cancer therapy. New key steps regulating translation have been discovered, and the combination of genetic and biochemistry will allow us to define which of these steps can be efficiently targeted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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