TRANSLATION AND PROTEIN QUALITY CONTROL

Translation deregulation in human disease

Soroush Tahmasebi[1,2,5], Arkady Khoutorsky[3], Michael B. Mathews[4] and Nahum Sonenberg[1,2]**

Abstract | Advances in sequencing and high-throughput techniques have provided an unprecedented opportunity to interrogate human diseases on a genome-wide scale. The list of disease-causing mutations is expanding rapidly, and mutations affecting mRNA translation are no exception. Translation (protein synthesis) is one of the most complex processes in the cell. The orchestrated action of ribosomes, tRNAs and numerous translation factors decodes the information contained in mRNA into a polypeptide chain. The intricate nature of this process renders it susceptible to deregulation at multiple levels. In this Review, we summarize current evidence of translation deregulation in human diseases other than cancer. We discuss translation-related diseases on the basis of the molecular aberration that underpins their pathogenesis (including tRNA dysfunction, ribosomopathies, deregulation of the integrated stress response and deregulation of the mTOR pathway) and describe how deregulation of translation generates the phenotypic variability observed in these disorders.

The first report to link a mutation of a translation component (mitochondrial $tRNA^{Lys}$) to an inherited human disease (myoclonic epilepsy with ragged red fibres (MERRF) syndrome) was published in 1990 (REF.[1]). Since then, the list of genetic diseases caused by translation deregulation has increased exponentially. Translation is deregulated in a wide spectrum of human diseases, including immunodeficiency[2,3], metabolic disorders[4], neurological disorders[5] and cancer, as well as during virus infection. In this Review, we discuss our current understanding of translation deregulation in non-cancer-related human diseases. For translational control of cancer and during virus infection, we refer the reader to recent comprehensive reviews[6–10].

Translation is a multistep process comprising initiation, elongation, termination and ribosome recycling[11]. During canonical initiation, the cytosolic ribosome is recruited to the mRNA and scans its 5′ untranslated region (5′UTR) for the presence of the translation start codon. Under most conditions, initiation is the rate-limiting step of translation (there are ~0.5–3.6 initiations per minute compared with elongation rates of 3–10 amino acids per second[12–14]), and therefore it is tightly regulated. Several key signalling pathways, including mammalian or mechanistic target of rapamycin (mTOR), mitogen activated protein kinases (MAPKs) and integrated stress response (ISR) pathways, converge on the initiation step to control the rate of protein synthesis in response to a variety of external and internal cues[15,16] (BOX 1). Control of mRNA translation plays a pivotal role in the regulation of gene expression in embryonic and adult tissues. Therefore, defects in the translation process are deleterious for organismal development and physiology. Mitochondria have a parallel translation system, which is more similar to the prokaryotic system than to eukaryotic cytosolic translation[17] (BOX 1), and mutations in this system contribute greatly to human disease by impairing the energy-generating machinery of the cell.

We categorize the translation-related human disorders into four groups: those involving deregulated tRNA synthesis or function, ribosomopathies, deregulation of the ISR pathway and deregulation of the mTOR pathway. Although this classification aims to simplify the description of the molecular mechanisms underlying human diseases, there is substantial overlap between the categories. For instance, on one hand, disruption of tRNA or mitochondrial functions in several disorders triggers activation of the ISR and inhibition of the mTOR pathway[18]. On the other hand, transcriptional and translational targets of the ISR and the mTOR pathways have crucial roles in tRNA, mitochondrial and ribosomal biogenesis[19].

Recent advances in whole exome and genome sequencing technologies have provided a wealth of knowledge on novel disease-causing mutations that affect translation factors[20–22], leading to a detailed understanding of disease pathogenesis and therapeutic opportunities. In some cases, however, the precise molecular mechanisms linking genotypic changes to phenotypes remain to be established. We first discuss human diseases linked

[1]*Goodman Cancer Research Center, McGill University, Montreal, Quebec, Canada.*

[2]*Department of Biochemistry, McGill University, Montreal, Quebec, Canada.*

[3]*Department of Anesthesia and Alan Edwards Centre for Research on Pain, McGill University, Montreal, Canada.*

[4]*Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA.*

[5]*Department of Pharmacology, University of Illinois at Chicago, Chicago, IL, USA.*

**e-mail: soroush@uic.edu; nahum.sonenberg@mcgill.ca*

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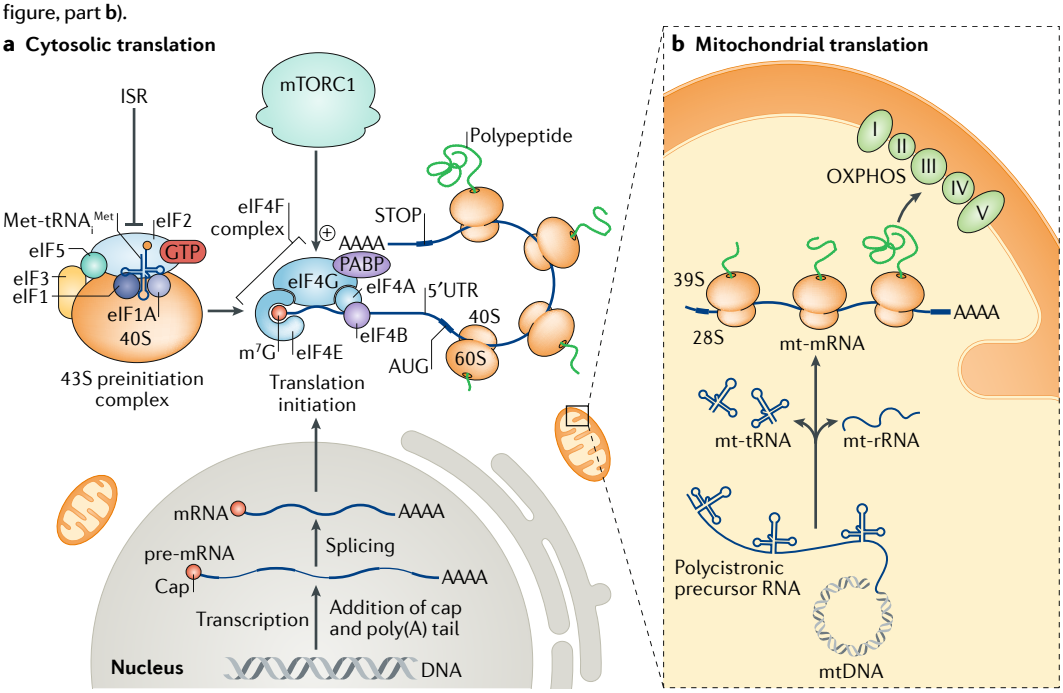
Box 1 | **mRNA translation in the cytosol and in mitochondria**

Nuclear-encoded eukaryotic mRNAs undergo several steps of processing in the nucleus, which include the addition of a 5′-terminal cap (7-methylguanosine (m^7G)) at the 5′-end and a poly(A) tail at the 3′-end, followed by internal base methylation, splicing and export to the cytosol (see the figure, part **a**). Ribosomes are recruited to the mRNA through the coordinated activity of multiple translation initiation factors. Two protein complexes, eukaryotic translation initiation factor 4F (eIF4F), which comprises eIF4E (a cap-binding protein), eIF4G (a scaffolding protein) and eIF4A (an RNA helicase), and the ternary complex, which comprises eIF2, GTP and the initiator tRNA (Met-$tRNA_i^{Met}$), have key roles in translation initiation. mRNA circularization occurs through the interaction of eIF4G with poly(A)-binding protein (PABP). The eIF4F complex unfolds secondary structures in the 5′ untranslated region (5′UTR) of mRNAs for translation initiation. In addition, an interaction (not shown) between eIF4G and eIF3 brings the 40S small ribosomal subunit, as a component of the 43S preinitiation complex, into the vicinity of the mRNA 5′-end to start the scanning process. The integrated stress response (ISR) and mTOR complex 1 (mTORC1) control translation initiation through regulation of the ternary complex and the eIF4F complex, respectively. Interaction of eIF4B with eIF4A increases the helicase activity of eIF4A. Unlike nuclear mRNAs, mitochondrial mRNAs (mt-mRNAs) are uncapped and have a short (up to three nucleotides in length) or no 5′UTR, obviating the need for initiation factors to unwind the 5′UTR (see the figure, part **b**).



AUG, translation initiation codon; mtDNA, mitochondrial DNA; mt-rRNA, mitochondrial ribosomal RNA; mt-tRNA, mitochondrial tRNA; OXPHOS, oxidative phosphorylation complexes; STOP, stop codon.

to defects in mitochondrial tRNA biogenesis, which are relatively frequent and accordingly were discovered early, and then discuss diseases caused by mutations affecting cytosolic tRNAs, aminoacyl-tRNA synthetases (ARSs; also known as tRNA ligases) and translation elongation factors (FIGS 1,2; Supplementary table 1). Next, we focus on ribosomopathies (FIG. 3; Supplementary table 1) and mutations that affect translation regulation through the ISR (FIG. 4; Supplementary table 1) and the mTOR pathway (FIG. 5; Supplementary table 1). Finally, we discuss the basis of phenotypic variability caused by translation deregulation.

Deregulation of tRNA function

Components of the mitochondrial translation machinery — mitochondrial tRNAs (mt-tRNAs), tRNA modifying enzymes, ARSs, elongation factors and ribosomal proteins — are often mutated in mitochondrial diseases (Supplementary table 1). Mitochondrial diseases are among the most common inherited human disorders. They result from mutations of nuclear-encoded or mitochondrial-encoded genes. Diseases associated with nuclear genes are usually autosomal recessive, manifest very early in life and exhibit multisystem phenotypes with fatal consequences. By contrast, diseases caused by mutations in mitochondrial DNA (mtDNA) genes are inherited maternally and are often less severe. Most mt-tRNAs are encoded by a single gene, whereas the ~50 cytosolic tRNA species are encoded by ~500 nuclear genes[23]. This may explain why no known human disease is caused by mutations in nuclear-encoded tRNAs. Nevertheless, mutations of tRNA splicing and modifying factors have been identified in several human disorders, primarily in neurodegenerative diseases[24–27].

Mitochondrial tRNA

The mitochondrial genome, which is transmitted exclusively through the female germ line, encodes 37 genes, including 22 mt-tRNAs and 2 ribosomal RNAs (rRNAs) (16S and 12S). The remaining 13 genes encode proteins that function in oxidative phosphorylation (OXPHOS). Most mitochondrial proteins (including those involved

Aminoacyl-tRNA synthetases (ARSs). Enzymes that catalyse the addition of an amino acid to the appropriate tRNA.

in mitochondrial translation) are encoded in the nucleus, translated from mRNAs in the cytosol and transported into the mitochondria. Mitochondrial genes undergo a much higher rate of deleterious mutations than nuclear genes[28]. Uniparental transmission, lack of introns, repetitive elements and recombination, and the low replication fidelity of the mtDNA polymerase contribute to the high mutation load in mitochondrial genes[29,30]. Fortunately, the deleterious effects of mutations are ameliorated by the existence of several copies (2–10) of the mitochondrial genome in each mitochondrion and multiple mitochondria in each cell, so diseases manifest only when the number of malfunctioning mitochondria surpasses a tolerable threshold[31]. Dysfunction of mt-tRNAs results from mutations in mt-tRNA sequences or from defects in nuclear-encoded tRNA modifying enzymes (FIGS 1,2; Supplementary table 1). Considering the limited number of mt-tRNAs (22 mt-tRNAs decode the 60 sense codons of the mitochondrial genetic code), mt-tRNA modifications, especially at the wobble position (tRNA nucleotide 34, which is the first (5′) base of the anticodon), have a crucial role in expanding codon recognition. Thus, in the context of disease, mutations of tRNA modifying enzymes limit the decoding capacity of mt-tRNA. A defect in the OXPHOS system is a common outcome of deregulation of mitochondrial translation[32]. Brain and muscle are particularly sensitive to OXPHOS activity because of their high energy requirements. However, in many cases, disease-causing mutations lead to defects in organs other than muscle or the nervous system, suggesting the existence of gene-specific effects[32].

Mutations in mt-tRNA genes can have either a multi-organ or a tissue-specific manifestation (FIG. 1; Supplementary table 1). The two best-characterized multi-organ syndromes associated with mt-tRNA mutations are MERRF and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). MERRF has been largely linked to mitochondrial complex IV deficiency[33], whereas MELAS has been attributed more predominantly to defects in mitochondrial complex I. Mutations in several mt-tRNA genes cause MELAS syndrome (Supplementary table 1), although in most cases, it is caused by mutation of mitochondrially encoded tRNA leucine 1 (*MT-TL1*). Most commonly, the mutation is located at the mt-tRNA^{Leu} wobble position (A3243G) and interferes with 5-taurinomethyluridine (τm5U) modification of this position[34] (FIG. 2). MERRF syndrome may also result from lack of taurine modification at the wobble position of mt-tRNA^{Lys}). Notably, lack of taurine modification in mt-tRNA^{Lys} interferes with decoding of both Lys codons, whereas lack of taurine modification in mt-tRNA^{Leu} affects decoding of only one Leu codon (UUG but not UUA)[35]. This decoding bias preferentially affects mitochondrial complex I through a defect in the translation of mitochondrially encoded NADH dehydrogenase 6 (*MT-ND6*) mRNA, which has high UUG content. This also explains the phenotypic differences between MERRF and MELAS syndromes. Indeed, a patient carrying a point mutation in *MT-ND6* had a substantial defect in complex I activity in muscle and displayed a phenotype similar to MELAS syndrome[36].

The importance of modifications at the tRNA wobble position is underscored by diseases caused by mutations in the enzymes that catalyse these modifications (for example, protein MTO1 homologue, mitochondrial, GTP-binding protein 3 (GTPBP3) and tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU; also known as mitochondrial tRNA-specific 2-thiouridylase 1))[37–39] (FIG. 2; Supplementary table 1). Modifications of mt-tRNA^{Met} are particularly important, as they enable a single tRNA to serve as both the elongator tRNA (Met-tRNA^{Met}) and the initiator tRNA (fMet-tRNA^{Met}), which is not the case in the cytosol, prokaryotes or yeast mitochondria. Methionyl-tRNA formyltransferase, mitochondrial (MTFMT) is the enzyme that modifies Met-tRNA^{Met} to fMet-tRNA^{Met}. Mutation in MTFMT has been linked to Leigh syndrome and cardiomyopathy[40] (FIG. 1). Cardiomyopathy, non-syndromic hearing loss and external ophthalmoplegia are examples of tissue-specific pathologies caused by mt-tRNA mutations (Supplementary table 1). Mutations in several mt-tRNA genes have been recently identified in patients with maternally inherited hypertension[41], but the molecular mechanisms of their action remain unknown.

Cytosolic tRNA

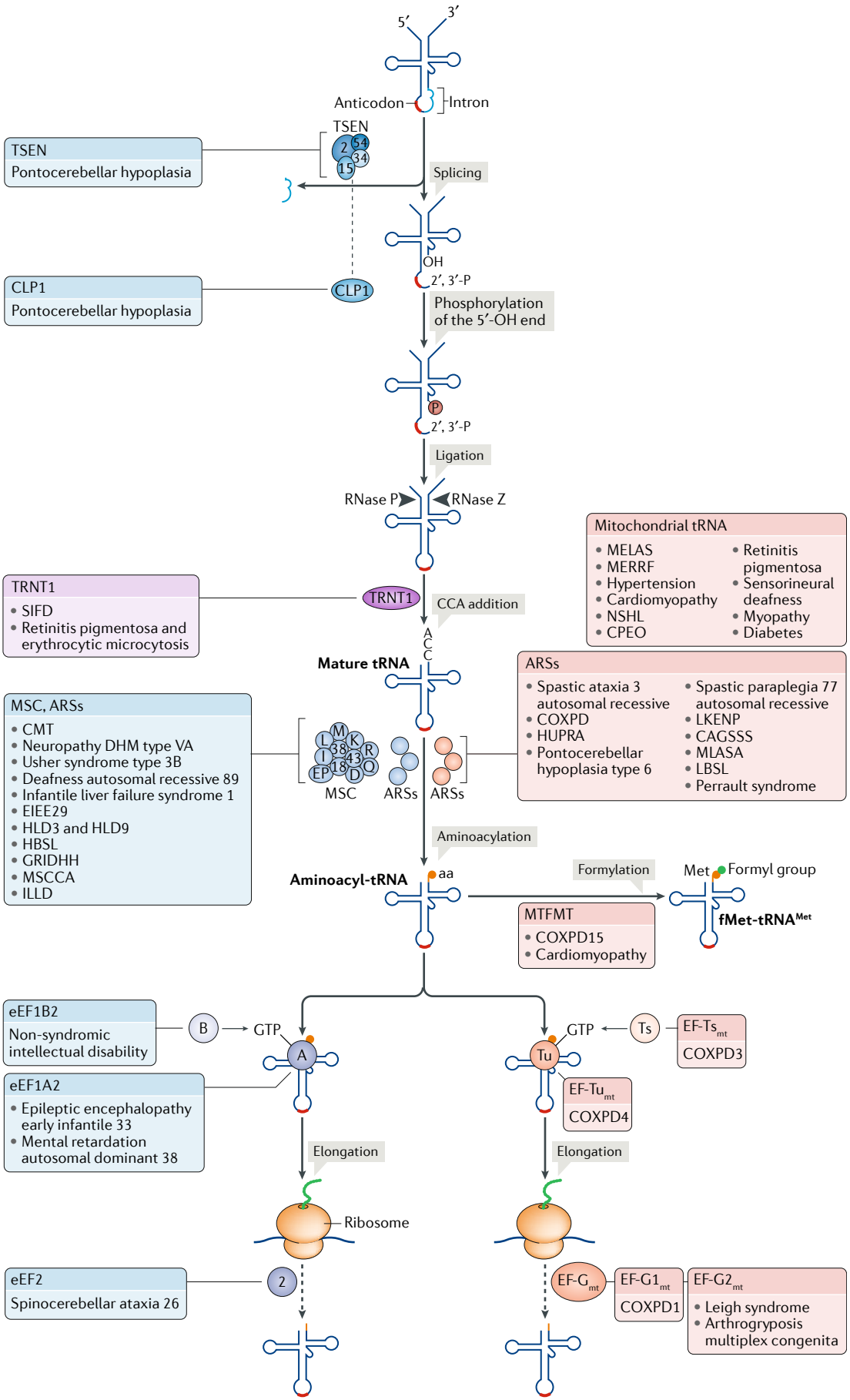
The wobble position of cytosolic tRNAs is also subject to modifications. The highly conserved hexameric Elongator complex adds 5-methoxycarbonylmethyl (mcm^5) and 5-carbamoylmethyl (ncm^5) to uridine residues at the wobble position of several cytosolic tRNAs[42] (FIG. 2). Loss-of-function mutation of Elongator complex protein 1 (ELP1; the scaffolding protein of Elongator) has been identified in Ashkenazi Jews with familial dysautonomia[43,44], which is an autosomal recessive neurodegenerative disease affecting sensory and autonomic neurons. A single nucleotide point mutation at the intron 20 donor splice site was identified in >99.5% of individuals with familial dysautonomia[44]. The mutation interferes with proper splicing of *ELP1* mRNA, causing skipping of exon 20. Interestingly, exon 20 skipping occurs more frequently in neurons than in other cells, explaining the predominantly neurodegenerative phenotype of familial dysautonomia and raising the possibility of splicing modification therapy for this disease (for example, by kinetin)[45]. Notably, mutations of other components of the Elongator complex have also been linked to neurodegenerative disorders[46,47].

Nucleotide 37 of tRNAs (the first nucleotide downstream of the anticodon) is also a hot spot for modifications. The highly conserved pentameric KEOPS–EKC (kinase, endopeptidase and other proteins of small size (KEOPS)–endopeptidase-like and kinase associated to transcribed chromatin (EKC)) complex mediates threonylcarbamoyladenosine (t^{6}A) modification at this position to control the accuracy and efficiency of translation (FIG. 2). Recent studies identified recessive mutations in four subunits of the KEOPS–EKC complex in patients with a renal–neurological disease known as Galloway–Mowat syndrome[20,48]. Deletion of the orthologous genes in mice and zebrafish recapitulates some of the phenotypes[20].

5-Taurinomethyluridine (τm5U). A post-transcriptional modification of uridine at the wobble position of the mammalian mitochondrial tRNAs for Leu (UUR) and Trp.

fMet-tRNA^{Met} A formylated form of the elongating Met-tRNA^{Met} that is used as an initiator of tRNA in mammalian mitochondria.

Threonylcarbamoyladenosine (t^{6}A). A universal tRNA modification at position 37 of tRNAs that decode ANN codons.


5′
3′
Anticodon
Intron
TSEN
TSEN
Pontocerebellar hypoplasia
Splicing
OH
2′, 3′-P
CLP1
CLP1
Pontocerebellar hypoplasia
Phosphorylation of the 5′-OH end
P
2′, 3′-P
Ligation
RNase P
RNase Z
Mitochondrial tRNA
• MELAS
• MERRF
• Hypertension
• Cardiomyopathy
• NSHL
• CPEO
• Retinitis pigmentosa
• Sensorineural deafness
• Myopathy
• Diabetes
TRNT1
• SIFD
• Retinitis pigmentosa and erythrocytic microcytosis
TRNT1
CCA addition
A
C
C
Mature tRNA
ARSs
• Spastic ataxia 3 autosomal recessive
• COXPD
• HUPRA
• Pontocerebellar hypoplasia type 6
• Spastic paraplegia 77 autosomal recessive
• LKENP
• CAGSSS
• MLASA
• LBSL
• Perrault syndrome
MSC, ARSs
• CMT
• Neuropathy DHM type VA
• Usher syndrome type 3B
• Deafness autosomal recessive 89
• Infantile liver failure syndrome 1
• EIEE29
• HLD3 and HLD9
• HBSL
• GRIDHH
• MSCCA
• ILLD
MSC
ARSs
ARSs
Aminoacylation
Aminoacyl-tRNA
aa
Formylation
Met
Formyl group
fMet-tRNA^Met
MTFMT
• COXPD15
• Cardiomyopathy
eEF1B2
Non-syndromic intellectual disability
B
GTP
A
GTP
Ts
EF-Ts_mt
COXPD3
Tu
EF-Tu_mt
COXPD4
eEF1A2
• Epileptic encephalopathy early infantile 33
• Mental retardation autosomal dominant 38
Elongation
Elongation
Ribosome
eEF2
Spinocerebellar ataxia 26
2
EF-G_mt
EF-G1_mt
COXPD1
EF-G2_mt
• Leigh syndrome
• Arthrogryposis multiplex congenita

◀ Fig. 1 | **Defects in tRNAs, aminoacyl-tRNA synthetases and translation elongation factors.** Diseases associated with cytosolic and mitochondrial defects are marked in blue and pink, respectively; diseases associated with both are marked in purple. tRNA splicing is affected by mutations in components of the tRNA-splicing endonuclease (TSEN) complex (TSEN2, TSEN15, TSEN34 and TSEN54) and in the polynucleotide kinase CLP1 (also part of TSEN). CCA tRNA nucleotidyltransferase 1, mitochondrial (TRNT1) catalyses CCA addition to tRNA 3′-ends. The tRNA multi-synthetase complex (MSC) comprises the aminoacyl-tRNA synthetases (ARSs) lysine–tRNA ligase (K), arginine–tRNA ligase, cytoplasmic (R), glutamine–tRNA ligase (Q), methionine–tRNA ligase, cytoplasmic (M), isoleucine–tRNA ligase, cytoplasmic (I), aspartate–tRNA ligase, cytoplasmic (D), leucine–tRNA ligase, cytoplasmic (L), bifunctional glutamate/proline–tRNA ligase (EP) and the scaffolding MSC auxiliary components p43, p38 and p18. Formylation of $tRNA^{Met}$ by mitochondrial methionyl-tRNA formyltransferase, mitochondrial (MTFMT) is required to generate the initiator tRNA fMet-$tRNA^{Met}$. Elongation factor Tu, mitochondrial (EF-Tu_{mt}) and eukaryotic elongation factor 1-A2 (eEF1A2) deliver aminoacyl-tRNAs to the mitochondrial and cytosolic ribosome, respectively. EF-Ts_{mt} and eEF1B2 are guanine nucleotide exchange factors for EF-Tu_{mt} and eEF1A, respectively. eEF2 is a GTPase and translocase that mediates ribosome movement on mRNA. There are two eEF2 homologues in mitochondria: EF-$G1_{mt}$ is a translocase, whereas EF-$G2_{mt}$ functions in ribosome recycling. CAGSSS, cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss and skeletal dysplasia; CMT, Charcot–Marie–Tooth; COXPD, combined oxidative phosphorylation deficiency; CPEO, chronic progressive external ophthalmoplegia; DHM, distal hereditary motor; EIEE29, early infantile epileptic encephalopathy 29; GRIDHH, growth retardation, intellectual developmental disorder, hypotonia and hepatopathy; HBSL, hypomyelination with brainstem and spinal cord involvement and leg spasticity; HLD, hypomyelinating leukodystrophy; HUPRA, hyperuricaemia, pulmonary hypertension, renal failure in infancy and alkalosis; ILLD, interstitial lung and liver disease; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate; LKENP, leukoencephalopathy, progressive, with ovarian failure; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibres; MLASA, myopathy, lactic acidosis and sideroblastic anaemia; MSCCA, microcephaly, progressive, seizures, cerebral and cerebellar atrophy; NSHL, non-syndromic hearing loss; SIFD, sideroblastic anaemia with B cell immunodeficiency, periodic fevers and developmental delay.

Deregulation of tRNA function is also associated with mutations that affect tRNA splicing factors. Pontocerebellar hypoplasia (PCH) is a spectrum of early-onset neurodegenerative disorders of the brain, which cause microcephaly, seizures and intellectual disability. Mutations in various genes can cause PCH, and several lines of evidence suggest that defects in global protein synthesis underlie this disorder[49]. Among the best-characterized aetiologies of PCH are mutations affecting the tRNA-splicing endonuclease (TSEN) complex (FIG. 1). Although only 6% of human tRNA genes contain introns, recessive mutations of all four subunits of the TSEN complex have been linked to different forms of PCH[24,25]. tRNA-intron removal and ligation also require the activity of cleavage and polyadenylation factor CLP1. CLP1, which was the first RNA kinase identified in mammals[50], interacts with the TSEN complex to promote tRNA splicing[51]. Two recent papers reported homozygous mutations of CLP1 in individuals with PCH with manifestation in both the central and the peripheral nervous systems (PCH type 10)[26,27].

Aminoacyl-tRNA synthetases

ARSs are enzymes that catalyse amino acid attachment to cognate tRNAs: 17 ARSs function in the cytosol, 18 function in mitochondria and 2 function in both the cytosol and mitochondria (glycine–tRNA ligase (GARS) and lysine–tRNA ligase (KARS)). The bi-functional glutamate/proline–tRNA ligase (EPRS) carries out tRNA aminoacylation with both Glu and Pro in the cytosol.

Mitochondrial aminoacyl-tRNA synthetases. Mutations of mitochondrial ARSs interfere with the mitochondrial respiratory chain and cause multisystemic disorders. The phenotypes of these mutations vary from encephalopathy to cardiomyopathy or sideroblastic anaemia (Supplementary table 1). These rare diseases are autosomal recessive and fatal in the first few years of life[52,53].

Cytosolic aminoacyl-tRNA synthetases. The tRNA multi-synthetase complex (MSC), which carries out the aminoacylation process, comprises eight cytosolic ARSs and three scaffolding proteins (MSC auxiliary component p43 (also known as AIMP1), MSC auxiliary component p38 (also known as AIMP2) and MSC auxiliary component p18 (also known as eEF1E1))[54]. Most disease-causing mutations of cytosolic ARSs spare the central nervous system (with few exceptions[55]) (Supplementary table 1) but cause peripheral neuropathies or Charcot–Marie–Tooth (CMT) disease (FIG. 1). This is especially the case for haploinsufficiency mutations, which exclusively give rise to peripheral neuropathies or distal hereditary motor neuropathies[56]. CMT is the most common inherited polyneuropathy (with a prevalence of 1 in 2,500 individuals in the United States). It is a genetically heterogeneous disease that affects both sensory and motor neurons through axonal degeneration or demyelination of neurons. To date, mutations of six ARSs (alanine–tRNA ligase, cytoplasmic (AARS), GARS, histidine–tRNA ligase, cytoplasmic (HARS), KARS, methionine–tRNA ligase, cytoplasmic (MARS) and tyrosine–tRNA ligase, cytoplasmic (YARS)) have been linked to CMT disease. As the nerve endings of peripheral neurons are remote from the soma, local mRNA translation has a central role in regulation of the axonal proteome. This feature is thought to make peripheral neurons more prone to impairments of cytosolic ARSs[57]. It is noteworthy that loss of aminoacylation activity is not the main consequence of all ARS mutations, indicating that non-canonical functions of ARSs have a role in the pathogenesis of some ARS-related disorders[58]. Some mutations cause conformational changes in ARSs that promote interaction of the enzymes with novel partners and result in new functions[59,60]. There is also evidence of non-canonical functions of ARSs in angiogenesis[61], immune response[62] and the DNA damage response[63].

Translation elongation factors

Mutations of three mitochondrial elongation factors (elongation factor Tu, mitochondrial (EF-Tu_{mt}), elongation factor Ts, mitochondrial (EF-Ts_{mt}) and elongation factor G, mitochondrial (EF-G_{mt})) and of their cytosolic counterparts (eukaryotic translation elongation factor 1A (eEF1A), eEF1B and eEF2, respectively) have been linked to human diseases that mainly affect the central nervous system (FIG. 1; Supplementary table 1).

Haploinsufficiency
A condition in diploid organisms where one gene copy is inactivated by mutation and the activity of the remaining copy is insufficient to maintain normal function.

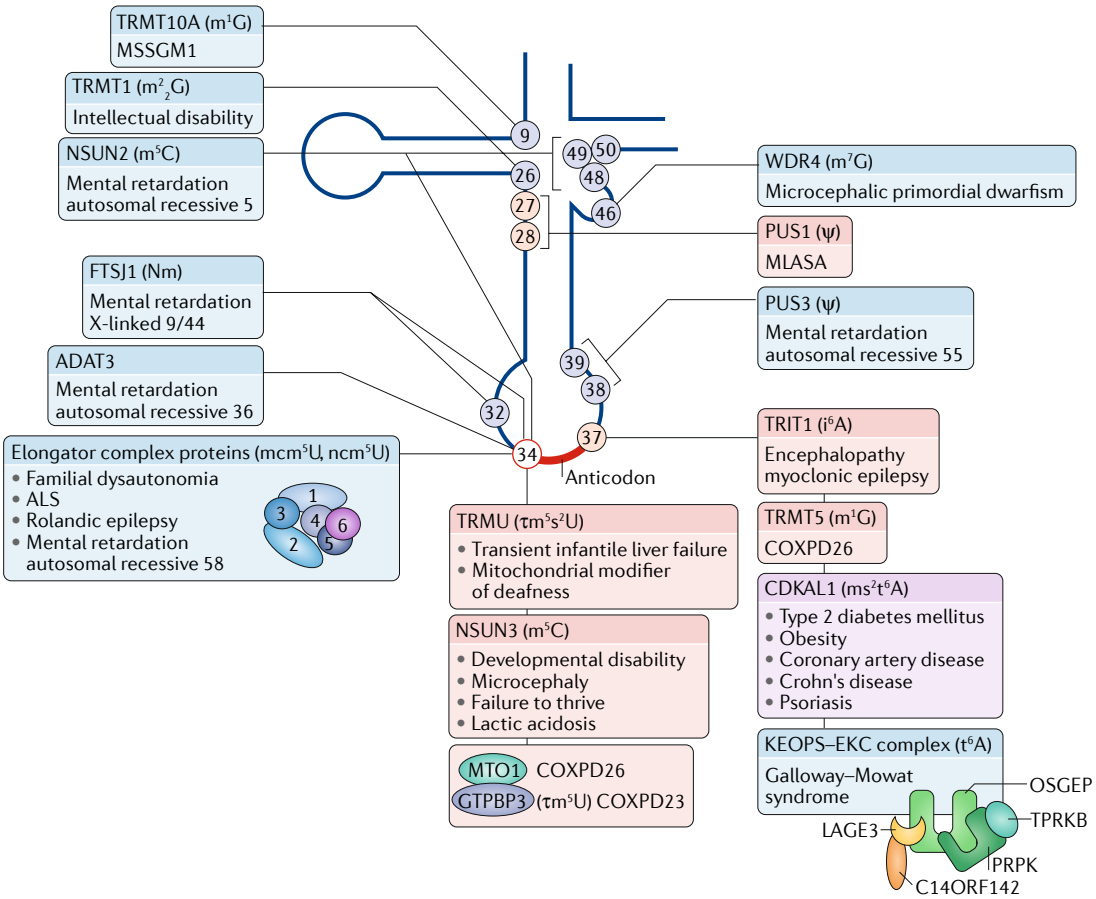


Fig. 2 | **Human diseases linked to mitochondrial or cytosolic tRNA modifications.** All factors involved in tRNA modification are encoded in the nuclear genome. Diseases associated with cytosolic and mitochondrial defects are marked in blue and pink, respectively; diseases associated with both cytosolic and mitochondrial defects are marked in purple. Ψ, pseudouridine; τm^{5}s^{2}U, 5-taurinomethyl-2-thiouridine; τm^{5}U, 5-taurinomethyluridine; ADAT3, probably inactive tRNA-specific adenosine deaminase-like protein 3; ALS, amyotrophic lateral sclerosis; CDKAL1, CDK5 regulatory subunit-associated protein 1-like 1; COXPD, combined oxidative phosphorylation deficiency; EKC, endopeptidase-like and kinase associated to transcribed chromatin; FTSJ1, protein ftsJ homologue 1; GTPBP3, GTP-binding protein 3; i^{6}A, *N*^{6}-(dimethylallyl)adenosine; KEOPS, kinase, endopeptidase and other proteins of small size; LAGE3, L antigen family member 3; m^{1}G, 1-methylguanosine; m$^2_2$G, *N*^{2},2′-*O*-dimethylguanosine; m^{5}C, 5-methylcytidine; m^{7}G, 7-methylguanosine; mcm^{5}U, 5-methoxycarbonylmethyluridine; MLASA, myopathy, lactic acidosis and sideroblastic anaemia; ms^{2}t^{6}A, 2-methylthio-*N*^{6}-threonylcarbamoyladenosine; MSSGM1, microcephaly, short stature and impaired glucose metabolism 1; MTO1, MTO1 homologue, mitochondrial; ncm^{5}U, 5-carbamoylmethyluridine; Nm, 2′-*O*-methylnucleotides; NSUN, NOL1/NOP2/Sun domain family member; OSGEP, *O*-sialoglycoprotein endopeptidase; PRPK, p53-related protein kinase (also known as TP53RK); PUS, tRNA pseudouridylate synthase; t^{6}A, threonylcarbamoyladenosine; TRMT1, tRNA (guanine(26)-*N*(2))-dimethyltransferase; TRMT5, tRNA (guanine(37)-*N*1)-methyltransferase; TRMT10A, tRNA methyltransferase 10 homologue A; TRMU, tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase; TPRKB, TP53RK-binding protein; TRIT1, tRNA dimethylallyltransferase; WDR4, WD repeat-containing protein 4.

Ribosomopathies

Defects in ribosome biogenesis and function cause a spectrum of diseases called ribosomopathies. The mammalian cytosolic ribosome consists of four rRNAs and a large number of ribosomal proteins (there are 80 core ribosomal proteins). Assembly of the pre-40S and pre-60S ribosomal particles commences in the nucleolus and is completed in the cytosol (FIG. 3a). Diseases associated with ribosomal gene haploinsufficiency surprisingly exhibit tissue-specific and sometimes cell type-specific phenotypes, with many causing impairments in bone marrow-derived cell lineages and skeletal or craniofacial abnormalities[64,65] (FIG. 3a; Supplementary table 1).

One of the first described ribosomopathies was Diamond–Blackfan anaemia (DBA), which is characterized by dramatic reduction in erythroid progenitors in the bone marrow, accompanied by macrocytic anaemia and reticulocytopenia[66]. This congenital anaemia is most often diagnosed during the first year of life. Up to 50% of patients with DBA have short stature, craniofacial defects (cleft lip or palate), thumb abnormalities (triphalangeal thumbs) and congenital heart malformations. Mutations in the gene encoding 40S ribosomal protein S19 (RPS19) account for ~25% of individuals with DBA, whereas mutations in other ribosomal proteins are less common[67] (Supplementary table 1). DBA is caused by

reduced ribosome biogenesis and impaired protein synthesis, but the mechanism of preferential manifestation in bone marrow erythroid cells is not well understood[68] (FIG. 3a). Recent studies uncovered the importance of GATA-binding factor 1 (GATA1), which is a crucial transcriptional regulator of erythropoiesis, in the pathogenesis of DBA and provide a potential explanation for the erythroid specificity of its phenotype[69,70]. Alternative splicing of human *GATA1* mRNA generates two GATA1 isoforms, a long isoform that contains the second exon and a short isoform that lacks this exon. Mutations in *GATA1* that reduce the production of the full-length protein (through interfering with splicing or translation of the GATA1 long isoform) can cause DBA[69,70]. In addition, translation of *GATA1* mRNA is specifically sensitive to downregulation of ribosomal proteins, which was

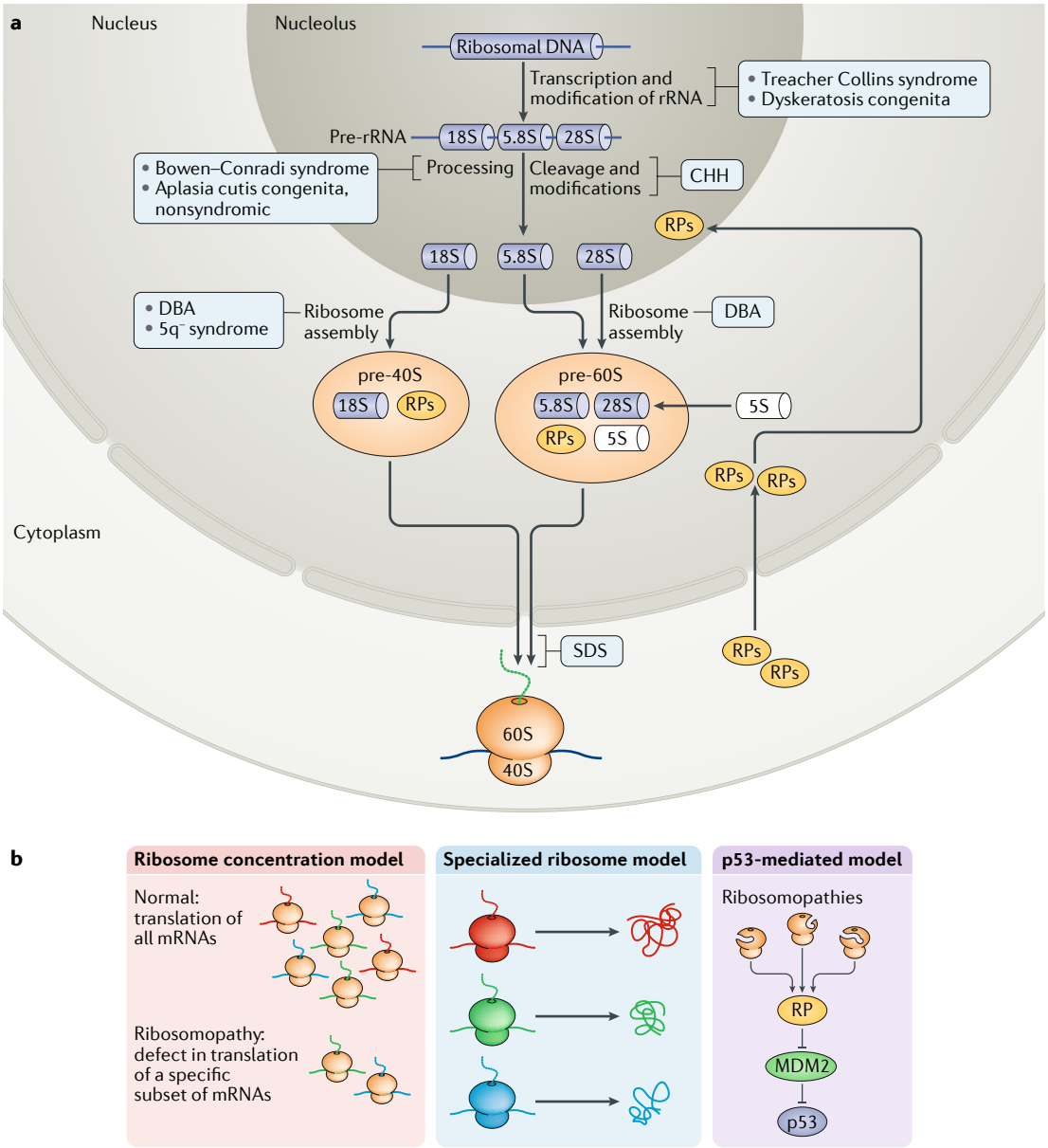


Fig. 3 | **A simplified overview of ribosome biogenesis. a** | The precursor to 18S, 5.8S and 28S ribosomal RNAs (rRNAs) is transcribed in the nucleolus by RNA polymerase I (Pol I), whereas 5S rRNA is transcribed in the nucleoplasm by Pol III. After processing and modification, the 18S, 5.8S and 28S rRNAs assemble with 5S rRNA and ribosomal proteins (RPs), which are synthesized in the cytoplasm and imported into the nucleolus to form pre-40S and pre-60S ribosomal subunits. Pre-40S and pre-60S subunits are then exported to the cytoplasm, where they undergo further maturation. **b** | Three models explaining tissue-specific phenotypes of ribosomopathies are depicted. The ribosome concentration model proposes that ribosome dysfunction affects global translation but that certain mRNAs and cell types are more sensitive to the change in ribosomal function. By contrast, the specialized ribosome model proposes that the composition of ribosomes varies depending on the tissue and stress conditions and that this unique composition determines which subset of mRNAs is translated. The tumour suppressor p53-mediated model suggests that impaired ribosome biogenesis activates the p53 pathway to induce cell cycle arrest or apoptosis in affected cell types. CHH, cartilage hair hypoplasia; DBA, Diamond–Blackfan anaemia; MDM2, E3 ubiquitin-protein ligase; SDS, Schwachman–Diamond syndrome.

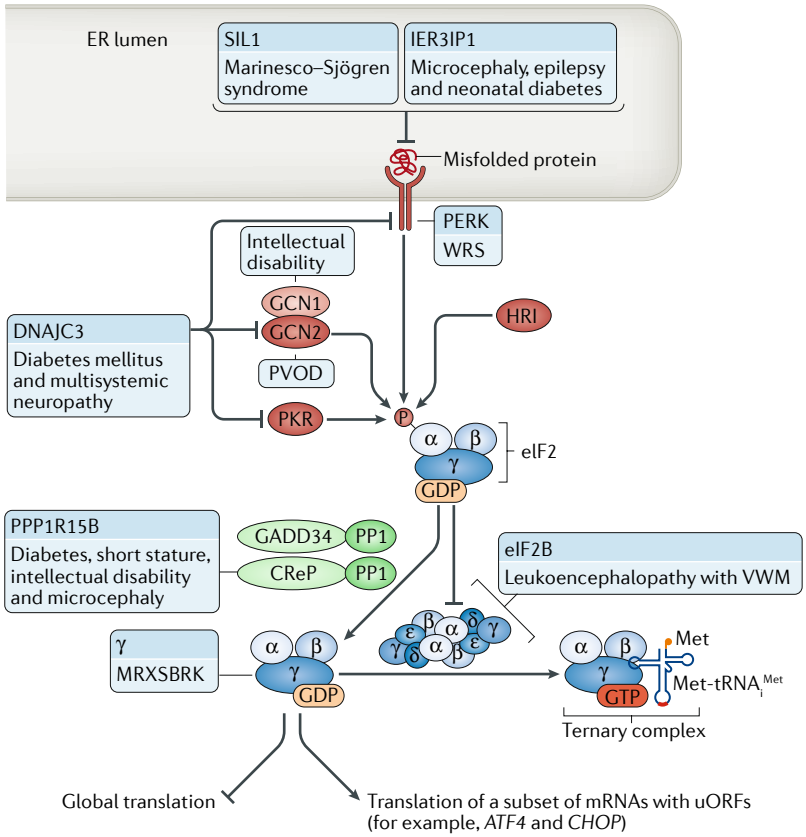


Fig. 4 | **Integrated stress response-related diseases.** Cellular stress leads to activation of the integrated stress response through phosphorylation of the α subunit of eukaryotic translation initiation factor 2 (eIF2α). This is mediated through stimulation of one of four eIF2α kinases: general control nonderepressible 2 (GCN2), PKR-like endoplasmic reticulum (ER) kinase (PERK), protein kinase RNA-activated (PKR) and haem-regulated inhibitor (HRI), each of which is responsive to different cellular stressors (not shown). Growth arrest and DNA damage-induced protein GADD34 (also known as PPP1R15A) and constitutive reverter of eIF2α phosphorylation CReP (also known as PPP1R15B) are regulatory subunits of PP1, which can dephosphorylate eIF2α. Phosphorylation of eIF2α attenuates general translation by inhibiting the assembly of the eIF2–GTP–Met-tRNA$_i^{Met}$ ternary complex, but also stimulates translation of stress response mRNAs such as those encoding activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP), which have upstream open reading frames in their 5′ untranslated regions and thus escape the inhibition of general translation by an indirect mechanism. eIF2B is a multisubunit (comprising eIF2Bα, eIF2Bβ, eIF2Bγ, eIF2Bδ and eIF2Bε) guanine nucleotide exchange factor for eIF2. DNAJC3, DnaJ homologue subfamily C member 3; GCN1, general control of amino-acid synthesis 1-like protein 1; IER3IP1, immediate early response 3-interacting protein 1; MRXSBRK, mental retardation, X-linked, syndromic, Borck type; PVOD, pulmonary veno-occlusive disease; SIL1, nucleotide exchange factor SIL1; VWM, vanishing white matter; WRS, Wolcott–Rallison syndrome.

linked to a higher threshold requirement for translation initiation of *GATA1* mRNA[69].

A well-studied syndrome exhibiting erythroid defects is 5q$^-$ syndrome, which is caused by a heterozygous deletion of the long arm of chromosome 5 (del(5q)). The macrocytic anaemia that is a hallmark of this disorder is caused by haploinsufficiency of the *RPS14* gene[71,72], whereas haploinsufficiency of other genes in the deleted chromosomal region contributes to non-erythroid phenotypes: haploinsufficiencies of the microRNAs miR-145 and miR-146a are linked to thrombocytosis[73], and haploinsufficiency of early growth response protein 1 (EGR1) is linked to clonal dominance[74]. A recent study demonstrated the importance of La-related protein 1 (LARP1), which is a translation regulator and effector of mTOR complex 1 (mTORC1)[75], in 5q$^-$ syndrome pathogenesis[76]. Anaemia in DBA and 5q$^-$ syndrome is ameliorated in animal models and patients by treatment with L-leucine[77,78]. L-leucine-induced activation of mTORC1, which promotes mRNA translation and ribosome biogenesis, has been suggested to mediate these beneficial effects[77]. Although there is growing concern regarding the possible cancer-promoting effect of mTORC1 activators[79], these findings offer a therapeutic option for patients with DBA or 5q$^-$ syndrome and provide a basis to test the efficacy of L-leucine in other ribosomopathies.

Other syndromes associated with mutations in proteins involved in ribosome biogenesis exhibit a wide range of symptoms. Schwachman–Diamond syndrome (SDS) is characterized by exocrine pancreatic dysfunction, impaired haematopoiesis and neutropenia and bone defects[80]. SDS is caused by mutation in the gene encoding ribosome maturation protein SBDS, which binds to the 60S ribosomal subunit and functions in 60S ribosome biogenesis and RNA processing[81] (FIG. 3a). Cartilage hair hypoplasia (CHH) is a disorder characterized by short-limb dwarfism and fine, sparse hair, as well as defective cellular immunity, hypoplastic anaemia and neuronal dysplasia of the intestine[82–84]. The disease is caused by mutations in the gene encoding RNA component of mtRNA processing endoribonuclease (*RMRP*), which encodes the non-coding RNA component of the RNase mtRNA processing (MRP) complex required for rRNA processing[82,85]. Defective rRNA processing, involved in the maturation of 40S subunit, has also been linked to Bowen–Conradi syndrome and Aplasia cutis congenita, non-syndromic[86,87]. Whereas Aplasia cutis congenita is a relatively mild condition that often manifests as a skin defect on scalp, Bowen–Conradi syndrome is a fatal congenital disorder presented by numerous developmental defects and early death. Treacher Collins syndrome is characterized by craniofacial growth defects without haematological abnormalities. The disease is caused by mutations in RNA polymerase I and III subunit D (*POLR1D*) and RNA polymerase I and III subunit C (*POLR1C*), each encoding a subunit of both the RNA polymerase I (Pol I) complex and the Pol III complex, and in treacle ribosome biogenesis factor 1 (*TCOF1*); the three encoded proteins are involved in the transcription of genes encoding ribosomal RNA, tRNA and other small RNAs and in rRNA methylation[88–90]. Defective rRNA modification in general may be responsible for ribosomopathies. For example, X-linked dyskeratosis congenita, which is loosely classified as a 'premature ageing syndrome', is caused by mutation of the gene encoding dyskerin (*DKC1*), which mediates pseudouridylation of rRNA[91].

The mechanisms by which aberrant ribosome biogenesis affects cellular functions and the reasons for the variability in the clinical manifestation of ribosomopathies remain elusive[92,93]. The ribosome concentration model posits that deregulated translation of specific mRNAs or reduced levels of global translation could link ribosomal mutations to impairments in cellular

Clonal dominance
A condition in which a single clone of haematopoietic stem cells (HSCs) supersedes the other HSC clones.

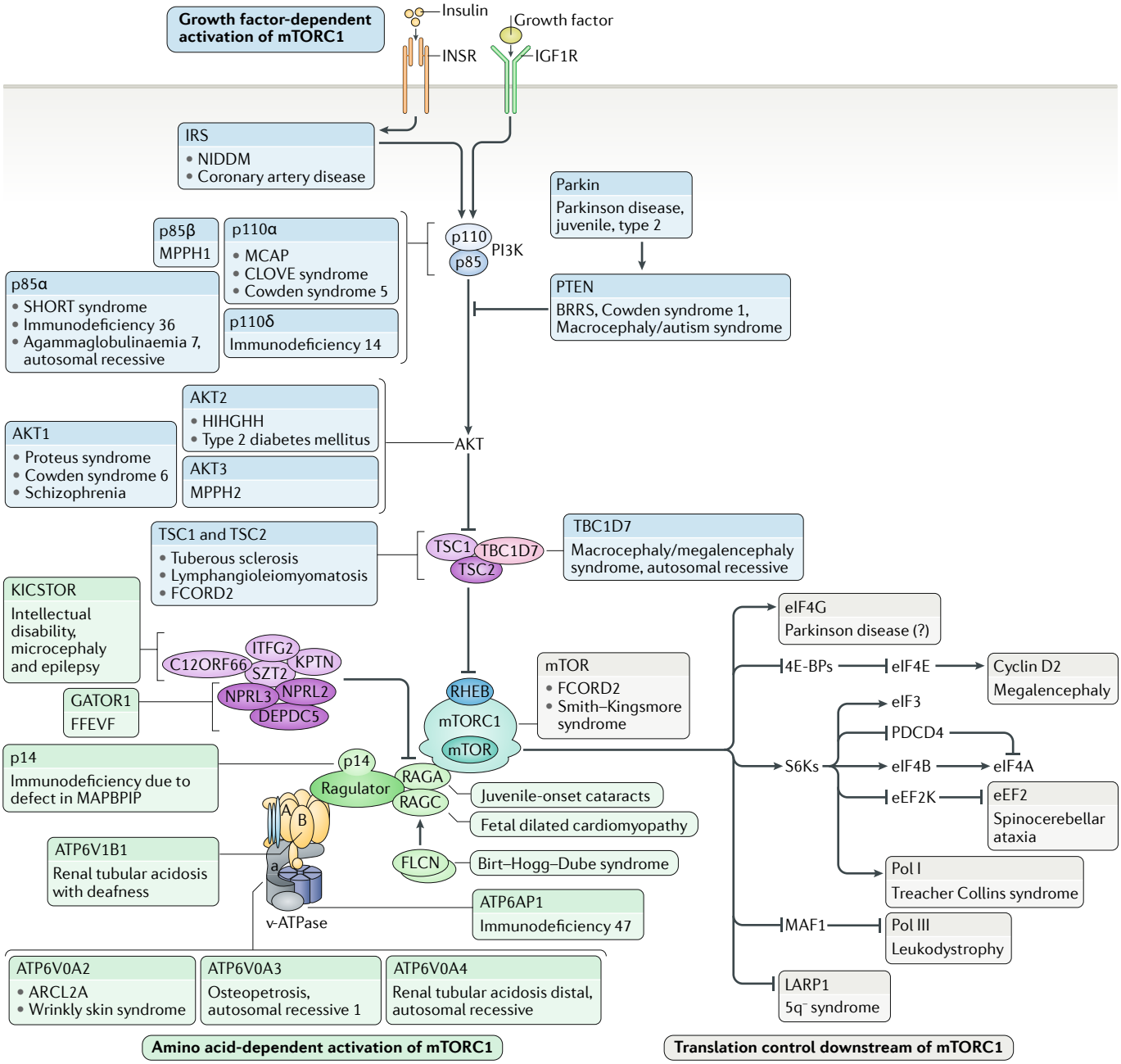


Fig. 5 | **Human diseases linked to the mTOR complex 1 pathway.** Diseases linked to growth factor-dependent activation of mTOR complex 1 (mTORC1) are highlighted in blue, and diseases linked to amino acid-dependent mTORC1 activation are in green. Brown denotes the diseases that are shared by both pathways. In response to growth factors and insulin, the PI3K–AKT pathway stimulates mTORC1 through inhibition of the tuberous sclerosis complex (TSC), a negative regulator of the small GTPase GTP-binding protein RHEB. Amino acids activate mTORC1 through activating RAS-related GTP-binding protein (RAG) GTPases. Both growth factor-dependent and amino acid-dependent pathways must be activated to stimulate mTORC1 activity. mTORC1 controls translation initiation through phosphorylation of several effectors. In addition to translation initiation, mTORC1 controls elongation through phosphorylation of ribosomal protein S6 kinases (S6Ks) and eukaryotic elongation factor 2 (eEF2) kinase (eEF2K). The activity of RNA polymerase I (Pol I) and Pol III and the transcription of mRNAs encoding ribosomal proteins are also controlled by mTORC1 through S6Ks and repressor of Pol III transcription MAF1 homologue (MAF1). 4E-BPs, eIF4E-binding proteins; ARCL2A, cutis laxa, autosomal recessive, type IIA; ATP6AP1, vacuolar proton pump subunit S1; ATP6V0, vacuolar proton translocating ATPase 116 kDa subunit; ATP6V1B1, vacuolar proton pump subunit B1; BRRS, Bannayan–Riley–Ruvalcaba syndrome; cyclin D2, G1/S-specific cyclin D2; CLOVE, congenital lipomatous overgrowth, vascular malformations and epidermal nevi; DEPDC5, DEP domain-containing 5; eIF, eukaryotic translation initiation factor; FCORD2, focal cortical dysplasia type II; FFEVF, familial focal epilepsy with variable foci; FLCN, folliculin; GATOR1, GAP activity towards Rag 1 ; HIHGHH, hypoinsulinaemic hypoglycaemia with hemihypertrophy; IGF1R, insulin-like growth factor 1 receptor; INSR, insulin receptor; IRS, insulin receptor substrate; ITFG2, integrin-α FG-GAP repeat-containing protein 2; KICSTOR, KPTN–ITFG2–C12ORF66–SZT2; KPTN, kaptin; LARP1, La-related protein 1; MAPBPIP (p14), (mitogen-activated protein-binding protein)-interacting protein; MCAP, megalencephaly–capillary malformation–polymicrogyria; MPPH, megalencephaly–polymicrogyria–polydactyly–hydrocephalus; NIDDM, non-insulin-dependent diabetes mellitus; p110, PI3K catalytic subunit; p85, PI3K regulatory subunit; PDCD4, programmed cell death protein 4; SHORT, short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay; SZT2, seizure threshold 2 protein homologue; TBC1D7, TBC1 domain family member 7; TSC1, hamartin; TSC2, tuberin; v-ATPase, lysosomal vacuolar H^+-ATPase.

activity[68] (FIG. 3b). The tissue specificity of ribosomopathies has been attributed to the differential sensitivity of the translation of specific mRNAs to ribosomal dysfunction in different tissues[69]. Alternatively, ribosomopathies may arise from an imbalance in the ratio of ribosomal proteins, which has been shown to activate the tumour suppressor p53 signalling pathway. According to this model, reduced synthesis of a certain ribosomal protein leads to impairment of ribosomal biogenesis and the accumulation of unassembled ribosomal proteins. These proteins bind the E3 ubiquitin–protein ligase MDM2 and suppress its activity[94,95]. MDM2 negatively regulates p53 by targeting it for proteasomal degradation[96]. Therefore, reduced MDM2 activity leads to stabilization and activation of p53 (REFS[95,97–99]). In turn, this promotes cell cycle arrest and apoptosis, which disproportionately affect fast-dividing haematopoietic cells. Inactivation of p53 in mouse models of DBA (mutation in *Rps19*)[100] and 5q$^-$ syndrome[101] rescued several phenotypes, including erythrocytic hypoplasia, thereby supporting the notion that p53 activation contributes to erythroid deficits in these ribosomopathies[102,103]. An alternative hypothesis suggests that 'specialized ribosomes' with unique ribosomal protein composition and tissue distribution are required for the translation of particular mRNAs[104,105]. Loss of such specialized ribosomes could explain the tissue specificity of ribosomal protein deficiency (FIG. 3b). Further studies are required to determine whether the so-called specialized ribosomes reflect unique properties of distinct ribosomal proteins or differential sensitivities of certain mRNAs to alterations in ribosome abundance (ribosome concentration model)[68,106]. The role of p53-dependent and p53-independent pathways in the response to aberrant ribosomal biogenesis and the mechanisms underlying tissue specificity are intensive areas of research[68,107], which should yield important insights into ribosomopathies.

The integrated stress response

The ISR senses diverse cellular stresses and mediates changes in gene expression to adapt to stress. Distinct stressors activate four kinases, which converge on a single phosphorylation site: Ser51 (in humans) of the α-subunit (or subunit 1) of human eukaryotic translation initiation factor 2 (eIF2α; also known as eIF2S1). The four kinases are haem-regulated inhibitor (HRI; also known as eIF2AK1), protein kinase RNA-activated (PKR; also known as eIF2AK2), PKR-like endoplasmic reticulum (ER) kinase (PERK; also known as eIF2AK3) and general control nonderepressible 2 (GCN2; also known as eIF2AK4) (FIG. 4). The eIF2 complex functions in translation initiation by forming a ternary complex with the initiator Met-tRNA and GTP, which is delivered to the small ribosomal subunit (40S) to form the 43S preinitiation complex (BOX 1). Phosphorylation of eIF2α blocks the activity of the guanine nucleotide exchange factor eIF2B, which recycles GDP-bound eIF2 to GTP-bound eIF2. Phosphorylation of eIF2α reduces general translation but selectively increases the translation of mRNAs harbouring upstream open reading frames in their 5′UTR, such as those encoding the transcription factors activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP; also known as DDIT3). The vital role of the ISR in cellular function is illustrated by several diseases caused by mutations in genes in this pathway, including those encoding the eIF2α kinases PERK and GCN2, eIF2B, the γ-subunit (subunit 3) of eIF2 (eIF2γ; also known as eIF2S3) and protein phosphatase 1 regulatory subunit 15B (PPP1R15B) (FIG. 4; Supplementary table 1).

PERK integrates ER-related stress to mediate translation attenuation during the unfolded protein response (UPR)[108]. The UPR is activated as a consequence of the accumulation of misfolded or unfolded proteins in the ER lumen, which is a major site of protein processing and folding[109]. PERK activation leads to eIF2α phosphorylation and translation attenuation, resulting in decreased protein load in the ER. Deregulation of PERK function leads to a failure in coping with the accumulation of misfolded proteins in the ER, especially in cells with high secretory demands, such as pancreatic β cells, resulting in cellular damage and dysfunction[110]. Mutations in the gene encoding PERK (*EIF2AK3*) cause a rare autosomal recessive disease, Wolcott–Rallison syndrome (WRS)[111]. Consistent with the vital role of PERK in secretory cells, the most prominent feature of WRS is neonatal or early infancy diabetes[112]. WRS also manifests with skeletal abnormalities (epiphyseal dysplasia, osteopenia and spine defects) that result in delayed growth, episodes of acute liver failure and intellectual deficits accompanied by microcephaly and epilepsy. Whole body knockout of *Eif2ak3* in mice recapitulates the WRS phenotype, including neonatal diabetes, skeletal malformation and growth retardation[113,114]. Specific deletion of *Eif2ak3* in insulin-secreting β cells causes defective β cell proliferation and differentiation during the fetal and neonatal periods[115,116]. A recent study showed that the detrimental effects of *Eif2ak3* deletion in the pancreas are caused by increased type I interferon receptor 1 (IFNAR1) expression and signalling. The authors proposed inhibiting IFNAR1 as a means to mitigate cellular damage caused by PERK deficiency[117].

Diabetes or nervous system phenotypes partially overlapping with WRS are caused by mutations in several other genes that encode ISR proteins, for example, DnaJ homologue subfamily C member 3 (DNAJC3), immediate early response 3-interacting protein 1 (IER3IP1) and nucleotide exchange factor SIL1 (REFS[118–120]) (FIG. 4). DNAJC3 is a heat shock co-chaperone that is induced by ER stress[121] and that inhibits PERK, PKR[122] and GCN2 (REF.[123]) to suppress eIF2α phosphorylation and prolong translation in stress conditions. Homozygous mutations in *DNAJC3* cause increased eIF2α phosphorylation, leading to diabetes mellitus (age of onset 11–18 years), central nervous system phenotypes (early-onset ataxia and pyramidal tract signs) and peripheral nervous system phenotypes (sensorimotor peripheral neuropathy and sensorineural hearing loss)[119]. The diabetes phenotype is recapitulated in *Dnajc3* knockout mice, which exhibit hyperglycaemia and glucosuria associated with apoptosis of pancreatic β cells and reduced insulin levels[124]. SIL1 is a nucleotide exchange factor for binding-immunoglobulin protein (BiP; also known as HSPA5), which is a crucial regulator of the UPR. Mutations of

SIL1 have been identified in patients with Marinesco–Sjögren syndrome, which is characterized by cerebellar ataxia, developmental delay, myopathy and cataracts[118]. *IER3IP1* encodes a small protein (~10 kDa) that is localized in the ER and is involved in the ER stress response. It is highly expressed in cerebral cortex and pancreatic β cells. Mutations in *IER3IP1* cause microcephaly with simplified gyration, epilepsy and permanent neonatal diabetes syndrome (MEDS), which has overlapping phenotypes with WRS[120].

Mutations in *PPP1R15B* impair the phosphatase activity of PP1, leading to increased eIF2α phosphorylation[125,126]. Clinically, this causes early-onset diabetes (age of 15–28 years), microcephaly, intellectual disability and bone dysplasia. The similarity of the clinical manifestations among ISR-related disorders supports the notion that any deviation from the optimal level of eIF2α phosphorylation, either an increase (for example, because of mutations in *DNAJC3* and *PPP1R15B*) or a decrease (through mutations in *EIF2AK3*), preferentially affects β cells, brain and bone tissues. This hypothesis is consistent with the phenotype (detailed below) caused by mutation in the γ-subunit of the trimeric eIF2 complex[127]. Missense mutations in *EIF2S3* (encoding eIF2γ) disrupt the eIF2 complex, causing mental retardation, X-linked, syndromic, Borck type (MRXSBRK (pronounced 'Marx Borck')), which is characterized by intellectual disability, microcephaly, epilepsy and growth retardation[127–129].

One of the most common inherited childhood leukoencephalopathies is vanishing white matter (VWM), which is also called childhood ataxia with central hypomyelination[130]. VWM is caused by autosomal recessive mutations in any one of the five genes encoding eIF2B subunits (*eIF2B1–eIF2B5*) and is characterized by selective dysfunction of brain glia cells (oligodendrocytes and astrocytes), diffuse lack of myelin and white matter cystic degeneration[131]. Early-childhood onset progressive cerebellar ataxia is a hallmark of VWM, but the disease can develop at older age and involve spasticity, optic atrophy with loss of vision and epilepsy. The onset of the disease and rapid neurological deterioration occur following stress, such as minor head trauma and febrile infections. Some female patients develop premature ovarian failure in addition to cerebral abnormalities (ovarioleukodystrophy). Notably, co-occurrence of ovarian failure and neurodegenerative disorders has also been reported for individuals with mutations in probable histidine–tRNA ligase, mitochondrial (HARS2) (REF.[132]) and probable leucine–tRNA ligase, mitochondrial (LARS2) (REF.[133]) in Perrault syndrome; and for individuals with mutations in alanine–tRNA ligase, mitochondrial (AARS2) in LKENP (leukoencephalopathy, progressive, with ovarian failure)[134], suggesting a common mechanism underlying these disorders (see below). Studies of transgenic mice harbouring mutations in eIF2B, supported by human data, provide evidence that astrocyte dysfunction is a core VWM feature, leading to inhibition of oligodendrocyte maturation and myelin production[135,136]. The mechanism causing the selective effect of eIF2B mutations in glia remains elusive, although a recent study demonstrated increased sensitivity of mouse astrocytes to eIF2B mutation-induced impairment in mitochondrial oxidative respiration[137]. An increase in mitochondrial abundance sufficed to meet the energy requirements of *Eif2b5*$^{R132H/R132H}$ mouse embryo fibroblasts (which are not involved in the pathogenesis of VWM) but failed to do so in mutant primary astrocytes[138].

Mutations in the eIF2α kinase GCN2 (encoded by *EIF2AK4*), have been linked to pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis[21]. PVOD is a rare form of pulmonary hypertension that is characterized histologically by fibrous intimal proliferation of septal veins and pre-septal venules, resulting in luminal narrowing and pulmonary capillary dilatation and proliferation[139]. The obstructive changes in pulmonary veins cause an increase in pulmonary vascular resistance, which in a large fraction of patients leads to right ventricle failure and death (72% mortality within 1 year of diagnosis)[140,141]. Despite evidence of autosomal recessive transmission of the *EIF2AK4* mutations in PVOD and the availability of a mouse model, the functional link between GCN2 and disease pathophysiology remains unknown. Several lines of evidence suggest that environmental stress has a crucial role in triggering the disease onset[140]. It is also not clear why mutations in GCN2 lead to pulmonary phenotypes, whereas other tissues commonly associated with deregulated ISR, such as brain and pancreas, remain unaffected. Notably, a recent study identified mutations of general control of amino-acid synthesis 1-like protein 1 (GCN1), an activator of GCN2, in individuals with intellectual disability[142].

The mTOR pathway in human diseases

mTOR is a serine/threonine protein kinase of the PI3K-related kinase family that participates in two multisubunit protein complexes, mTORC1 and mTORC2. mTORC1 integrates various internal and external stimuli to coordinate major anabolic (for example, protein synthesis, lipogenesis and nucleic acid production) and catabolic (for example, autophagy) processes in the cell. The discovery that rapamycin (an allosteric inhibitor of mTORC1) inhibits translation initiation across species revealed the importance of protein synthesis as a major downstream target of mTORC1 (REFS[143,144]). The eIF4E-binding proteins (4E-BPs), ribosomal protein S6 kinases (S6Ks), eIF4G, LARP1 and repressor of Pol III transcription MAF1 homologue (MAF1) function as direct mTORC1 effectors in controlling protein synthesis (FIG. 5). mTORC1 controls global protein synthesis indirectly by regulating the transcription and translation of ribosomal proteins and translation factors. Studies in animal cancer models have demonstrated that impairing protein synthesis through pharmacological or genetic manipulation substantially attenuates the oncogenic effect of mTORC1 activation[145,146]. Here, we summarize the human diseases linked to deregulation of two major signalling pathways upstream of mTORC1, the PI3K and amino acid-sensing pathways. Diseases associated with deregulation of other regulators of mTORC1 have been discussed extensively in other reviews[147,148].

Overgrowth syndromes
A group of genetic diseases that are manifested as abnormal growth of the whole body or of body parts.

The PI3K–AKT–mTORC1 pathway

The PI3K–AKT pathway is a major growth factor-stimulated signalling pathway that activates mTORC1 through inhibition of the tuberous sclerosis complex (TSC) (FIG. 5). It is also the most frequently activated signalling pathway in cancer; therefore, most of the disorders discussed in this section are in fact cancer prone or accompanied by benign or malignant tumours. Deregulation of the PI3K–AKT–mTORC1 pathway has been implicated in a large number of human diseases, including metabolic diseases, neurodevelopmental disorders, overgrowth syndromes and immunodeficiencies[149,150] (FIG. 5; Supplementary table 1). Several common oncogenic mutations of the PI3K–AKT–mTORC1 pathway have also been identified in non-cancer-associated disorders, providing an opportunity to repurpose drugs developed for cancer treatment for non-cancer diseases[151,152]. mTORC1 is a major regulator of cell growth. Accordingly, mutations that activate this pathway are accompanied by a variety of overgrowth phenotypes (FIG. 5; Supplementary table 1). Brain disorders are frequently observed with deregulation of the mTORC1 pathway, underscoring the importance of this pathway in brain development and function[153]. Megalencephaly is associated with mutations in *PIK3CA*, *PIK3R2*, *PTEN*, *AKT3*, *TSC1*, *TSC2*, *MTOR* and *DEPDC5* (which encodes a component of the GAP activity towards Rag 1 (GATOR1) complex; see below)[154–156]. Autism spectrum disorder (ASD), focal cortical dysplasia and seizures are also frequently observed in mTOR-related syndromes[155,157,158]. Here, we discuss the role of components of the PI3K–AKT–mTORC1 pathway in human disorders.

PI3K. Mutations in both the catalytic (p110) and the regulatory (p85) subunits of class IA PI3Ks have been linked to human disorders[149]. Disease outcome largely depends on tissue distribution as well as on the functional consequence of the mutations (activating or suppressing). Whereas mutations in the ubiquitously expressed genes *PIK3CA* (encoding p110α) and *PIK3R2* (encoding p85β) frequently cause brain malformation[156], activating mutations in *PIK3CD* (encoding p110δ, which is an immune-specific isoform of p110) or in its regulatory subunit, *PIK3R1* (encoding p85α), cause an immunodeficiency syndrome known as activated PI3Kδ syndrome (OMIM: Immunodeficiency 14 and Immunodeficiency 36, respectively)[159,160] (FIG. 5). Importantly, loss-of-function mutations in *PIK3CD* or *PIK3R1* have been linked to immunodeficiency, indicating that precise regulation of PI3Kδ activity is required for proper function of immune cells[2]. Some immunodeficiency phenotypes of gain-of-function mutations are rescued by rapamycin treatment[161], indicating that mTOR activation has a crucial role in the pathogenesis of immunodeficiency.

PTEN: dose-dependent effects on disease. The tumour suppressor PTEN is a lipid phosphatase that counteracts PI3K activity, resulting in inhibition of AKT phosphorylation (FIG. 5). In addition to its prominent role in cancer, germline mutations in PTEN have been associated with several distinct overgrowth syndromes and with ASD. The phenotypes observed in patients carrying PTEN mutations cover a wide range of tissues and severities, such as macrocephaly, intellectual disability, ASD, seizures, immunodeficiency and skeletal abnormalities[155,162–167]. Several genotype–phenotype studies have provided compelling evidence that the extent of PTEN deficiency determines disease severity. Partial inactivation of PTEN, by mutations that render the protein unstable or reduce its ability to suppress AKT, is largely associated with ASD and macrocephaly, whereas complete inactivation of PTEN is associated with overgrowth syndromes and cancer[168].

AKT: the intriguing case of the E17K mutation. AKT has three isoforms, AKT1, AKT2 and AKT3, which are encoded by three genes. Whereas AKT1 is ubiquitously expressed, AKT2 is expressed at the highest level in insulin-sensitive tissues, and AKT3 is expressed at the highest level in the brain. A somatic activating mutation of AKT1, E17K, causes an overgrowth syndrome known as Proteus syndrome[169]. Interestingly, the same mutation of E17K in AKT2 or AKT3 causes different phenotypes. The mutation in AKT2 produces a metabolic disorder known as hypoinsulinaemic hypoglycaemia with hemihypertrophy (HIHGHH)[170], whereas in AKT3, it has been associated with a megalencephaly syndrome (specifically, megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome 2 (MPPH2))[171]. The overlapping and unique consequences of homologous mutations in AKT1, AKT2 and AKT3 highlight the importance of tissue distribution of the affected protein in disease manifestation. Strikingly, E17K in AKT1 is also frequently found in cancer. The timing of mutation (germline versus somatic) and predisposing factors (genetics or environmental) dictate whether E17K promotes cancer or a non-malignant phenotype. Notably, loss of AKT2 or AKT3 generates phenotypes opposite to those of the E17K mutation in AKT2 or AKT3 (REFS[172,173]).

Tuberous sclerosis complex. Tuberous sclerosis is a neurocutaneous disorder resulting from inactivating mutations of hamartin (TSC1) or tuberin (TSC2) (REFS[174,175]); it is characterized by benign tumours in multiple organs, seizures, intellectual disability and ASD[176]. TSC consists of TSC1, TSC2 and TBC1 domain family member 7 (TBC1D7) and functions as a GTPase activating protein for GTP-binding protein RHEB to inhibit mTORC1 activity (FIG. 5). Notably, mutation of TBC1D7 has been identified in patients with macrocephaly, intellectual disability, osteoarticular defects, myopia and coeliac disease[177].

mTOR. Although mutations of various upstream regulators of mTORC1 have long been associated with various non-cancer-related human diseases, no mutations of components of mTORC1 (mTOR, regulatory-associated protein of mTOR (RAPTOR), proline-rich AKT1 substrate 1 (AKT1S1), target of rapamycin complex subunit LST8 and DEP domain-containing mTOR-interacting protein (DEPTOR)) had been identified until recently. This delay was attributed to the rarity of such mutations owing to the crucial role of mTORC1 in development.

Codon usage
The frequency with which a specific codon is used in the coding sequence of a mRNA or set of mRNAs.

However, recent whole exome sequencing studies have uncovered several de novo and somatic *MTOR* mutations in patients with megalencephaly, focal cortical dysplasia and epilepsy[154,178].

Amino acid-dependent mTORC1 activation

In 2007, a novel primary immunodeficiency syndrome was reported — immunodeficiency owing to a mutation in MAPBP (mitogen-activated protein-binding protein)-interacting protein (MAPBPIP; also known as LAMTOR2 and p14) — which is characterized by congenital neutropenia, B cell and T cell deficiency, hypopigmented skin and short stature[179] (FIG. 5). The growth defect distinguishes the syndrome from lysosomal diseases that also manifest immunodeficiency and hypopigmentation. MAPBPIP (p14) is a component of a pentameric complex termed Ragulator[180]. Upon activation by amino acids, Ragulator recruits RAS-related GTP-binding protein (RAG) GTPases to lysosomes to mediate mTORC1 activation[180–182]. In addition to Ragulator, mTORC1 relies on several other protein complexes to sense the levels of lysosomal and cytosolic amino acids, including the complexes lysosomal vacuolar H^+-ATPase (v-ATPase), GATOR1, GATOR2 and KICSTOR (kaptin (KPTN)–integrin-α FG-GAP repeat-containing protein 2 (ITFG2)–C12ORF66–seizure threshold 2 protein homologue (SZT2))[183] (FIG. 5). Mutations in different components of these complexes (except GATOR2) have been linked to various human disorders. In particular, defects in GATOR1 or KICSTOR, which are inhibitors of mTORC1 in response to nutrient deprivation, generate neurological phenotypes similar to those observed in PI3K–AKT–mTOR-linked disorders. Mutations affecting DEP domain-containing protein 5 (DEPDC5) (REF.[184]), NPRL2 and NPRL3 (REF.[185]) (components of the GATOR1 complex) and SZT2 (REF.[186]), KPTN[187] and C12ORF66 (REF.[188]) (components of the KICSTOR complex) have been identified in patients with seizures, ASD, intellectual disability and neurodevelopmental disorders. The v-ATPase is a multisubunit proton pump that interacts with the Ragulator–RAG complex. Mutations in different subunits of v-ATPase have been linked to various human disorders (FIG. 5; Supplementary table 1). To what extent v-ATPase-linked disorders are associated with mTORC1 dysfunction remains to be determined.

Other factors in neuronal diseases

Mutations in translation regulatory factors such as GRB10-interacting GYF protein 1 (GIGYF1), GIGYF2, zinc-finger protein 598 (ZNF598) (components of a translation repressor complex[189]) and eIF4G1 have been linked to various neurodegenerative and neurodevelopmental disorders including Parkinson disease[190–192], autism and intellectual disabilities (Supplementary table 1). In addition, recent studies highlighted the importance of translation deregulation in repeat-associated disorders such as Fragile X syndrome and amyotrophic lateral sclerosis (ALS), further emphasizing the crucial role of translation control in neurodegenerative diseases. For recent reviews on repeat-associated disorders, the reader is referred to REFS[193–195].

The basis of phenotypic variability

How does deregulation of general protein synthesis generate such a diverse range of human disorders? Undoubtedly, several factors contribute to this diversity. First, not all mRNAs are equally sensitive to translation deregulation. Differences in sequence, length and secondary structure of 5′UTRs and 3′UTRs make mRNAs differentially sensitive to the activity of distinct translation factors. For example, mRNAs with long and structured 5′UTRs, mitochondria-related mRNAs with short 5′UTRs and mRNAs with 5′-terminal oligopyrimidine motifs are sensitive to deregulation of the mTOR pathway[196–198]. The differential response of mTORC1-sensitive mRNA subsets to distinct translation initiation factors controls the expression of functionally related transcripts[196]. In addition, as described for mt-tRNA mutations, differences in codon usage between distinct mRNAs (for example, high UUG content in *MT-ND6*) may contribute to disease outcomes (for example, in MELAS syndrome)[36]. Despite our knowledge of translation deregulation of a few disease-related mRNAs (*GATA1* and *MT-ND6*), important questions remain unanswered. First, for each disease, what are the specific mRNAs that are translationally deregulated and responsible for disease onset? Second, what features of mRNAs make them more or less sensitive to deregulation by translation regulators? Finally, can this knowledge be tailored for targeted therapy, and, if so, how?

In addition, gene expression varies in time and between tissues. The phenotypes of mutations in the genes encoding AKT and PI3K clearly show that the tissue distribution of mutated genes has a crucial role in disease outcome, as homologous mutations in three AKT isoforms with over 80% sequence identity are associated with different pathologies (FIG. 6a). Loss of essential genes is incompatible with embryogenesis. Thus, disease-causing mutations tend to only partially reduce the activity of essential genes, rather than engender complete inactivation, or appear as somatically mosaic mutations. Differences in the extent of inactivation or the distribution of mutations in the body cause diverse pathological manifestations, as documented for PTEN and PI3Kδ (*PIK3CD* or *PIK3R1*) mutations (FIG. 6b). In addition, different tissues and cell types respond differently to translation deregulation. Tissues with high energy consumption are more prone to deregulation of mitochondrial translation, and peripheral neurons with long processes are more susceptible to ARS mutations. Finally, as described for GCN2 mutations, predisposing genetic and environmental factors contribute to the pathogenesis of diseases.

The nervous system is particularly vulnerable to deregulation of mRNA translation, likely owing to both structural and metabolic features. Neurons have an extraordinarily complex and polarized morphology, in which dendrites and axons are distinct functional compartments, and these compartments depend on local translation of pre-existing, localized mRNAs to rapidly respond to a bevy of stimuli (FIG. 6c). The remote regulation of mRNA translation renders neurons more susceptible to translation deregulation. In addition,

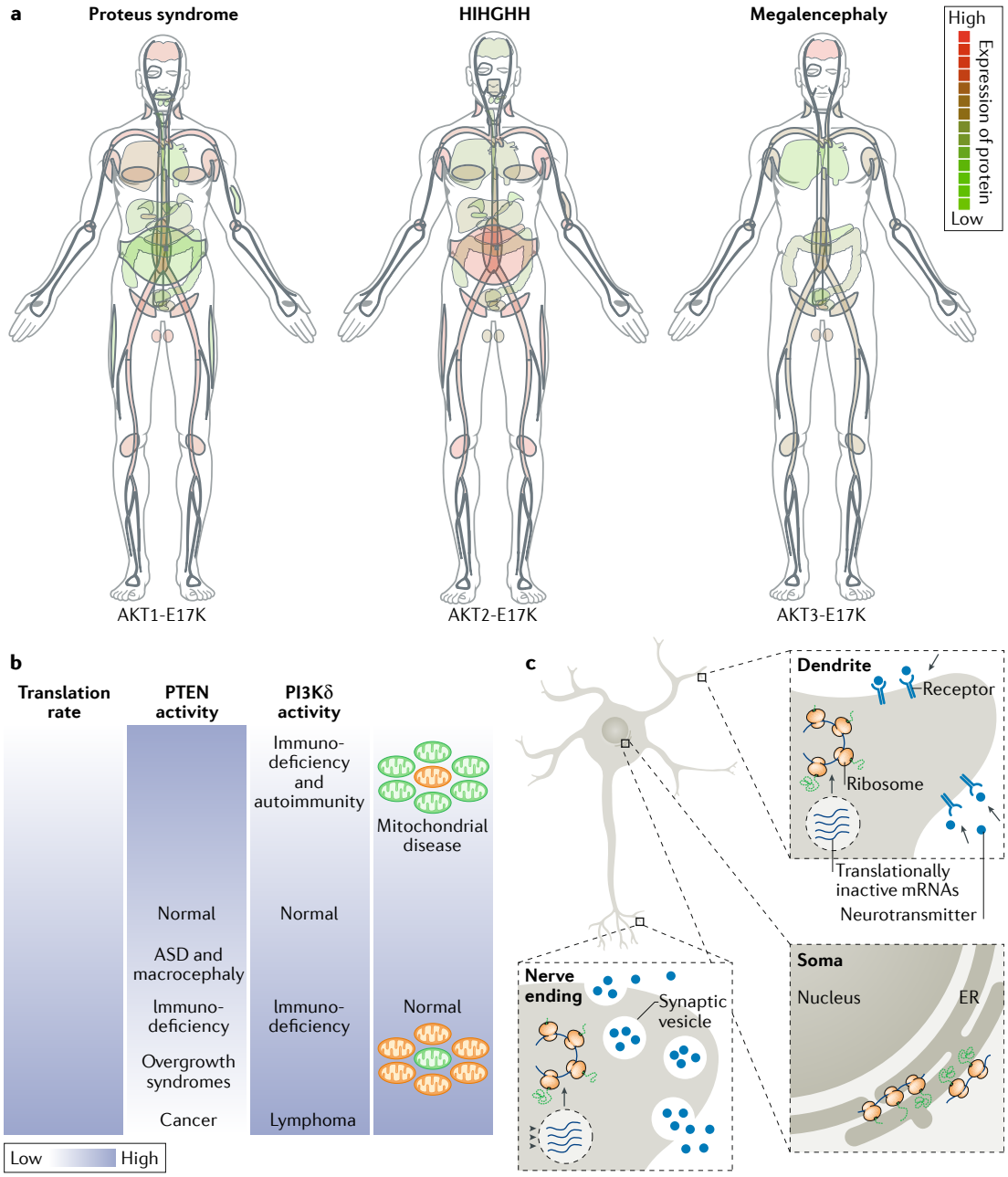


Fig. 6 | **Proposed mechanisms for tissue specificity of diseases caused by deregulation of protein synthesis.** **a** | Tissue-specific gene expression has a crucial role in phenotype tissue specificity. This is exemplified by E17K mutations in the AKT genes. The figure was generated using the ProteomicsDB server[203]. **b** | The dose-dependent effect of PTEN inactivation is well established in cancer and may also explain the tissue-specific phenotypes observed with various PTEN mutations. PTEN partial inactivation often correlates with autism spectrum disorder (ASD) and macrocephaly, whereas complete inactivation correlates with overgrowth syndromes or cancer. Both loss-of-function and gain-of-function mutations affecting PI3Kδ activity can cause an immunodeficiency phenotype, suggesting that precise regulation of PI3Kδ activity is required for immune cell functions. There are multiple copies of mitochondrial DNA (mtDNA) in each cell, and most often, mitochondria carrying mutated (green) or wild-type (orange) copies are both present in each cell (heteroplasmy). Disease severity correlates with the amount of mutated mtDNA. **c** | Several models have been proposed to explain the vulnerability of neurons to translation deregulation[57]. The prevailing hypothesis postulates that a subset of functionally related mRNAs is stored in distal compartments of neurons (dendrites and axons). These localized mRNAs engage in translation only if they receive the proper internal (arrowheads) and/or external (arrows) cues. Although such remote regulation of translation is beneficial for supporting abrupt neuronal response, the long distance between the nucleus and synapses renders neurons hypersensitive to translation deregulation. ER, endoplasmic reticulum; HIHGHH, hypoinsulinaemic hypoglycaemia with hemihypertrophy.

glucose is the main energy source in the brain. Although brain represents only 2% of the body weight, it consumes the highest amount of glucose-derived energy (20%) of all organs[199]. It is thus conceivable that translation deregulation of mRNAs whose products are involved in glucose metabolism preferentially leads to brain disorders. This is consistent with the observation that several neurodevelopmental disorders caused by translation deregulation are associated with defects in glucose metabolism and with diabetes, as in the case of diseases linked to deregulation of the ISR and the mTOR pathway. Development of therapeutic approaches that target glucose metabolism (such as ketogenic diet[200] and anti-diabetic drugs[201]) could be a promising strategy for treatment of neurological disorders caused by translation deregulation.

An understanding of the pathophysiology of rare human diseases could benefit from the use of induced pluripotent stem cells[202] in combination with widely used gene-editing techniques (for example, CRISPR–Cas9) to interrogate translation at the genome-wide level (for example, using ribosome profiling). Such technologies provide an unprecedented opportunity for discovering new mechanism-based therapeutics.

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