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ADVANCED REVIEW

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A (dis)integrated stress response: Genetic diseases of eIF2α regulators

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Abstract

The integrated stress response (ISR) is a conserved mechanism by which eukaryotic cells remodel gene expression to adapt to intrinsic and extrinsic stressors rapidly and reversibly. The ISR is initiated when stress-activated protein kinases phosphorylate the major translation initiation factor eukaryotic translation initiation factor 2α (eIF2α), which globally suppresses translation initiation activity and permits the selective translation of stress-induced genes including important transcription factors such as activating transcription factor 4 (ATF4). Translationally repressed messenger RNAs (mRNAs) and noncoding RNAs assemble into cytoplasmic RNA–protein granules and polyadenylated RNAs are concomitantly stabilized. Thus, regulated changes in mRNA translation, stability, and localization to RNA–protein granules contribute to the reprogramming of gene expression that defines the ISR. We discuss fundamental mechanisms of RNA regulation during the ISR and provide an overview of a growing class of genetic disorders associated with mutant alleles of key translation factors in the ISR pathway.

This article is categorized under:

RNA Interactions with Proteins and Other Molecules > Protein-RNA Interactions: Functional Implications

RNA in Disease and Development > RNA in Disease

Translation > Translation Regulation

RNA in Disease and Development > RNA in Development

KEYWORDS

eIF2α, genetic diseases, integrated stress response, RNA–protein granules, translation

1 | INTRODUCTION

The integrated stress response (ISR) is activated when eukaryotic cells experience dramatic changes in intrinsic or extrinsic conditions. Such changes include temperature, osmolarity, ultraviolet (UV) radiation, oxidation, and endoplasmic reticulum (ER) stressors, the accumulation of aggregated proteins or in response to certain proinflammatory cytokines, and pathogen-associated molecular patterns. These diverse stressors activate any of four protein kinases that phosphorylate eukaryotic translation initiation factor 2α (eIF2α), suppressing its activity to globally repress translation initiation while enhancing the translation of stress-induced genes, including key transcription factors that launch a gene expression program to allow the cell to adapt to stress or drive it to undergo apoptosis (Costa-Mattioli &

Walter, 2020; Hershey et al., 2019; Pakos-Zebrucka et al., 2016). One key stress-induced gene is *PPP1R15A* which encodes GADD34 (growth arrest and DNA damage-inducible gene 34). GADD34 promotes the dephosphorylation of phosphorylated eIF2α (p-eIF2α) and reverses the ISR in a negative feedback loop (Novoa et al., 2001). Constitutively expressed RNAs are globally stabilized, and translationally repressed RNAs accumulate in cytoplasmic RNA–protein (RNP) granules termed stress granules and processing bodies (P-bodies; P. Ivanov et al., 2019; Protter & Parker, 2016). The release of p-eIF2α-mediated translation repression coincides with the disassembly of stress-induced RNP granules and resolves the ISR. Thus, regulation of messenger RNA (mRNA) at the levels of translation and stability enables a rapid, global response to stress that results in the formation and accumulation of RNP granules and drives cell fate.

Recent studies point to a key role in the initial stages of the ISR in human development and health, as a growing list of genetic diseases are associated with mutant alleles of eIF2α kinases, a p-eIF2α phosphatase, a member of the eIF2 heterotrimer, and the heteropentameric eIF2 guanine nucleotide exchange factor (GEF) eIF2B. While the molecular mechanisms underlying the divergent pathogenesis and phenotypes of these disorders mostly remain undefined, key insights suggest defects in the kinetics and intensity of the ISR contribute to these disease states. We present a comprehensive overview of the mechanisms of translation regulation, RNA stability, and RNA localization to RNP granules during the ISR, as well as the current understanding of genetic diseases associated with mutant alleles of the ISR machinery including Vanishing White Matter (VWM) disease, Wolcott–Rallison syndrome, and MEHMO syndrome.

2 | TRANSLATION AND THE INTEGRATED STRESS RESPONSE

2.1 | Translation overview

Translation is an energy-intensive process (Buttgereit & Brand, 1995; G.-W. Li et al., 2014) and is consequently highly regulated during cellular stress conditions. Translation takes place in three main stages: (1) initiation, (2) elongation, and (3) termination and ribosome recycling. Translation initiation begins with formation of the ternary complex which is composed of eIF2 bound to GTP and methionyl-initiator tRNA (Met-tRNA$_i$). EIF2 is a heterotrimer of the subunits α, β, and γ. Once formed, the ternary complex binds the 40S small ribosomal subunit along with the initiation factors eIF1, eIF1A, eIF3, and eIF5 to form the 43S preinitiation complex (Hershey et al., 2019; Merrick & Pavitt, 2018). For mRNA to be used as a template for protein synthesis, it must assemble into the eIF4F complex, a protein complex composed of the initiation factors eIF4E, eIF4G, and eIF4A, at the 5′-7-methylguanosine cap and the poly(A)-binding protein (PABP) at the 3′-poly(A) tail (Jackson et al., 2010; Merrick & Pavitt, 2018). The eIF4F complex facilitates recruitment of the 43S preinitiation complex to the 5′-untranslated region (UTR) of the mRNA near the 7-methylguanosine cap. Next, the 43S preinitiation complex scans toward the 3′-end of the mRNA in search of an AUG codon and, once identified, the AUG codon base pairs with the Met-tRNA$_i$ anticodon in the peptidyl (P) site of the small ribosomal subunit. Subsequently, the eIF2-bound GTP is hydrolyzed to GDP promoting the release of the Met-tRNA$_i$. This frees eIF2-GDP to be acted on by the GEF eIF2B to generate eIF2-GTP to be available for another translation initiation cycle. Translation initiation ends with the arrival of the 60S large ribosomal subunit to produce the 80S ribosome (reviewed in Hershey et al., 2019; Merrick & Pavitt, 2018).

Initiation is the rate-limiting stage of translation and therefore is imperative to regulate. Phosphorylation regulates a major element of translation initiation, 7-methylguanosine cap-recognition by the eIF4F complex (eIF4E, eIF4G, and eIF4A; Hershey et al., 2019; Sonenberg & Hinnebusch, 2009). A class of proteins termed eIF4E-binding proteins (4E-BPs) binds eIF4E which prevents eIF4G binding, eIF4F assembly, 7-methylguanosine cap-recognition, and inhibits initiation. 4E-BPs are regulated by phosphorylation—dephosphorylated 4E-BPs bind strongly to eIF4E, and phosphorylated 4E-BPs bind weakly to eIF4E. In unstressed or nutrient-replete conditions, the well-known kinase mammalian target of rapamycin (mTOR) phosphorylates 4E-BPs. This promotes eIF4F assembly by allowing eIF4E and eIF4G to interact which drives translation initiation. In stressed or nutrient-limited conditions when active translation could be detrimental to cell health, 4E-BPs are not phosphorylated and inhibit eIF4E, thereby preventing 7-methylguanosine cap-recognition and inhibiting initiation (Sonenberg & Hinnebusch, 2009).

Translation continues with the production of a nascent peptide chain via elongation. At the onset of translation elongation, Met-tRNA$_i$ is positioned in the ribosomal P site, allowing the next tRNA to enter the aminoacyl (A) site of the ribosome. Like translation initiation, several factors are required for translation elongation. A ternary complex containing the elongation factor eukaryotic translation elongation factor 1A (eEF1A), GTP, and the tRNA complementary to the codon following AUG binds the ribosomal A site. Upon base pairing of the mRNA codon and the aminoacyl-tRNA anticodon,

GTP is hydrolyzed, and eEF1A-GDP is released from the ribosome. The GEF eEF1B swaps GDP for GTP, allowing eEF1A-GTP to bind another tRNA destined for the ribosomal A site. Next, eIF5A localizes to the ribosomal exit (E) site and promotes the formation of a peptide bond between the carboxyl group of the peptidyl-tRNA and the amino group of the aminoacyl-tRNA. The newly generated peptide is passed from the peptidyl-tRNA to the aminoacyl-tRNA. eEF2 bound to GTP promotes translocation of the peptidyl-tRNA and aminoacyl-tRNA to the E and P sites, respectively, and the ribosome progresses down the mRNA by one codon. Finally, the deacylated tRNA is released from the E site, and another cycle of elongation is poised to begin (reviewed in Dever et al., 2018; Hershey et al., 2019).

The final events of translation are termination and ribosome recycling. Translation is terminated when the ribosome encounters a stop codon (UAA, UGA, or UAG) in its A site as no tRNA anticodons match stop codons. Termination requires the action of a ternary complex made up of the eukaryotic translation release factors eRF1 and eRF3, and GTP (Dever & Green, 2012; Hellen, 2018; Jackson et al., 2012). First, eRF1 identifies the stop codon in the A site. Next, eRF3, a GTPase, hydrolyzes GTP and triggers the hydrolysis of the peptidyl-tRNA by eRF1. As a result, the nascent polypeptide is released. While the protein product has been freed, the 80S ribosome, deacylated tRNA, and the mRNA, altogether termed the post-termination complex, remains. The ATP-binding cassette protein ABCE1 aids in post-termination complex recycling by splitting the 80S ribosome to release the 60S ribosomal subunit. Next, the deacylated tRNA and mRNA are released from the 40S ribosomal subunit by the initiation factors eIF1, eIF1A, and eIF3, or by eIF2D, or MCTS1 (multiple copies in T-cell lymphoma-1) and DENR (density regulated protein). Finally, the released materials can be used for further rounds of translation (reviewed in Hellen, 2018; Hershey et al., 2019).

2.2 | The integrated stress response

In addition to phosphorylation of 4E-BPs, another key way that translation initiation is regulated is by the phosphorylation of the α subunit of eIF2 at serine 51 during the ISR (Hershey et al., 2019; Sonenberg & Hinnebusch, 2009). The ISR is a pathway that modifies transcription and translation to promote cell survival in response to stress. Alternatively, if the stress is insurmountable, the ISR promotes cell death. Upon activation of the ISR, translation is globally suppressed, and stress-induced genes are expressed. In tandem, RNP granules including stress granules are induced and regulated changes in mRNA stability occur. The ISR is activated upon eIF2α phosphorylation by stress-induced kinases. Phosphorylation of eIF2α by any of the kinases inhibits global translation by converting eIF2 into an inhibitor of eIF2B. Subsequently, eIF2B cannot exert its GEF activity on the eIF2 complex, eIF2 is unable to bind GTP, the ternary complex fails to assemble, and translation initiation is prevented (Figure 1). Phosphorylation of eIF2α is thus an efficient mechanism for inhibiting global translation to prevent further compounding the cause of cellular stress, for example, by preventing further amino acid consumption during nutrient deprivation, generating more misfolded proteins during ER stress, or producing viral proteins when foreign double-stranded RNA (dsRNA) is detected.

To promote the expression of genes needed to recover from stress, or conversely to activate apoptosis if recovery is not possible, translation of selective stress-resistant mRNAs is refractory to, or enhanced by, eIF2α phosphorylation. Multiple strategies are used by these mRNAs to promote their translation during the ISR including the use of regulatory upstream open reading frames (uORFs; reviewed in Young & Wek, 2016), non-AUG start codons (reviewed in Kearse & Wilusz, 2017), recruitment of initiator tRNAs through noncanonical initiation factors (Starck et al., 2016), and internal ribosome entry sites (IRESs). One of the best characterized stress-induced genes is the transcription factor ATF4 (activating transcription factor 4, GCN4 in yeast; Harding et al., 2003). ATF4 is a master regulator that promotes the expression of additional genes required for the stress response and its mRNA contains two uORFs. Under basal conditions when ternary complex levels are plentiful, the ribosome translates the first uORF and is able to recruit the ternary complex in time to reinitiate at the second uORF (Figure 2a). Because the second uORF overlaps with the primary open reading frame (ORF), ATF4 translation is suppressed (Vattem & Wek, 2004). When the ISR is active and ternary complex levels are limited, the ribosome requires more time to acquire a ternary complex after translating the first uORF, allowing it to bypass the inhibitory second uORF and translate the primary ORF (Silva et al., 2019; Figure 2b). Because different ATF4 ORFs are translated depending on ISR activity, ATF4 uORF translation can be used to determine when the ISR is active (T. E. Dever, 1997; Helseth et al., 2021). A recent example of this is the development of an ATF4 reporter that produces a different color fluorophore depending on whether the primary ORF or the second uORF is translated. This reporter was used to uncover that the ISR is constitutively activated in a small population of neurons in mice, specifically striatal cholinergic interneurons, and that this is important for skill learning (Helseth et al., 2021).

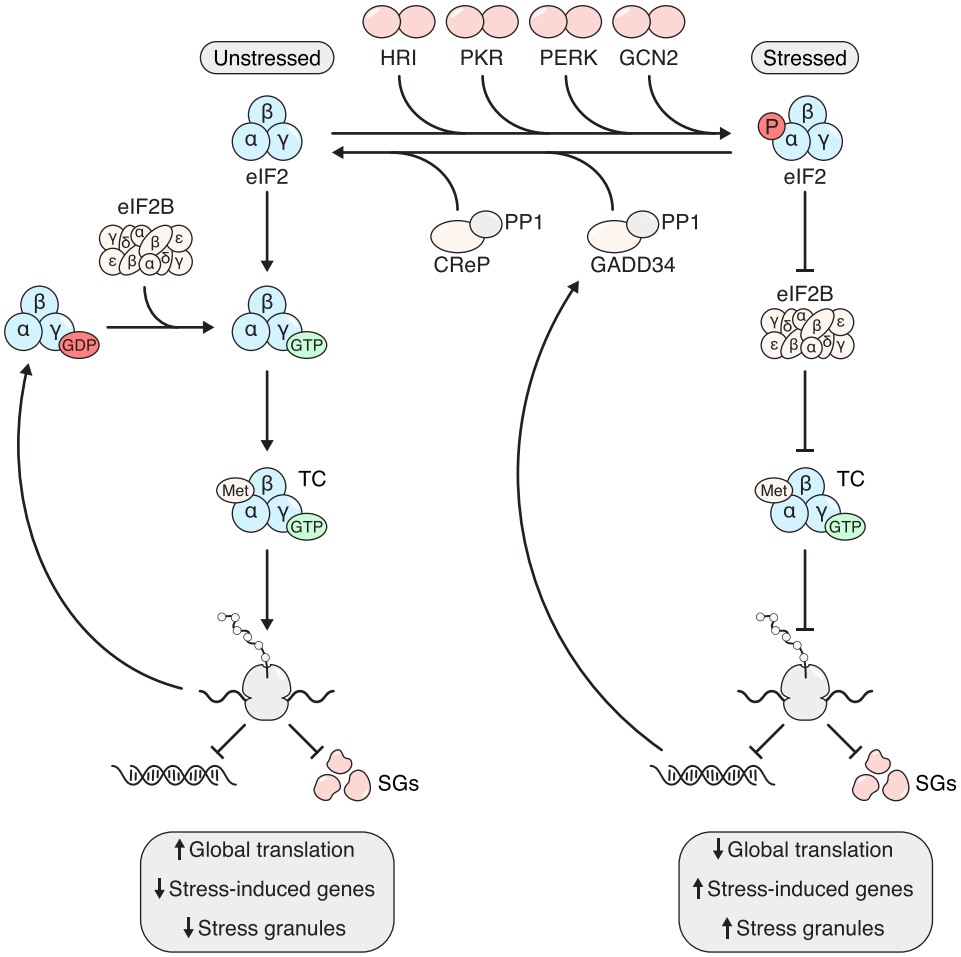

FIGURE 1 Schematic depicting the roles of the key factors that drive the ISR in translation initiation, stress-induced gene expression, and stress granule (SG) formation. In unstressed cells, low levels of p-eIF2α enable high eIF2B function to generate abundant ternary complex (TC) comprised of eIF2, GTP, and Met-tRNA$_i$. High TC facilitates high global translation activity, suppressing stress-induced gene expression, and SG formation. Upon stress, stress-activated protein kinases (HRI, PKR, PERK, and GCN2) increase p-eIF2α levels and suppress the guanine exchange activity of eIF2B. Resulting limited TC causes reduced global translation activity, SG formation, and stress-induced gene induction (e.g., *ATF4* and *PPP1R15A* (GADD34)). The GADD34 protein interacts with PP1 to dephosphorylate p-eIF2α and reverse the ISR

Interestingly, a recent report found that depletion of the noncanonical initiation factors eIF2D and DENR prevented enhanced ATF4 expression in *Drosophila melanogaster* and human cells during stress (Vasudevan et al., 2020), suggesting that a combination of strategies can be used to promote ISR-resistant translation. Examples of other uORF-containing genes that are expressed at the transcriptional and translational levels upon ISR activation include *DDIT3* (CHOP) and *PPP1R15A* (GADD34; Y.-Y. Lee et al., 2009; Marciniak et al., 2004; Palam et al., 2011).

A key feature of the ISR is that it is reversible, which is achieved by the dephosphorylation of p-eIF2α. The stress-induced protein GADD34 and CReP (constitutive repressor of eIF2α phosphorylation), which is constitutively expressed, are regulatory subunits that direct protein phosphatase 1 (PP1) to dephosphorylate p-eIF2α. Upon chronic stress or stress resolution, p-eIF2α is dephosphorylated, allowing increased global translation initiation to take place once again. Genetic depletion of the CReP gene *Ppp1r15b* is invariably lethal following birth in mice, which exhibit increased p-eIF2α levels in the liver and defects in erythropoiesis that is partially rescued by expression of the phosphorylation-insensitive *Eif2a*^{S51A} allele (Harding et al., 2009). In contrast, genetic depletion of the GADD34 gene *Ppp1r15a* does not markedly affect organismic development in a mouse model (Marciniak et al., 2004). Importantly, p-eIF2α dephosphorylation is vital for mammalian development as mice lacking both *Ppp1r15a* and *Ppp1r15b* fail to develop and are embryonic lethal (Harding et al., 2009). Thus, regulation of eIF2α function in the ISR is important for the cellular response to diverse stresses and mammalian development.

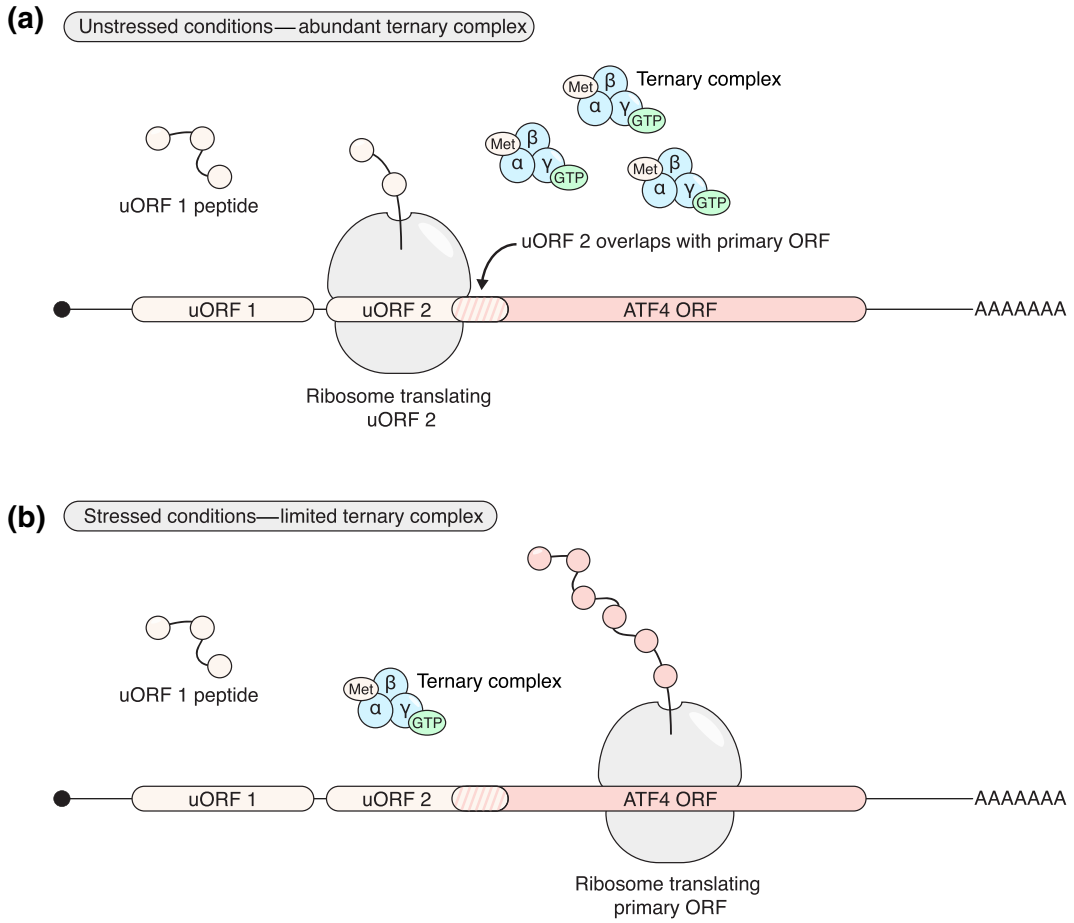

FIGURE 2 Schematic depicting ATF4 translation during the integrated stress response. Two upstream open reading frames (uORFs) in the 5′ leader of ATF4 regulate its translation. (a) Ternary complex levels are abundant in unstressed conditions enabling the ribosome to recruit another ternary complex in time to reinitiate at the start codon of uORF 2 after translating uORF 1. Because uORF 2 overlaps with the primary ORF of ATF4, this inhibits synthesis of the ATF4 protein. (b) In contrast, ternary complex levels are limited in stressed conditions (i.e., when eIF2α is phosphorylated). As a result, the ribosome is unable to recruit another ternary complex in time to reinitiate at uORF 2, releasing the primary ORF from repression by uORF 2, and allowing ATF4 protein synthesis

Suppression of ribosome biogenesis is an additional mechanism by which the translation machinery may be regulated during the ISR. Ribosome biogenesis occurs in the nucleolus, a biomolecular condensate in the nucleus where ribosomal RNAs (rRNAs) are transcribed, processed, and assembled with ribosomal proteins into pre-ribosomal particles (K. Yang, Yang, & Yi, 2018). Chemical or genetic inhibitors of rRNA transcription, processing, ribosomal assembly, or export from the nucleus, in addition to numerous insults that also activate the ISR (e.g., heat, nutrient deprivation, UV light, and hypoxia) trigger nucleolar stress (K. Yang, Yang, & Yi, 2018). Ribosome biosynthesis is rapidly suppressed upon amino acid deprivation stress when mTOR is inhibited and GCN2, an eIF2α kinase that induces the ISR in response to amino acid starvation, is activated. Inhibition of mTOR by rapamycin suppresses ribosomal protein mRNA and rRNA transcription (Mahajan, 1994; T. Powers & Walter, 1999; Zaragoza et al., 1998). MTOR-regulated changes in the phosphorylation state of the RNA polymerase I transcription factor TIF-IA downregulates rRNA synthesis in this context (Mayer et al., 2004). Ribosomal protein mRNAs are also translationally suppressed upon amino acid deprivation and mTOR inhibition (Thoreen et al., 2012). Many ribosomal protein mRNAs, in addition to transcripts encoding translation elongation factors (e.g., eEF1A and eEF2) and PABP, harbor 5′-terminal oligopyrimidine (TOP) motifs that cause translation suppression upon mTOR inhibition or amino acid starvation (Meyuhas, 2000; Thoreen et al., 2012). Intriguingly, the RNA binding proteins TIA-1 (T-cell-restricted intracellular antigen-1) and TIAR (TIA-1-related) associate with mRNAs harboring 5′-TOP motifs during amino acid starvation and suppress their translation in a process that requires both GCN2 and mTOR pathways (Damgaard & Lykke-Andersen, 2011). These findings suggest that translation suppression upon amino acid deprivation stress first occurs via GCN2 and mTOR pathways and consequently

downregulates the translation machinery to further limit global protein biosynthesis in the cell under conditions where resources are limited.

2.2.1 | Activation of the integrated stress response

The ISR is triggered by the phosphorylation of eIF2α in response to several distinct sources of stress. Depending on the stress, any of four protein kinases—heme-regulated inhibitor (HRI), protein kinase R (PKR), PKR-like ER kinase (PERK), and general control nonderepressible 2 (GCN2)—are activated and phosphorylate eIF2α. Activation of each kinase requires dimerization and autophosphorylation (Lavoie et al., 2014; Pakos-Zebrucka et al., 2016). Interestingly, the localization of the kinases could confer subcellular specificity to the ISR, as HRI, PKR, and GCN2 are localized to the cytosol, while PERK is localized to the ER membrane (Costa-Mattioli & Walter, 2020). GCN2 is highly conserved as it is present from yeast to mammals and therefore has been extensively investigated (Pakos-Zebrucka et al., 2016). In contrast, HRI, PKR, and PERK are generally present in metazoans (Taniuchi et al., 2016). Therefore, the four kinases serve as critical regulators of ISR activation upon stress.

HRI is encoded by *EIF2AK1* and is primarily expressed in erythroid cells (Han et al., 2001). In addition to two kinase domains, HRI contains two heme-binding sites (Bhavnani et al., 2017; Donnelly et al., 2013; Figure 3) that respond to cellular heme levels—the presence of heme inhibits HRI activation, while the absence of heme stimulates HRI activation—to pair hemoglobin synthesis with heme availability (Bruns & London, 1965; Chefalo et al., 1998; Han et al., 2001; Pakos-Zebrucka et al., 2016; Suragani et al., 2012). Heat and osmotic shock (Lu et al., 2001), hydrogen peroxide (Zhan et al., 2004), nitric oxide (Ill-Raga et al., 2015), arsenite treatment (Lu et al., 2001; McEwen et al., 2005), and 26S proteasome inhibition (Yerlikaya et al., 2008) have also been demonstrated to activate HRI (Pakos-Zebrucka et al., 2016; Table 1). In unstressed conditions, mice lacking HRI are normal, however, upon iron deprivation, their erythroid precursors undergo increased cell death causing the mice to be anemic (Han et al., 2001). Interestingly, upon proteasome inhibition, HRI protein levels are elevated and HRI is activated in neurons with low baseline heme levels resulting in reduced protein synthesis (Alvarez-Castelao et al., 2020). Thus, HRI functions in a cell-type-specific manner via the ISR to promote proteostasis in heme-deficient environments.

The primary function of PKR, encoded by *EIF2AK2*, is to inhibit protein synthesis in response to viral infection to prevent viral gene expression and aid the cellular response to infection (Eiermann et al., 2020). The expression of *EIF2AK2* is induced by interferon and, in addition to its kinase domain, PKR contains two N-terminal double-stranded RNA-binding motifs (Donnelly et al., 2013; Mao et al., 2020; E. Meurs et al., 1990; Figure 3). PKR is activated by dsRNA (Lemaire et al., 2008) that is often of viral origin, however, it can also be activated by endogenous dsRNA in the absence of viral infection by stimuli such as mitochondrial dsRNA (Y. Kim et al., 2018), dsRNA created by Alu repeats (W. M. Chu et al., 1998; Y. Kim et al., 2014), or the viral dsRNA mimic poly(I:C). In addition to dsRNA, the protein

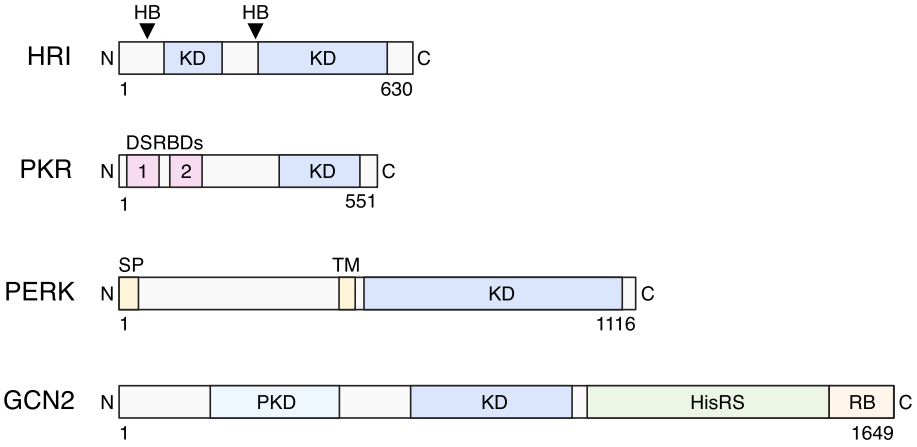

FIGURE 3 Diagrams depicting the protein domains of the integrated stress response protein kinases. HRI contains two heme-binding (HB) sites and two kinase domains (KD). PKR contains two N-terminal double-stranded RNA-binding domains (DSRBDs), and one KD. PERK contains a signal peptide (SP), a transmembrane domain (TM), and a cytoplasmically located KD. GCN2 contains a pseudokinase domain (PKD), a KD, a histidyl-tRNA synthetase-like domain (HisRS), and a ribosome-binding (RB) region.

TABLE 1 Characteristics of the integrated stress response kinases

Gene	Kinase	Activators/stressors	References
EIF2AK1	HRI	Heme deprivation, heat shock, osmotic shock, hydrogen peroxide, nitric oxide, arsenite treatment, 26S proteasome inhibition	(Bruns & London, 1965; Chefalo et al., 1998; Han et al., 2001; Ill-Raga et al., 2015; Lu et al., 2001; McEwen et al., 2005; Pakos-Zebrucka et al., 2016; Suragani et al., 2012; Yerlikaya et al., 2008; Zhan et al., 2004)
EIF2AK2	PKR	Double-stranded RNA, PACT, heparin, osmotic shock	(Anderson et al., 2011; W. M. Chu et al., 1998; Eiermann et al., 2020; George et al., 1996; Hovanessian & Galabru, 1987; Y. Kim et al., 2014, 2018; Lemaire et al., 2008; Marques et al., 2008; Taniuchi et al., 2016)
EIF2AK3	PERK	ER stress, UV light, heat shock, osmotic shock	(Taniuchi et al., 2016; S. Wu et al., 2002)
EIF2AK4	GCN2	Amino acid deprivation, UV light, hydrogen peroxide, heat shock, osmotic shock	(Deng et al., 2002; Goossens et al., 2001; Grousl et al., 2009; Hans et al., 2020; Hinnebusch & Fink, 1983; Shenton et al., 2006; Taniuchi et al., 2016; R. C. Wek et al., 1989)

activator of PKR termed PACT binds to and directly activates PKR independently of dsRNA in response to a range of stressors including cytokines, arsenite, and ceramide (Marques et al., 2008). Heparin and osmotic shock are also reported activators of PKR (Anderson et al., 2011; George et al., 1996; Hovanessian & Galabru, 1987; Taniuchi et al., 2016; Table 1). PKR is particularly important in the brain as *Eif2ak2*-deficient mice exhibit neurological abnormalities such as increased cognition and memory, and hyperactive brain activity causing seizures (P. J. Zhu et al., 2011). Therefore, PKR preserves cell health by reducing translation upon viral infection and promotes proper brain function.

Encoded by *EIF2AK3*, PERK is an ER transmembrane protein that functions in the unfolded protein response (UPR; Pakos-Zebrucka et al., 2016). The C terminus of PERK faces the cytosol and includes its kinase domain, and the N terminus lies within the ER lumen (Donnelly et al., 2013; Shi et al., 1998; Figure 3). PERK is highly expressed in the pancreas (Shi et al., 1998) and is activated by ER stress as well as UV light (S. Wu et al., 2002), heat shock (Taniuchi et al., 2016), and osmotic shock (Taniuchi et al., 2016; Table 1). Activation of PERK upon the accumulation of unfolded or misfolded proteins is thought to occur by the direct binding of dysfunctional proteins to its luminal domain (P. Wang et al., 2018) or by the dissociation of BiP, an ER chaperone that is associated with PERK in the absence of stress (Bertolotti et al., 2000; Carrara et al., 2015). PERK is required for cell survival in response to ER stress, highlighting its importance as an effector of the ISR.

GCN2 is encoded by *EIF2AK4* and contains a pseudokinase domain, protein kinase domain, histidyl-tRNA synthetase-like domain, and ribosome-binding region (Donnelly et al., 2013; Ramirez et al., 1991; S. A. Wek et al., 1995; S. Zhu et al., 1996; S. Zhu & Wek, 1998; Figure 3). While GCN2 is expressed broadly among tissues, its expression is particularly high in the brain and liver (Berlanga et al., 1999; Sood et al., 2000). Amino acid deprivation activates GCN2 (Hinnebusch & Fink, 1983; R. C. Wek et al., 1989) via a mechanism that may occur by its sensing accumulated uncharged tRNAs (Dong et al., 2000; Lageix et al., 2015; H. Qiu et al., 2001; Qiu et al., 2002; Ramirez et al., 1992) or ribosome stalling and collisions (Harding et al., 2019; Inglis et al., 2019; C. C.-C. Wu et al., 2020; Yan & Zaher, 2021). Thus, GCN2 is an important sensor of translation defects that serves as a link between translation elongation and initiation. In addition to limited amino acids, GCN2 can also be activated by UV irradiation (Deng et al., 2002; Taniuchi et al., 2016), hydrogen peroxide (Shenton et al., 2006; Taniuchi et al., 2016), heat shock (Grousl et al., 2009; Taniuchi et al., 2016), and osmotic shock (Goossens et al., 2001; Hans et al., 2020; Taniuchi et al., 2016; Table 1). *Gcn2*$^{-/-}$ mice are hypersensitive to the depletion of essential amino acids, exhibiting impaired fetal development with reduced neonatal viability compared to wild-type mice (P. Zhang, McGrath, Reinert, et al., 2002). Thus, the function of GCN2 is important to restrict protein synthesis in conditions of limited nutrients.

3 | RIBONUCLEOPROTEIN GRANULES AND THE INTEGRATED STRESS RESPONSE

3.1 | Stress granules

A microscopically visible hallmark of the ISR is an increase in the formation and/or size and abundance of cytoplasmic biomolecular condensates termed stress granules (Figure 4) and P-bodies that form through liquid–liquid phase

separation. Stress granules consist primarily of translationally arrested mRNAs, RNA binding proteins, and translation factors (reviewed in P. Ivanov et al., 2019; Protter & Parker, 2016). They rapidly form following the inhibition of translation initiation by eIF2α phosphorylation (N. Kedersha et al., 2000). Current models suggest that runoff of elongating ribosomes leaves mRNAs exposed to RNA binding proteins such as G3BP1/2 (Ras GTPase-activating protein-binding protein 1/2) and TIA-1. Multivalent RNA–RNA, RNA–protein and protein–protein interactions between low-complexity or intrinsically disordered protein domains then promote mRNP phase separation into stress granules (reviewed in Hofmann et al., 2021).

Transcriptome analysis of purified stress granule cores has revealed that mRNAs from nearly all genes localize to stress granules, but that increased mRNA length and translation efficiency correlates with enrichment (Khong et al., 2017). Likewise, longer isoforms of the same gene are more likely to be recruited to granules during ER stress (Namkoong et al., 2018). Interestingly, mRNAs containing AU-rich elements (AREs) are also enriched in cytoplasmic granules during ER stress, heat-shock, and arsenite stress, as are proto-oncogenes in which AREs are often found (Namkoong et al., 2018). MRNAs localized to stress granules are largely nontranslating, and 60S ribosomal proteins are depleted from stress granules (Nancy Kedersha et al., 2002; Moon et al., 2019). However, live-cell and single mRNA molecule imaging experiments indicate that polysome-associated mRNAs can dynamically interact with stress granules, but these events are relatively rare and the interactions are generally short-lived compared to nontranslating mRNAs (Mateju et al., 2020; Moon et al., 2019). Following the resolution of stress, mRNAs sequestered within stress granules are thought to resume translation, but interestingly, single-molecule experiments showed that translation from fluorescently labeled mRNA reporters occurred only once stress granules were fully disassembled (Moon et al., 2019). Thus, stress granules are primarily composed of translationally repressed RNAs thought to be assembled into pre-initiation complexes.

Despite the fact that the vast majority of translation is arrested during the ISR, only approximately 10%–13% of cellular mRNA is targeted to stress granules (Khong et al., 2017; Namkoong et al., 2018). Furthermore, while virtually all mRNA transcripts expressed in the cell could be detected in stress granules at some level, only a small subset of genes have >50% of their mRNA molecules sequestered within stress granules (Khong et al., 2017). This is consistent with evidence that stress granules are not necessary for mRNA translational suppression, as this still occurs through ISR activation in genetically manipulated cells that cannot form stress granules (Kedersha et al., 2016). However, there is a large

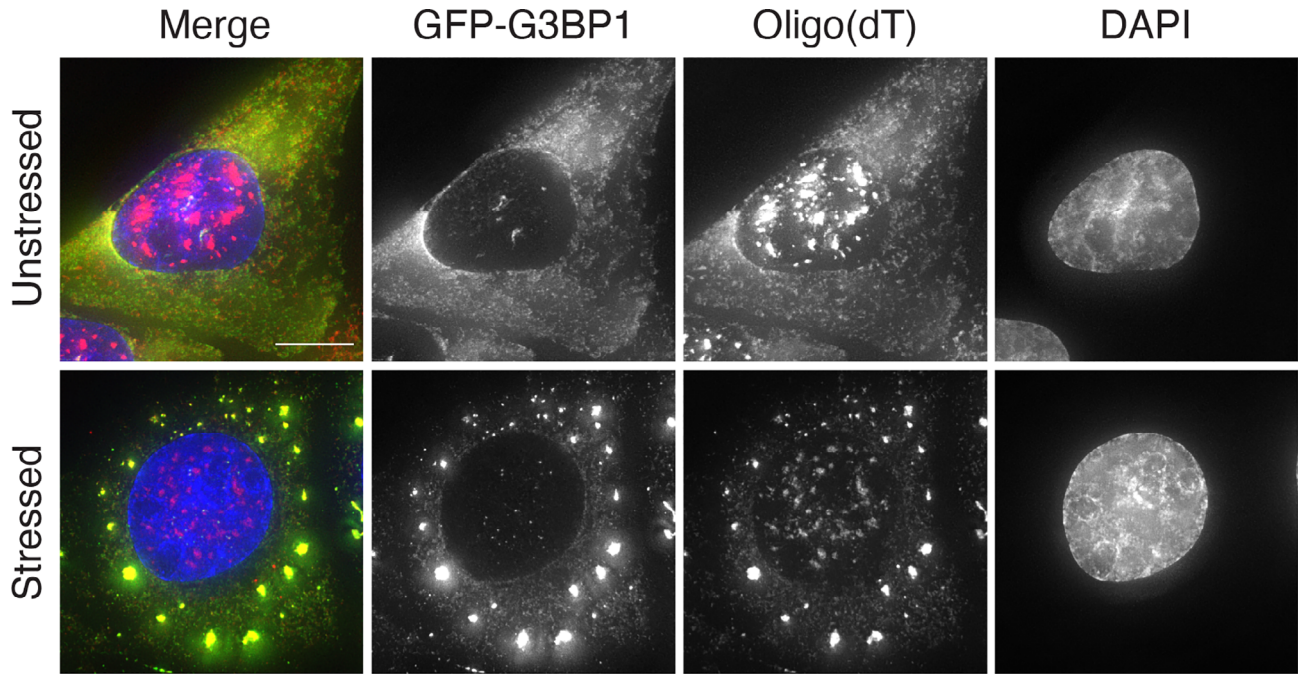

FIGURE 4 Polyadenylated RNA is localized to stress granules during arsenite stress. Human U-2 OS cells stably expressing the stress granule protein GFP-G3BP1 (green) were stressed with sodium arsenite (0.5 mM) for 45 min. Fluorescence *in situ* hybridization was performed with oligo(dT)-Cy3 probes (red) to detect polyadenylated mRNAs, and nuclei were visualized with DAPI (scale bar 10 μM). Reprinted with permission from Moon et al., 2020.

degree of heterogeneity with the extent to which mRNAs are recruited to stress granules (Khong et al., 2017), and some mRNAs that are needed for promoting recovery from stress are mostly excluded from stress granules, as has been observed for HSP70 and HSP90 mRNAs following heat stress or arsenite stress (Moon et al., 2020; Stöhr et al., 2006). Further, quantitative proteomics and genome-wide RNA-seq analysis demonstrated the transcripts encoding newly translated proteins during arsenite stress are depleted from stress granules (Baron et al., 2019). As such, by sequestering a portion of translationally repressed mRNAs, stress granules may facilitate the continued translation of select mRNAs during the ISR.

Although their cellular function is not fully established, disruption of stress granule biology is implicated in human disease. Mutations in stress granule resident RNA binding proteins with low-complexity or intrinsically disordered domains such as TIA-1 (Mackenzie et al., 2017), TDP-43 (TAR DNA-binding protein; van Deerlin et al., 2008), FUS (fused in sarcoma; Vance et al., 2009), and hnRNPA2/B1 (heterogeneous nuclear ribonucleoprotein A2/B1; H. J. Kim et al., 2013) cause amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Current models propose that these mutations alter stress granule dynamics and may help seed pathological protein inclusions that are a hallmark of these diseases (Wolozin & Ivanov, 2019).

3.2 | Processing bodies

Like stress granules, P-bodies are cytoplasmic RNP granules that form through liquid–liquid phase separation. They are present in steady-state conditions in unstressed cells but, also like stress granules, increase in size and abundance during cellular stress caused by nutrient deprivation, hypo- or hyper-osmolarity, and UV radiation (Teixeira et al., 2005). While there is considerable overlap in the protein components of both cytoplasmic granule types, P-bodies contain the machinery for both 5′–3′ and 3′–5′ exonucleolytic mRNA degradation, which is absent from stress granules (reviewed in P. Ivanov et al., 2019; Luo et al., 2018).

Like stress granules, mRNA reporters interact with P-bodies in mammalian cells in either a highly transient or highly stable manner (Moon et al., 2019; Pitchiaya et al., 2019). Recent sequencing analysis of the mRNA content from fluorescence-activated particle sorted P-bodies indicate that about one-fifth of total cellular mRNAs localize to P-bodies and that P-body-enriched transcripts are more poorly translated and have more variable poly(A) tail lengths, compared to total cellular mRNAs (Hubstenberger et al., 2017). Additionally, mRNA reporters that are translationally repressed via microRNA (miRNA) targeting are more likely to be sequestered within P-bodies than those that are not translationally repressed (Pitchiaya et al., 2019). These observations are consistent with data indicating that translation factors (with the exception of eIF4E, which is bound to its inhibitor 4E-T within P-bodies) and 40S ribosomal proteins, which are enriched in stress granules, are depleted from P-bodies (Hubstenberger et al., 2017; Matheny et al., 2019; Teixeira et al., 2005). Furthermore, although not necessary for their recruitment (Brengues & Parker, 2007), mRNAs localized to P-bodies are often deadenylated and PABP is depleted within these structures in mammalian cells (Nancy Kedersha et al., 2005; Zheng et al., 2008). While P-bodies are present in unstressed conditions when stress granules are absent, during the ISR the mRNA transcriptome of P-bodies shifts and become very similar to the transcriptome of stress granules (Matheny et al., 2019). Together, these findings strongly suggest that translation is a key determinant of mRNA localization to both stress granules and P-bodies. Thus, the ISR increases the pool of cellular mRNAs that can be recruited into P-bodies via the global suppression of translation.

Three pieces of evidence suggest that mRNAs may be degraded within P-bodies. First, P-bodies are enriched in components of the exonucleolytic degradation machinery. Second, decay intermediates of Xrn1-resistant mRNAs accumulate within P-bodies in yeast (Sheth & Parker, 2003), and XRN1-resistant viral RNAs colocalize with P-bodies in human cells (Pijlman et al., 2008). Third, yeast mutants lacking Xrn1 have enlarged P-bodies (Sheth & Parker, 2003). However, recent single-molecule imaging studies have found that the signal from fluorescent-protein-labeled PP7 and/or MS2-tagged mRNAs decay in the cytoplasm, and their decay intermediates do not colocalize with P-body markers (Horvathova et al., 2017; Tutucci et al., 2018). This is consistent with RNA-seq experiments that failed to identify truncated mRNA decay intermediates within P-bodies in human cells (Hubstenberger et al., 2017), although it is possible that such decay intermediates are degraded too rapidly in wild-type cells for their capture and identification. Additionally, mRNAs localized to P-bodies can return to being actively translated (Brengues et al., 2005), and mRNA degradation still occurs in cells lacking P-bodies (Arribas-Layton et al., 2016; Eulalio et al., 2007). Therefore, like stress granules, P-bodies appear to serve as reservoirs for poorly translated mRNAs, but the exact role they play in mRNA decay is still unclear.

4 | MRNA DEGRADATION AND THE INTEGRATED STRESS RESPONSE

4.1 | Mechanisms of mRNA degradation

Cellular mRNA turnover is another important mechanism by which gene expression is regulated. The median mammalian mRNA half-life is 3.4 h, but this ranges widely from less than an hour to more than a day (Tani et al., 2012). Many factors influence the rate at which an mRNA is degraded, including its cellular function (i.e., housekeeping genes are generally longer lived; Tani et al., 2012), its degree of secondary structure (Mauger et al., 2019), the length of its 3′-UTR as well as the number of miRNA and protein binding sites (Spies et al., 2013), its rate of translation (as reduced translation is associated with more rapid decay; Presnyak et al., 2015), RNA modifications (reviewed in Boo & Kim, 2020), specific RNA motifs, and cellular conditions such as cellular stress, as will be discussed below.

The bulk of mammalian mRNA decay occurs through either 5′–3′ or 3′–5′ exonucleolytic degradation (reviewed in Mugridge et al., 2018), with endonucleases contributing in specialized circumstances such as surveillance pathways occurring with ribosome-associated quality control (Section 5). In both exonucleolytic pathways, deadenylation is the initial rate-limiting step and is carried out by either the PAN2-PAN3 or CCR4-NOT complexes (reviewed in C.-Y. A. Chen & Shyu, 2011; Muhlrad et al., 1994; Mugridge et al., 2018). Degradation of an mRNA's poly(A) tail excludes PABP, which both destabilizes the mRNA and suppresses its translation. In the 5′–3′ exonucleolytic decay pathway, once deadenylation is complete, the Dcp1–Dcp2 decapping complex is recruited to the mRNA through interactions either between its cofactor DD6X and the deadenylation complex or with its other cofactors that bind the shortened poly(A) tail (Y. Chen et al., 2014; Chowdhury et al., 2007; Mugridge et al., 2018). Decapped mRNAs become vulnerable to processive degradation by the 5′–3′ exoribonuclease Xrn1 (Hsu & Stevens, 1993).

The 3′–5′ exonucleolytic decay is mediated by the large, multi-protein RNA exosome complex (reviewed in Łabno et al., 2016). The RNA exosome has widespread roles in the processing and degradation of both nuclear and cytoplasmic RNAs, with many target-specific cofactors (reviewed in Kilchert, 2020). For human cytoplasmic mRNA degradation, the core RNA exosome with the DIS3L catalytic subunit is recruited to the 3′-end of deadenylated or cleaved transcripts (Kilchert, 2020; Łabno et al., 2016). For degradation of defective mRNAs first cleaved by endonucleases, the SKI complex is important for RNA exosome recruitment (van Hoof et al., 2002). For deadenylated ARE-containing mRNAs, ARE binding proteins play a role in exosome recruitment (C. Y. Chen et al., 2001). After near complete degradation, the scavenging decapping enzyme DCPS removes the 5′ cap from the remaining 5′ mRNA fragment (reviewed in Milac et al., 2014).

4.2 | RNA stability during the integrated stress response

Global RNA stability is highly regulated during acute stresses including those that activate the ISR. Changes in the localization and/or availability of specific RNA binding proteins that mediate mRNA stability and decay occur during stress and mediate regulated changes in mRNA stability. For example, short-lived transcripts containing AREs in their 3′-UTRs are stabilized upon heat stress (Laroia et al., 1999), proteasome inhibition stress (Laroia et al., 1999), and UV-C stress (W. Wang et al., 2000). Reorganization of RNA–protein complexes may underlie ARE-containing mRNA stability during stress. For example, the RNA binding protein AUF1 (ARE/poly[U]-binding/degradation factor 1) destabilizes ARE-containing mRNAs (Gratacós & Brewer, 2010), and AUF1 relocalization from the cytoplasm to the nucleus during heat stress or proteasome inhibition by MG-132 was associated with ARE-containing transcript stabilization in these contexts (Laroia et al., 1999). Additionally, the nuclear protein human antigen R (HuR) interacts with ARE-containing transcripts such as the mRNA encoding the cyclin-dependent kinase inhibitor p21 in the cytoplasm during UV-C stress, and genetic depletion experiments demonstrated HuR was required for p21 mRNA stabilization upon UV-C stress in mammalian cells (W. Wang et al., 2000). Relocalization of HuR from the nucleus to the cytoplasm was also observed when cells were exposed to other stressors including hydrogen peroxide (W. Wang et al., 2000). Further, zipcode binding protein 1 (ZBP1) localizes to stress granules and was required for the stabilization of specific mRNAs such as c-myc, and not others, during the ISR in response to heat and arsenate stress (Stöhr et al., 2006). In response to arsenite stress, changes in alternative mRNA polyadenylation are also associated with changes in mRNA stability. For example, binding of the cytotoxic granule-associated RNA binding protein TIA-1 to mRNAs with longer alternative 3′-UTRs is associated with their destabilization (Zheng et al., 2018). Therefore, regulated changes in the localization and binding targets

of stabilizing and destabilizing mRNA binding proteins can alter the stability of specific classes of mRNAs during acute stress and remodel the transcriptome.

A second mechanism by which mRNA turnover is regulated during the ISR is via downregulation of the general RNA decay machinery. Short-lived mRNA reporters, and the transcripts of induced or constitutively expressed endogenous genes are stabilized upon UV-B and UV-C stresses (Blattner et al., 2000; Bollig et al., 2002; Gowrishankar et al., 2005; W. Wang et al., 2000; White et al., 1997), ER stress (Kawai et al., 2004), and arsenite stress (Horvathova et al., 2017) in mammalian cells. Global mRNA stabilization is also observed in baker's yeast upon severe osmotic stress (Romero-Santacreu et al., 2009), glucose deprivation (Jona et al., 2000), and hyperosmotic glucose stress (Greatrix & van Vuuren, 2006). Intriguing evidence supports the idea that reduced deadenylation activity underlies global RNA stabilization in response to many acute stressors that activate the ISR. First, polyadenylated RNAs accumulate upon hyperosmotic glucose stress (Greatrix & van Vuuren, 2006) and deadenylation rates are reduced upon glucose starvation (Hilgers et al., 2006; Jona et al., 2000), potassium chloride stress, and heat stress (Hilgers et al., 2006) in yeast. Second, the rate of deadenylation of reporter mRNAs in mammalian cells is slowed during the response to arsenite stress (Yamagishi et al., 2014), hydrogen peroxide stress, sorbitol, and heat (Gowrishankar et al., 2006). These reports support the idea that this phenomenon is conserved and generalizable across the response to many acute stressors. Stress-induced deadenylation suppression is not necessarily limited to those stress conditions that activate the ISR. Deadenylation is dramatically slowed during heat stress, which causes eIF2α phosphorylation. However, deadenylation is also suppressed upon potassium chloride or glucose deprivation stresses, which do not cause eIF2α phosphorylation (Ashe et al., 2000; Goossens et al., 2001) in baker's yeast (Hilgers et al., 2006). Thus, downregulation of the rate-limiting step of the major mRNA decay pathway is an evolutionarily conserved response to acute stress.

Three pieces of evidence suggest the mechanism by which deadenylation and decay rates are slowed during acute stress is through down-regulation of the major RNA degradation machinery in the cell. First, genetic depletion of either the major deadenylase *ccr4* to impair the activity of the Ccr4p/Pop2p/Notp complex, or the deadenylase *pan2* to inhibit the Pan2p/Pan3p complex did not result in increased deadenylation rates of reporter mRNAs during osmotic stress in baker's yeast (Hilgers et al., 2006). This observation suggests that the activities of both Ccr4p/Pop2p/Notp and Pan2p/Pan3p complexes are inhibited during acute stress. Second, the deadenylase Pan3 and the Caf1 deadenylase-interacting protein Tob (Hosoda et al., 2011) are degraded rapidly upon arsenite stress when the deadenylation of mRNA reporters is significantly delayed in human cells (Yamagishi et al., 2014). Thus, the selective degradation of key mRNA decay factors is likely an important mechanism by which deadenylation is downregulated during acute stress. Third, the 5′–3′ decay machinery may also be compromised during acute stress. Reporter mRNAs sensitive to 5′–3′ mediated degradation by Xrn1 are stabilized in yeast spheroplasts upon amino acid deprivation caused by 3-AT (3-amino-1,2,4-triazole; Benard, 2004). Further, reporter mRNAs in yeast strains lacking the deadenylation factors *pan2* and *ccr4* still display a 40% increase in half-life upon potassium chloride hyperosmotic stress (Hilgers et al., 2006). Of note, global mRNA stabilization by suppression of deadenylation is unlikely due to global suppression of translation. The suppression of deadenylation occurs prior to translation shutoff in UV-B stress (Gowrishankar et al., 2006). Additionally, hyperosmotic stress causes suppressed deadenylation in yeast in the presence or absence of cycloheximide, which traps mRNAs in polysomes (Hilgers et al., 2006). Finally, arsenite stress suppresses the degradation of reporter mRNAs in the presence or absence of HRI and phosphorylated eIF2α (Yamagishi et al., 2014). Therefore, specific changes in the abundance and/or activities of major mRNA decay factors may drive global stabilization of polyadenylated mRNAs during acute stress. Such a regulatory mechanism could enable the cell to preserve the constitutively expressed transcriptome to re-enter translation upon the resolution of stress.

5 | RIBOSOME-ASSOCIATED QUALITY CONTROL AND THE INTEGRATED STRESS RESPONSE

In addition to general turnover, cells have evolved specialized mRNA surveillance mechanisms to rapidly detect and degrade defective mRNAs through processes linked with the ribosome-associated quality control (RQC) pathway. By operating co-translationally, RQC helps guard against the production of miscoded or misfolded proteins in real time, before the faulty peptide is fully synthesized and released into the cell (reviewed in Brandman & Hegde, 2016; Simms et al., 2017). Three mRNA surveillance pathways synergize with the RQC machinery to promote rapid degradation of faulty mRNA. MRNA defects detected by RQC include (1) premature termination codons (PTCs), often a result of mis-splicing, undergo nonsense-mediated decay (NMD; Losson & Lacroute, 1979), (2) lack of a proper stop codon causes

nonstop decay (NSD; Frischmeyer et al., 2002; van Hoof et al., 2002), and (3) unresolvable RNA secondary structure (Doma & Parker, 2006), mRNA nucleotide damage (Simms et al., 2014; Yan et al., 2019), or mRNA truncation products (Meaux & Van Hoof, 2006) undergo no-go decay (NGD). The unifying consequence of each of these defects is ribosome stalling. In addition to mRNA defects, ribosome stalling can also be caused by insufficiencies in amino acid or tRNA availability.

Despite being triggered by different types of defective mRNA or translation elongation defects, each RQC pathway accomplishes the same overall outcome—degradation of both the instigating mRNA and the nascent peptide—through the same general steps. First, the stalled ribosome is detected by the cell. In NGD, and potentially NSD, stalling results in ribosome collisions, which are sensed by the RQC-trigger complex (Matsuo et al., 2017). In NMD, ribosomes stalled at PTCs are recognized by up-frameshift proteins associated with downstream exon-junction complexes (P. V. Ivanov et al., 2008; Kashima et al., 2006; Neu-Yilik et al., 2017; K. T. Powers et al., 2020).

Next, RQC-specific factors mediate the release of the stalled ribosome and initiate degradation of the mRNA through its endonucleolytic cleavage (Doma & Parker, 2006). In NMD, SMG6 is the endonuclease responsible for mRNA cleavage (Eberle et al., 2009), whereas recent reports identified Cue2 as the endonuclease involved in NGD in yeast (D'Orazio et al., 2019) and its homolog NONU-1 as the endonuclease required for both NGD and NSD in *Caenorhabditis elegans (*Glover et al., 2020*)*. MRNA degradation is completed by subsequent 5′–3′ and 3′–5′ exonucleolytic degradation of the resulting mRNA fragments by Xrn1 and the exosome, respectively (Doma & Parker, 2006). As for the nascent peptide, foundational genetics and structural studies in *Saccharomyces cerevisiae* revealed that it is typically targeted for degradation following ribosome release. Nuclear export mediator factor (NEMF) recruits its cofactor and E3 ligase Listerin (LTN1) to 60S ribosomal subunits and ubiquitinate the nascent chain (Bengtson & Joazeiro, 2010; Lyumkis et al., 2014). Finally, the AAA+ ATPase VCP (valosin-containing protein, also known as p97) promotes the extraction of the nascent protein from the 60S ribosome and targets it to the proteasome or lysosome for degradation (Defenouillère et al., 2013; Verma et al., 2013).

However, recent studies from our group and others applying single mRNA imaging approaches suggest that mRNA degradation may not always follow ribosome stalling in human cells. During acute cellular stress by arsenite or heat, inhibition of VCP prevents nascent peptide and ribosome dissociation from a subset of constitutively expressed mRNAs through a pathway that also involves LTN1, NEMF, and the proteasome (Moon et al., 2020). This may suggest either the existence of feedback mechanisms that restricts ribosome–nascent protein–mRNA dissociation when downstream RQC factors are inhibited, or a fourth RQC pathway that specifically acts in response to ribosome stalling under certain stress conditions, in which LTN1, NEMF, VCP, and the proteasome play a role before ribosome splitting. Furthermore, nascent proteins accumulate on mRNA reporters encoding poly-lysine tracts, suggesting ribosome pileups, without causing a substantial reduction in mRNA abundance (Goldman et al., 2021). As such, mRNAs in human cells that are targeted by the RQC pathway may not necessarily be degraded (Goldman et al., 2021; Moon et al., 2020). These results suggest that during cellular stress the mRNA surveillance pathways may be uncoupled from the RQC pathway.

The interplay between the ISR and RQC was further established in recent studies showing that widespread ribosome collisions can overwhelm the RQC system (C. C.-C. Wu et al., 2020). Such collisions are sensed by the kinase ZAKα, which triggers GCN2-mediated eIF2α phosphorylation in human cells (C. C.-C. Wu et al., 2020). Multiple distinct cellular stressors are capable of causing global ribosome collisions, including amino acid starvation and treatment with intermediate concentrations of translation elongation inhibitors, which permits a subset of ribosomes to continue translating until colliding with paused ribosomes that are effectively targeted by the inhibitors (C. C.-C. Wu et al., 2020). Additionally, environmental or chemical stressors that cause widespread mRNA damage can also induce widespread ribosome collisions. This is the case with UV irradiation, which results in the disproportionate stalling of ribosomes at codons containing adjacent pyrimidines (C. C.-C. Wu et al., 2020), presumably due to the formation of pyrimidine dimers (Jackle & Kalthoff, 1978). Furthermore, in yeast, chemical agents that cause mRNA alkylation or oxidation also cause eIF2α phosphorylation via GCN2 (Yan & Zaher, 2021). As a downstream consequence of ISR activation, failure to resolve ribosome collisions triggers apoptosis, which emphasizes the importance of RQC to cellular fitness (C. C.-C. Wu et al., 2020).

The nervous system appears to be particularly vulnerable to failures in RQC. Mutations or isoforms of genes encoding multiple RQC proteins, including LTN1 (J. Chu et al., 2009), NEMF (Martin et al., 2020), and VCP (Johnson et al., 2010; Watts et al., 2004), cause neurodegeneration. Moreover, mice with a mutation in a single tRNA gene develop severe neurodegeneration when *GTPBP1* or *GTPBP2* are also mutated (R. Ishimura et al., 2014; Ishimura et al., 2016; Terrey et al., 2020). GTPBP1 and GTPBP2 are GTPases that share homology with HBS1L, a ribosome release factor required for NGD and NSD, and promote the resolution of stalled ribosomes caused by the tRNA insufficiency in

these mice (R. Ishimura et al., 2014; Ishimura et al., 2016; Terrey et al., 2020). Before degeneration, the ISR is activated in the neurons of these mice through GCN2 (R. Ishimura et al., 2014; Ishimura et al., 2016; Terrey et al., 2020). Thus, an important area of future work will examine the role of the ISR in the increased vulnerability of neurons to disturbances in RQC.

6 | GENETIC DISEASES OF THE INTEGRATED STRESS RESPONSE

Numerous rare genetic diseases are caused by mutations in the genes encoding at least seven of the ISR components described to date that drive the ISR (Tables 2–5). Alleles of the eIF2α kinases HRI (*EIF2AK1*), PKR (*EIF2AK2*), PERK (*EIF2AK3*), and GCN2 (*EIF2AK4*) are associated with developmental syndromes and diseases that affect a variety of organ systems including the nervous, endocrine, circulatory, and skeletal system. Mutations in the constitutively expressed eIF2α phosphatase regulatory subunit CReP (*PPP1R15B*) are associated with intellectual disability and diabetes, variants in the gamma subunit of the eIF2 complex cause an X-linked neurodevelopmental syndrome, and alleles of any of the five eIF2B genes are associated with the leukodystrophy VWM disease. This growing class of genetic disorders reveals the importance of the ISR in human development and health.

6.1 | Genetic diseases of *EIF2S3* (eIF2γ)

Mutations in *EIF2S3*, the gene that codes for eIF2γ of the eIF2 complex, cause the rare, X-linked intellectual disability (XLID) MEHMO syndrome (OMIM #300148; Skopkova et al., 2017; Table 2). The acronym MEHMO represents the primary clinical symptoms of the syndrome—mental retardation, epileptic seizures, hypogonadism, hypogenitalism, microcephaly, and obesity. Individuals with MEHMO syndrome typically exhibit large ears and talipes and, in severe cases, are diagnosed with diabetes. As an X-linked recessive disorder, all reported cases of MEHMO syndrome have been males (Delozier-Blanchet et al., 1989; Leshinsky-Silver et al., 2002; Skopkova et al., 2017; Steinmüller et al., 1998). The symptoms of MEHMO syndrome were first described in two brothers in 1989 (Delozier-Blanchet et al., 1989). In 1998 following the investigation of a large three-generation family with five affected males, the syndrome was termed MEHMO, and the disease locus was determined to be Xp21.1–p22.13 (Steinmüller et al., 1998). It was recently determined by massively parallel sequencing of four families affected by MEHMO syndrome that causative mutations lie in *EIF2S3* (Skopkova et al., 2017). The most prevalent mutation uncovered was a four base pair deletion that created a frameshift and premature stop codon (c.1394_1397delTCAA p.Ile465Serfs*4), and individuals with the mutation displayed the full range of severe MEHMO syndrome symptoms, often with diabetes. Several missense mutations in *EIF2S3* (c.324T>A p.Ser108Arg, c.665T>C p.Ile222Thr, c.777T>G p.Ile259Met, and c.451G>C p.Val151Leu) have also been identified and linked to XLIDs with a subset of MEHMO syndrome symptoms and a range of severity (Borck et al., 2012; Moortgat et al., 2016; Skopkova et al., 2017; Tarpey et al., 2009), including the recent report of three related males with mild intellectual disability, hypoglycemia, and hypopituitarism, specifically with deficient growth hormone and thyroid-stimulating hormone, caused by the substitution of a conserved proline to a serine (c.1294C>T p.Pro432Ser; Gregory et al., 2019). Interestingly, exome sequencing did not reveal mutations in the *EIF2S3* coding regions or adjacent introns in three males from two families affected by MEHMO syndrome (Skopkova et al., 2017), indicating that

TABLE 2 Disease-associated alleles of *EIF2S3*

Gene	Alleles	Disease/syndrome	References
EIF2S3	c.1394_1397delTCAA (p.Ile465SerfsTer4)	MEHMO syndrome and X-linked intellectual disability	(Moortgat et al., 2016)
EIF2S3	c.433A>G (p.Met145Val)	MEHMO syndrome	(Moortgat et al., 2021)
EIF2S3	c.665T>C (p.Ile222Thr); c.777T>G (p.Ile259Met); c.451G>C (p.Val151Leu)	X-linked intellectual disability	(Borck et al., 2012; Moortgat et al., 2016; Tarpey et al., 2009)
EIF2S3	c.1294C>T (p.Pro432Ser)	X-linked hypopituitarism with glucose dysregulation	(Gregory et al., 2019)

MEHMO syndrome in these patients may be due to variants in a gene other than *EIF2S3* (Delozier-Blanchet et al., 1989; Leshinsky-Silver et al., 2002; Skopkova et al., 2017).

Studies have been conducted to determine how disease-associated variants of *EIF2S3* impact cell health and lead to the extreme symptoms of MEHMO syndrome. The frameshift mutation that generates a truncated protein (c.1394_1397delTCAA p.Ile465Serfs*4) is perhaps the most studied *EIF2S3* variant to date (Skopkova et al., 2017; Young-Baird et al., 2020). The eIF2 complex unites with GTP and Met-tRNA$_i$ to form the ternary complex and initiates translation at an AUG start codon. Work in yeast showed that cells expressing the frameshift mutation (c.1394_1397delTCAA p.Ile465Serfs*4) exhibited decreased translation start codon fidelity and increased expression of the ISR target gene *GCN4* (*ATF4* in mammals; Skopkova et al., 2017). This work was expanded upon in patient-derived cells as it was demonstrated that frameshift mutants displayed increased protein levels of ATF4 and its target CHOP, as well as GADD34 (Skopkova et al., 2017; Young-Baird et al., 2020). In addition, global translation and cell viability are reduced in patient-derived induced pluripotent stem cells (iPSCs) expressing the frameshift mutation (c.1394_1397delTCAA p.Ile465Serfs*4; Young-Baird et al., 2020). Global translation suppression and expression of *ATF4*, *DDIT3* (CHOP), and *PPP1R15A* (GADD34) are exacerbated in frameshift mutants treated with the ISR activator thapsigargin (Young-Baird et al., 2020; Figure 5a,b). Thus, the ISR is active in frameshift mutants in the absence of stress and is hyperactive in the presence of stress. Altogether, these findings are likely explained by the discovery that eIF2α and Met-tRNA$_i$ binding to the ternary complex is disrupted in frameshift mutants (Young-Baird et al., 2020).

The MEHMO syndrome-associated *EIF2S3* missense mutation c.665T>C p.Ile222Thr is located in the GTP-binding domain of eIF2γ and has also been examined. Like the frameshift variant, the missense variant caused increased *GCN4* expression and impaired translation start codon fidelity (Borck et al., 2012; Skopkova et al., 2017). In contrast to the frameshift variant, the binding of eIF2β to eIF2γ is disrupted in the missense mutant (Borck et al., 2012). Consistent with disease severity, yeast expressing the missense variant associated with mild symptoms (c.1294C>T p.Pro432Ser) displayed only slightly elevated *GCN4* expression and minimally defective translation start codon fidelity (Gregory et al., 2019).

Despite a significant amount of work, many questions remain surrounding how *EIF2S3* mutations lead to MEHMO syndrome. First, how do all of the reported *EIF2S3* variants affect the function of eIF2γ and cell health? The frameshift variant c.1394_1397delTCAA p.Ile465Serfs*4 disrupts the binding of eIF2α to eIF2γ (Young-Baird et al., 2020), while

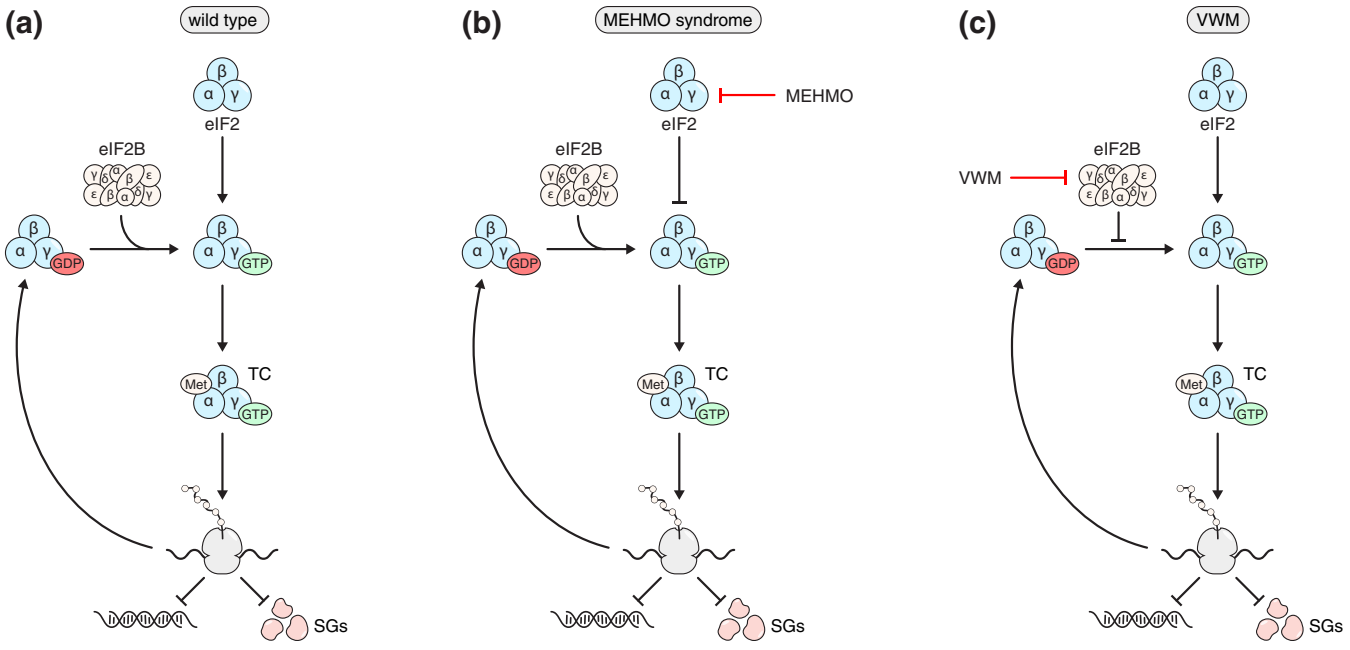

FIGURE 5 Diagram depicting the possible impacts of alleles of *EIF2S3* and *EIF2B1–5* associated with MEHMO syndrome and vanishing White matter (VWM) disease, respectively, on translation initiation and the ISR. (a) In wild-type cells, the guanine exchange activity of eIF2B ensures abundant ternary complex (TC) to enable translation initiation and suppress stress granule (SG) formation and stress-induced gene expression. Cells harboring (b) *EIF2S3* (eIF2γ) and (c) *EIF2B1–5* (eIF2Bα, β, γ, δ, ε) mutations are predicted to impair TC formation and perturb translation initiation activity

the missense variant c.665T>C p.Ile222Thr disrupts the binding of eIF2β to eIF2γ (Borck et al., 2012). Thus, it will be important to determine if the additional *EIF2S3* missense variants affect interactions within the eIF2 complex and/or with other initiation factors. Second, what cell types are targeted by *EIF2S3* mutations? It is evident that MEHMO syndrome targets the central nervous system (Delozier-Blanchet et al., 1989; Leshinsky-Silver et al., 2002; Skopkova et al., 2017; Steinmüller et al., 1998). Interestingly, iPSCs harboring the frameshift mutation demonstrate impaired neuronal differentiation (Young-Baird et al., 2020). However, various cell types support the proper function of the central nervous system. It will be interesting to determine if specific cell types besides neurons are impacted by alleles of *EIF2S3* associated with MEHMO syndrome. Ultimately, it will be critical to establish animal models of MEHMO syndrome to examine the effects of disease-associated variants and potential therapies in multicellular organisms. Intriguingly, knockdown of zebrafish *eif2s3* mimicked some clinical symptoms of MEHMO syndrome including microcephaly suggesting that zebrafish may be an informative model organism (Moortgat et al., 2016).

6.2 | Genetic diseases of *EIF2B1–5* (eIF2B)

VWM disease or childhood ataxia with central nervous system hypomyelination (OMIM #603896) is a chronic progressive leukodystrophy that is caused by autosomal recessive mutations in any of the genes that encode the five eIF2B subunits (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*; Bugiani et al., 2018; Leegwater et al., 2001; M. S. van der Knaap et al., 2002). Over 180 different mutations associated with VWM and the systemic eIF2B-related disorders have been reported to date (Table 3). Missense alleles of *EIF2B5* are the most frequently observed (Pavitt & Proud, 2009). The symptoms of VWM include progressive and episodic hypomyelination, white matter loss, cerebellar ataxia, spasticity, cataracts, and optic atrophy, and is invariably fatal (Hanefeld et al., 1993; Schiffmann et al., 1994; M. S. van der Knaap et al., 1997). Importantly, neurologic deterioration is often triggered by febrile infection, physical trauma to the head, or severe fright responses (Hanefeld et al., 1993; Schiffmann et al., 1994; M. S. van der Knaap et al., 1997). Because phosphorylated eIF2α is elevated in models of traumatic brain injury (Chou et al., 2017) and in response to pro-inflammatory cytokines such as J2 prostaglandins (Tauber & Parker, 2019; Weber et al., 2004), one possibility is that defects in the ISR underlie such episodes of neurologic deterioration. Additionally, females with VWM may also exhibit ovarian failure (Bugiani et al., 2018; Fogli et al., 2003; Mathis et al., 2008). VWM affects infants, children, adolescents, and adults, however, patients with late onset VWM experience milder symptoms than patients with early-onset VWM (Bugiani et al., 2018; M. S. van der Knaap et al., 1998). In the first study that related variants in the *EIF2B* genes with VWM, 16 distinct mutations in *EIF2B5* and six distinct mutations in *EIF2B2* were identified, and the majority were missense mutations (Leegwater et al., 2001). Since the initial report, a plethora of mutations, largely missense, associated with VWM in all five *EIF2B* genes have been described (M. S. van der Knaap et al., 2002). Mutations in *EIF2B* affect eIF2B in a number of ways and have been demonstrated to alter its GEF activity, modify binding to its substrate eIF2, and impair its assembly and stability (Leng et al., 2011; R. Liu et al., 2011; W. Li et al., 2004; Matsukawa et al., 2011; X. Wang et al., 2012; Wortham & Proud, 2015; Figure 5a,c).

As the GEF for eIF2, eIF2B promotes the exchange of GDP for GTP to permit translation initiation. Thus, mutations that reduce the function of eIF2B would be expected to decrease global translation. Unexpectedly, cells with *EIF2B* mutations display baseline protein synthesis levels similar to wild-type cells (Kantor et al., 2005; Moon & Parker, 2018a; Sekine et al., 2016; van Kollenburg et al., 2006; Wong et al., 2018). However, upon activation of the ISR, global translation, which is normally suppressed during the ISR, is hyper-suppressed in *EIF2B* mutants (Moon & Parker, 2018a; Sekine et al., 2016; Wong et al., 2018). Moreover, VWM patient-derived *EIF2B2* mutant lymphoblasts exhibit prolonged eIF2α phosphorylation and global translation repression, as well as delayed GADD34 expression, which is consistent with delayed global translation restoration due to extended eIF2α phosphorylation (Moon & Parker, 2018a). As a result, *EIF2B2* mutants are vulnerable to ER stress (Moon & Parker, 2018a). One consequence of such a delay in the dephosphorylation of p-eIF2α may be that cells experiencing acute stress may enter into a prolonged, chronically stressed state. In support of this idea, VWM mouse models and VWM patient-derived brain tissue also exhibit defects in the ISR. Specifically, in the absence of stress, the expression of ATF4 and its targets are increased and the levels of p-eIF2α are decreased in these systems (Abbink et al., 2019). It is interesting to note that VWM-associated mutations do not consistently impact stress-induced RNP granules in the absence of *gcn2* (the only eIF2 kinase in yeast) in yeast models, but P-bodies were elevated in *EIF2B2* mutant lymphoblasts derived from patients with VWM and in several yeast strains expressing analogous *EIF2B2* and *EIF2B5* mutations to those associated with VWM in unstressed conditions (Moon & Parker, 2018b). A low level of translationally repressed mRNAs could contribute to elevated P-body formation in these

TABLE 3 Disease-associated alleles of *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*

Gene	Alleles	Disease/syndrome	References
EIF2B1	c.131G>A (p.Gly44Asp); c.230G>A (p.Ser77Asn); c.101T>G (p.Leu34Trp); c.915_916del (p.*306Thrext*12)	Neonatal/early-onset diabetes and episodic hepatic dysfunction	(De Franco et al., 2020)
EIF2B1	c.131G>T (p.Gly44Val)	Neonatal/early-onset diabetes	(De Franco et al., 2020)
EIF2B1	c.328A>G (p.Lys110Glu); c.323_325delGAA (p.108delArg); c.715T>G (Phe239Val); c.ivs2+20G>A (p.S84ins22aa*); c.610_612del (p.G204del); c.547G>T (p.Val183Phe); c.622A>T (p.Asn208Tyr); c.824A>G (p.Tyr275Cys); c.833C>G (p.Pro278Arg)	Vanishing White Matter disease	(Güngör et al., 2020; Pavitt & Proud, 2009; Shimada et al., 2015; H. Zhang et al., 2015)
EIF2B1	c.146T>G (p.Leu49Arg)	Vanishing White Matter disease and diabetic ketoacidosis	(Alamri et al., 2016)
EIF2B2	c.375T>A (p.Val85Glu); c.682A>G (p.Arg228Gly); c.995C>T (p.Ala332Val); c.529_543del (p.177_181del); c.547C>T (p.Arg183Ter); c.548del (p.Arg183fsTer); c.607_612delinsTG (p.Met203fsTer); c.910G>T (p.Glu304Ter); c.512C>T (p.Ser171Phe); c.586C>T (p.Pro196Ser); c.599G>C (p.Gly200Ala); c.599G>T (p.Gly200Val); c.638A>G (p.Glu213Gly); c.653C>T (p.Thr218Ile); c.818A>G (p.Lys273Arg); c.871C>T (p.Pro291Ser); c.947T>A (p.Val316Asp); c.986G>T (p.Gly329Val)	Vanishing White Matter disease	(Matsukawa et al., 2011; Pavitt & Proud, 2009; Shimada et al., 2015; H. Zhang et al., 2015)
EIF2B2	c.817A>C (p.Lys273Gln); c.939_948del (p.Asp314ProfsTer23)	Vanishing White Matter disease with hepatomegaly and hypertriglyceridemia	(Unal et al., 2013)
EIF2B2	c.496A>G (p.Met166Val)	Ovarioleukodystrophy	(C. Wei et al., 2019)
EIF2B2	c.677T>A (p.Met226Lys)	Vanishing White Matter disease & eIF2B-related multisystem disorder	(J. S. Lee et al., 2017)
EIF2B3	c.272G>A (p.Arg91His); c.1270T>G (pCys424Gly); c.80T>A (p.Leu27Gln); c.C590T (p.Thr197Met); c.706C>G (p.Gln236Glu); c.503T>C (p.Leu168Pro); c.935G>A (p.Arg312Gln); c.1106_1113del (p.Ser369Serfs*13); c.965C>G (p.Ala322Gly); c.1193_1194del (p.Val398fs); c.32G>T (p.Gly11Val); c.136G>A (p.Val46Ile); c.140G>A (p.Gly47Glu); c.260C>T (p.Ala87Val); c.407A>C (p.Gln136Pro); c.674G>A (p.Arg225Gln); c.687T>T (p.Ile229Met); c.1023T>G (p.His341Gln); c.1037T>C (p.Ile346Thr); c.1118C>T (p.Ser373Leu); c.1124T>G (p.Ile375Ser)	Vanishing White Matter disease	(Gowda et al., 2017; Hyun et al., 2019; Khorrami et al., 2021; La Piana et al., 2012; Y.-R. Lee et al., 2021; Matsukawa et al., 2011; Pavitt & Proud, 2009; H. Zhang et al., 2015)
EIF2B4			

TABLE 3 (Continued)

Gene	Alleles	Disease/syndrome	References
	c.1090C>T (p.Arg364Trp); c.691G>A (p.Gly231Ser); c.1382A>G (p.Tyr461Cys); c.1565C>T (p.Thr522Met); c.1306T>A (p.Ser416Thr); c.1397G>A (p.Arg446His); c.407A>G (p.Gln136Arg); c.556T>A (p.Tyr186Asn); c.617T>C (p.Met206Thr); c.614C>T (p.Pro205Leu); c.952A>G (p.Ile318Val); c.625C>T (p.Arg209Ter); c.ivs11G>A (p.Glu397_ins_11aa); c.877_879del (p.Glu293del); c.ivs12+1insT (splice mutation); c.626G>A (p.Arg209Gln); c.702C>T (p.Alal228Val); c.728C>T (p.Pro243Leu); c.806T>G (p.Leu269Arg); c.1070G>A (p.Arg357Gln); c.1069C>T (p.Arg357Trp); c.1091G>A (p.Arg364Gln); c.1120C>T (p.Arg374Cys); c.1172C>A (p.Arg391Asp); c.1393T>C (p.Cys465Arg); c.1399C>T (p.Arg467Trp); c.1447C>T (p.Arg483Trp); c.1465T>C (p.Tyr489His)	Vanishing White Matter disease	(Hettiaracchchi et al., 2018; Kanbayashi et al., 2015; Pavitt & Proud, 2009; Shimada et al., 2015; Turón-Viñas et al., 2014; H. Zhang et al., 2015)
EIF2B4	c.1301T>C (p.Leu434Pro); c.628G>T (p.Gly210Cys)	Vanishing White Matter disease and hyperinsulinemic hypoglycemia	(Bursle et al., 2020)
EIF2B4	c.1117C>T (p.Arg373Cys)	Ovarioleukodystrophy	(Herrera-García et al., 2018)
EIF2B5	c.915G>A (p.Met305Ile); c.1518delA (p.Glu506fsTer52); c.947A>G (p.Arg316Gln); c.1352T>C (p.Leu451Ser); 784G>A (p.Asp262Asn); c.1223T>C (p.Ile408Thr); c.1827-1838del (p.Ser610–D613del); c.1154T>C (p.Ile385Thr); c.915G>A (p.Met305Ile); c.808G>C (p.Asp270His); c.314A>G (p.His105Arg); c.877C>T (p.Ala293Ser); c.1688G>A (p.Arg563Gln); c.1694delAins45 (p.Lys565IlefsTer38); c.395G>C (p.Gly132Ala); c.449T>G (p.Leu150Arg); c.1355A>G (p.His452Arg); c.453_454del (p.Tyr152fsTer); c.766G>A (p.256_281del); c.892T>delinsACA (p.Phe264fs); c.805C>T (p.Arg269Ter); c.1264C>T (p.Arg422Ter); c.1444G>ins17 (p.Gly481fsTer); c.1827_1838del (p.610_613del); c.1884G>A (p.Trp628Ter); c.1997_2017del (p.665_671del); c.C47A (p.Ala16Asp); c.G161C (p.Arg54Pro); c.T166G (p.Phe56Val); c.T167G (p.Phe56Cys); c.A185T (p.Asp62Val); c.T203C (p.Leu68Ser); c.T218G (p.Val73Gly); c.G220A (p.Ala74Thr); c.A233C (p.Tyr78Ser); c.C236T (p.Thr79Ile); c.G241A (p.Glu81Lys); c.A271G (p.Thr91Ala); c.A318T (p.Leu106Phe); c.T331C (p.Trp111Arg); c.C337T (p.Arg113Cys); c.G338A (p.Arg113His); c.T380C (p.Leu127Pro); c.C406T (p.Arg136Cys); c.G407A (p.Arg136His); c.C468G (p.Ile156Met); c.C545T (p.Thr182Met); c.C583T (p.Arg195Cys); c.G584A (p.Arg195His); c.G592A (p.Glu198Lys); c.C758A (p.Ser253Tyr); c.C805G (p.Arg269Gly); c.G806A (p.Arg269Gln); c.G806T (p.Arg269Leu); c.	Vanishing White Matter disease	(Alías Hernández et al., 2013; Bektaş et al., 2018; Matsukawa et al., 2011; Pavitt & Proud, 2009; Pena et al., 2018; Sharma et al., 2011; Shimada et al., 2015; Takano et al., 2015; Turón-Viñas et al., 2014; Woody et al., 2015; Y. Wu et al., 2009; H. Zhang et al., 2015)

(Continues)

TABLE 3 (Continued)

Gene	Alleles	Disease/syndrome	References
	G895A (p.Arg299His); c.A911C (p.His304Pro); c.G925C (p.Val309Leu); c.G929T (p.Cys310Phe); c.A935G (p.Asp312Gly); c.C943G (p.Arg315Gly); c.G944A (p.Arg315His); c.G952A (p.Val318Ile); c.C967T (p.Pro323Ser); c.T1003C (p.Cys335Arg); c.G1004C (p.Cys335Ser); c.C1015T (p.Arg339Trp); c.G1016C (p.Arg339Pro); c.G1016A (p.Arg339Gln); c.A1028G (p.Tyr343Cys); c.A1126G (p.Asn376Asp); c.A1153G (p.Ile385Val); c.G1157T (p.Gly386Val); c.A1160G (p.Asp387Gly); c.C1208T (p.Ala403Val); c.A1244G (p.Asp415Gly); c.T1274G (p.Leu425Arg); c.C1280T (p.Pro427Leu); c.T1289C (p.Val430Ala); c.C1340T (p.Ser447Leu); c.C1360T (p.Pro454Ser); c.G1459A (p.Glu487Lys); cA1484G (p.Tyr495Cys); c.C1810T (p.Pro604Ser); c.T1882C (p.Trp828Arg); c.T1946C (p.Ile649Thr); c.G1948A (p.Glu650Lys)		
EIF2B5	c.896G>A (p.Arg299His); c.638A>G (p.Glu213Gly); c.818A>G (p.Lys273His); c.1448A>G (p.Tyr483Cys); c.641A>G (p.His214Arg); c.805C>T (p.Arg269Ter); c.743A>T (p.His248Leu)	Adult-onset eIF2B-related disorder	(Labauge et al., 2009)
EIF2B5	c.725A>G (p.Tyr242Cys); c.1156+13G>A (splice mutation)	Ovarioleukodystrophy	(Rodríguez-Palmero et al., 2020)

contexts. Thus, partial loss of eIF2B function may specifically impact the ability of the cell to respond to acute stress rapidly and reversibly.

An important outstanding question is how specific mutations confer a wide range of phenotypes in terms of disease severity and tissue specificity of eIF2B-related multisystem disorders that can often be categorized as VWM. While it may be predicted that disease severity correlates with the degree to which the causative *EIF2B* mutation alters the function of eIF2B, this does not always seem to be the case. For instance, some *EIF2B* mutations that are linked to severe VWM do not affect the GEF activity or assembly of eIF2B (R. Liu et al., 2011). Furthermore, a recent study demonstrated that, while severe phenotype-associated mutations generally localized to regions of eIF2B predicted to significantly impact its function, and mild phenotype-associated mutations generally localized to regions of eIF2B predicted to minimally impact its function, this was not true for all cases (Slynko et al., 2021). Finally, phenotypic variability has been observed among family members carrying the same VWM-associated *EIF2B* variant (Bugiani et al., 2018). Consistent with the neurological symptoms associated with VWM, astrocytes and oligodendrocytes are the dominant cell type targeted by the disease (Bugiani et al., 2011, 2013; Dietrich et al., 2005; Dooves et al., 2016). Yet, females affected by VWM frequently experience ovarian failure. Additionally, mutations in *EIF2B1* have been linked to permanent neonatal diabetes and diabetic ketoacidosis (Alamri et al., 2016; De Franco et al., 2020). Insulin translation is highly regulated to allow rapid upregulation of insulin protein production in response to glucose (Vasiljević et al., 2020), suggesting the possibility that reduced eIF2B function contributes to diabetes by altering the dynamic biosynthesis of insulin. Thus, an important avenue of future research should investigate the molecular mechanisms by which mutations in essential translation factors such as the *EIF2B* genes confer tissue-specific defects. Going forward, it will be informative to investigate the ISR in the context of additional *EIF2B* mutations. It may reveal a possible relationship between the degree to which the ISR is impacted and the phenotypic severity of a VWM-associated *EIF2B* mutation.

6.3 | Genetic diseases of *PPP1R15B* (CReP)

Mutations in *PPP1R15B*, the gene that encodes CReP, lead to microcephaly, short stature, and impaired glucose metabolism 2 (MSSGM2, OMIM #616817; Table 4). In 2015, two separate groups identified a homozygous missense variant in *PPP1R15B* (c.1972G>A p.Arg658Cys) that affects the arginine at position 658 of CReP (Abdulkarim et al., 2015; Kernohan et al., 2015) which is well conserved and resides in the C-terminal region of the protein where it interacts with the phosphatase PP1 (Jousse et al., 2003). Individuals with the arginine to cysteine substitution exhibited microcephaly, short stature, and intellectual disability (Abdulkarim et al., 2015; Kernohan et al., 2015). Some patients were also diagnosed with early-onset diabetes (Abdulkarim et al., 2015) or presented decreased brainstem and cord volume and delayed myelination (Kernohan et al., 2015). The missense mutation caused reduced association of CReP with PP1 and impaired dephosphorylation of p-eIF2α (Abdulkarim et al., 2015; Kernohan et al., 2015). Rat beta cells with *PPP1R15B* knockdown displayed decreased total insulin levels and elevated baseline insulin secretion, suggesting that glucose metabolism is dysregulated in the absence of *PPP1R15B* (Abdulkarim et al., 2015). In addition to the missense variant, heterozygous compound mutations in *PPP1R15B* (c.63G>A p.Trp21* and c.674delC p.Pro225LeufsX10) were described in two female siblings and are predicted to generate extremely truncated CReP proteins that lack the PP1-interacting domain. The patients harboring the variants primarily suffered from infantile cirrhosis and, like those expressing the missense variants, also displayed microcephaly, short stature, and intellectual disability. Patient-derived liver cells exhibited increased eIF2α and p-eIF2α protein levels (Mohammad et al., 2016). Thus, elevated p-eIF2α suggests one consequence of *PPP1R15B* alleles associated with these syndromes is either hyper-activation of the ISR and/or chronic activation of the ISR without resolution (Figure 6a,b).

TABLE 4 Disease-associated alleles of *PPP1R15B*

Gene	Alleles	Disease/syndrome	References
PPP1R15B	c.1972G>A (p.Arg658Cys)	Microcephaly, short stature, and intellectual disability	(Abdulkarim et al., 2015; Kernohan et al., 2015)
PPP1R15B	c.63G>A (p.Trp21Ter); c.674delC (p.Pro225LeufsX10)	Infantile cirrhosis, growth impairment, and neurodevelopmental anomalies	(Mohammad et al., 2016)

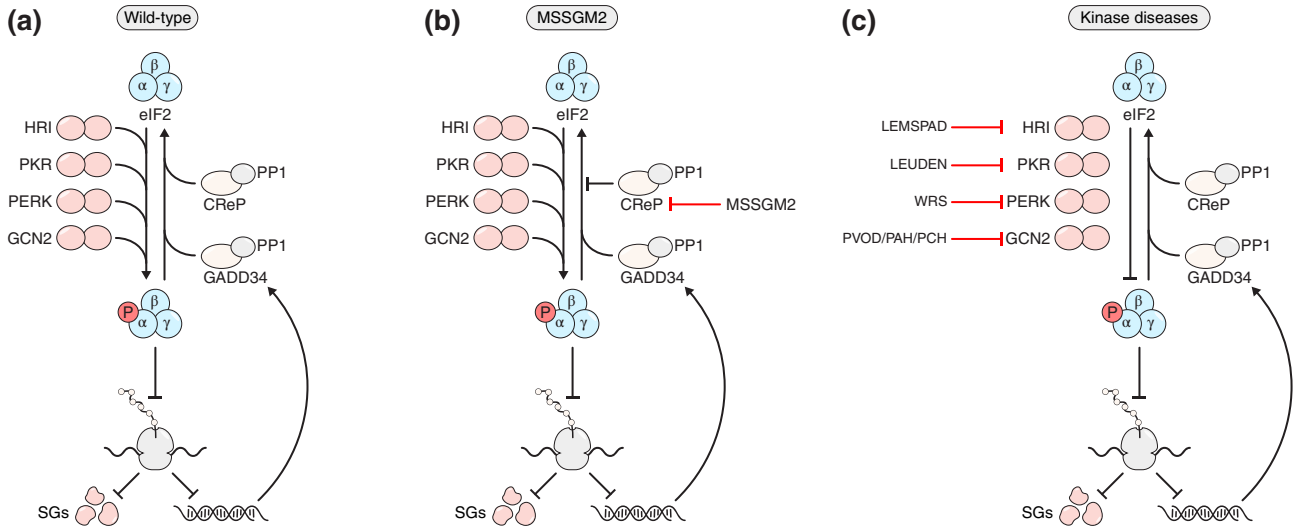

FIGURE 6 Diagram representing the predicted impacts of disease-associated alleles of the CReP gene *PPP1R15B* and the eIF2α kinase genes on the ISR. (a) Wild-type cells undergo a normal ISR upon stress that is resolved with GADD34 induction. (b) Cells harboring mutations in *PPP1R15B* encoding CReP are predicted to reduce p-eIF2α dephosphorylation in unstressed cells. (c) Loss of eIF2α kinase activity due to disease-associated alleles of the genes encoding HRI (*EIF2AK1*), PKR (*EIF2AK2*), PERK (*EIF2AK3*), or GCN2 (*EIF2AK4*) are predicted to reduce eIF2α phosphorylation upon stress

Further studies are required to understand the consequences of the reported *PPP1R15B* mutations on the ISR and the diverse phenotypes associated with these syndromes. It is interesting that the same amino acid substitution in two sets of siblings is associated with diabetes in one set of siblings, but not the other. While this could be due to differences in genetic backgrounds or environments between the families, it will be important to examine the cell-type-specific impacts of *PPP1R15B* alleles to understand how defects in CReP perturb human health and development.

6.4 | Genetic diseases of *EIF2AK1* (HRI)

A heterozygous de novo missense variant in *EIF2AK1*, the gene that encodes HRI, is associated with Leukoencephalopathy, Motor Delay, Spasticity, and Dysarthria (LEMSPAD) syndrome (OMIM #618878; Table 5). The variant (c.1342A>G p.Ile448Val) was identified by trio exome sequencing and is located in the second kinase domain of HRI. The patient, a 6-year-old female, presented numerous symptoms including motor developmental delay, white matter abnormalities, speech disorder, and attention deficit hyperactivity disorder. 293T cells expressing the missense variant displayed reduced baseline levels of p-eIF2α indicating that the mutation is loss of function and compromises the kinase activity of HRI (Mao et al., 2020; Figure 6a,c).

Beyond reduced eIF2α phosphorylation in unstressed conditions, it is unclear how the c.1342A>G p.Ile448Val mutation impacts the ISR. Because the mutation appears to diminish the function of HRI, it is expected that the ISR will fail to be activated in the presence of HRI-responsive stressors such as mitochondrial stress (Guo et al., 2020). It is also likely that mutant cells will be more sensitive to activators of HRI and may exhibit increased cell death. As with other genetic diseases of the translation and ISR machinery, it will be critical to examine the impact of this missense variant on the cell types primarily affected by LEMSPAD syndrome, including central nervous system cells. Additional cases of LEMSPAD syndrome will need to be reported to fully understand the spectrum of symptoms and systems targeted by *EIF2AK1* mutations.

6.5 | Genetic diseases of *EIF2AK2* (PKR)

Heterozygous de novo missense variants in *EIF2AK2*, the gene that encodes PKR, are associated with the neurodevelopmental disorder Leukoencephalopathy, Developmental Delay, and Episodic Neurologic Regression

TABLE 5 Disease-associated alleles of *EIF2AK1*, *EIF2AK2*, *EIF2AK3*, and *EIF2AK4*

Gene	Allele	Disease/ syndrome	References
EIF2AK1	c.1342A>G (p.Ile448Val)	LEMSPAD syndrome	(Mao et al., 2020)
EIF2AK2	c.31A>C (p.Met11Leu); c.398A>T (p.Tyr133Phe); c.973G>A (p.Gly325Ser); c.1382C>G (p.Ser461Cys); c.326C>T (p.Ala109Val); c.325G>T (p.Ala109Ser); c.95A>G (p.Asn32Ser); c.290C>T (p.Ser97Phe)	LEUDEN syndrome	(Mao et al., 2020)
EIF2AK2	c.388G>A (p.Gly130Arg); c.413G>C (p.Gly138Ala); c.95A>C (p.Asn32Thr)	Early-onset generalized dystonia	(Kuipers et al., 2021)
EIF2AK3	c.1745_1746del (p.Ser582fs); c.733dup (p.Arg245fs); c.1149_1150del (p.Asn383fs); c.869_870del (p.Glu290fs); c.536C>A (p.Ser179Ter); c.205G>T (p.Glu69Ter); c.1080T>A (p.Tyr360Ter); c.2731_2732delAG (p.Lys911Glu); c.2980G>A (p.Glu944Lys); c.1474C>T (p.Arg492Ter); c.2081C>G (p.Ser694Ter); c.1A>G (p.Met?); c.568_575dupGATGATGT (p.Val193Metfs10Ter); c.1570_1573 del (Glu524fs); chr2g.88857412G>A (not provided); c.3193C>T (not provided); c.997C>T (p.Gln333Ter); c.1471C>T (p.Arg491Ter); c.679G>T (p.Glu227Ter); c.2589_2593delAAGTT (p.Leu863fs); c.3112_3113insA (p.Phe1038fs); c.2476C>T (p.Arg826Ter); c.2866G>C (p.Gly956Arg); g.53051_53062delinsTG (p.Pro627AspfsTer7); c.2972G>A (p.Ser991Asn); c.3029G>A (p.Gly1010Asp); c.1427-?_2490+ ?del (p.?); c.802_803dup (p.Pro269fs); c.2967T>A (p.Tyr989Ter); c.1647+2T>A (p.?); c.1764-2A>G (p.Tyr589IlefsTer4); c.1764T>G (p.Tyr588Ter); c.1764T>G (p.Tyr588Ter); c.1973G>C (p.Trp658Ser); c.3150+1G>T (IVS16+1G>T); c.1408_14; 09insT (p.Ser470PhefsTer7); c.1596T>A (p.Cys532Ter); c.2776C>T (p.Arg902Ter); c.3038A>G (p.Tyr989Cys); c.1798T>A (Cys532Ter); c.1192C>T (p.Gln398Ter); c.851dupA (p.Pro285AlafsTer3); c.604A>G (p.Glu166Arg); c.137_del GCCTCGGGGCGGCCGCTGCTCCCACCTCAGCGACG (p.Gly46AlafsTer19); c.1978G>A (p.Glu660Lys); c.2812C>T (p.Leu938Phe); c.402delC (p.Gly135fs); Not provided (p.Leu742Ter); c.2758C>T (p.Gln920Ter); c.2758C>T (p.Gln920Ter); Not provided (p.Gly1010Val); Not provided (p.Lys151fs); Not provided (p.Ala160fs); Not provided (p.Trp164Ter); Not provided (p.Ser170fs); Not provided (p.Ser313Ter); Not provided (p.Glu330fs); Not provided (p.Glu332Ter); Not provided (p.Lys346Ter); Not provided (p.Val350fs); Not provided (p.Asn421fs); Not provided (p.Leu426Ter); Not provided (p.Trp431Ter); Not provided (p.Ser470Ter); Not provided (p.Val516fs); Not provided (p.Trp522Ter); Not provided (p.Glu524Ter); Not provided (p.Tyr565Ter); Not provided (p.Arg588Ter); Not provided (p.Ser719fs); Not provided (p.	Wolcott–Rallison syndrome	(Abali et al., 2020; Abbasi et al., 2018; Al-Aama et al., 2018; Alkorta-Aranburu et al., 2014; Al-Sinani et al., 2015; Anne et al., 2021; Asl et al., 2019; Behnam et al., 2013; Davoodi et al., 2018; Fatani, 2019; Feng et al., 2011; Furdela et al., 2016; Gürbüz et al., 2016; Habeb et al., 2015; Huang & Wei, 2019; Jahnavi et al., 2014; Julier & Nicolino, 2010; Mihci et al., 2012; Nayak et al., 2021; Reis et al., 2011; Sang et al., 2011; Sümegi et al., 2020; Triantafyllou et al., 2014; Valamparampil et al., 2019; Welters et al., 2020; H.-J. Zhang et al., 2019)

(Continues)

TABLE 5 (Continued)

Gene	Allele	Disease/ syndrome	References
	Cys769Ter); Not provided (p.Leu863fs); Not provided (p.Arg903Ter); Not provided (p.Glu910fs); Not provided (p.Met1025fs); Not provided (p.Arg1065Ter); Not provided (p.Arg588Gln); Not provided (p.Phe593Leu); Not provided (p.Arg633Trp); Not provided (p.Leu646Pro); Not provided (p.Ile651Thr); Not provided (p.Asn656Lys); Not provided (p.Ser878Pro); Not provided (p.Trp899Cys); Not provided (p.Gly957Glu); Not provided (p.Gly986Arg); Not provided (p.Phe1015Ser); Not provided (p.Leu1058Pro)		
EIF2AK4	c.2609C>T (p.Ala870Val); c.4910C>T (p.Leu1637Pro); c.3633dup (p.His1212ThrfsTer8); c.361G>A (p.Val121Met); c.4318C>T (p.Gln1440Ter); c.4833_4836dup (p.Gln1613LysfsTer10); c.951G>A (p.Trp317Ter); c.2475_2476del (p.Trp826GlufsTer15); c.2968C>T (p.Pro990Ser); c.4593del (p.Ile1533LeufsTer2); c.2403+1G>A (not provided); c.2632-1G>A (not provided); c.2965C>T (p.Arg989Trp); c.4724T>C (p.Leu1575Pro); c.4414_4417del (p.1472_1473del); c.168delT (p.Asn56fs); c.4660-1G>A (not provided); c.594+1G>A (splice mutation); c.986_987del (p.329_329del); c.1739dupA (p.Arg581GlufsTer9); c.2968C>T (p.Pro990Ser); c.354_355del (p.Cys188Tfpfs*7); c.1554-4C>A (p.Cys519AspfsTer17); c.2319+1G>A (splice mutation); c.745C>T (p.Arg249Ter); c.2136_2139dup (p.Ser714HisfsTer21); c.1329del (p.Arg465ValfsTer38); c.3802C>T (p.Gln1268Ter); c.567dup (p.Leu190GlufsTer8); c.3159G>A (p.Lys975_Lys1053del); c.3406C>T (p.Arg1136Ter); c.1754G>A (p.Arg585Gln); c.4065+1G>C (splice mutation); c.1387C>T (p.Arg463Ter); c.3448C>T (p.Arg1150Ter); c.4728+1_4728+13delinsTTCT (splice mutation); c.3244C>T (p.Gln1082Ter); c.1928T>G (p.Leu643Arg); c.560_564del (p.Lys187ArgfsTer9); c.3159G>A (p.Lys975_Lys1053del); c.2857C>T (p.Gln953Ter); c.3576+1G>T (p.?); c.4205dup (p.Ser1403LysfsTer45); c.2458C>T (p.Arg820Ter)	Pulmonary veno-occlusive disease	(Eyries et al., 2014, 2019; Haarman et al., 2020; Montani et al., 2017; H. Yang, Zeng, et al., 2018; X. Zeng, Yang, et al., 2020)
EIF2AK4	c.2403+1G>A (not provided); c.3344C>T (p.Pro1115Leu); c.4724T>C (p.Leu1575Pro); c.170del (p.Asn57fs); c.4460-1G>A (not provided); c.597+1G>A (not provided); c.2965C>T (p.Arg989Trp); c.989_990del (p.Lys330fs); c.1753C>T (p.Arg585Ter); c.1628C>T (p.Pro543Leu); c.4833_4836dup (p.Gln1613fs); c.1804G>A (p.Gly602Arg); c.3460A>T (p.Lys1154Ter); c.4736T>C (p.Leu1579Pro); c.1942A>T (p.Ile648Phe); c.3964C>T (p.Gln1322Ter); c.3884T>G (p.Leu1295Arg); c.3055_3064delCTGACCAACG (p.Leu1019TrpfxTer9); c.4400dupT (p.Glu1468ArgfsTer14); c.1739dupA (p.Arg581GlufsTer9); c.2827A>G (p.Thr943Ala); c.4418_4421delCAGA (p.Thr1473ArgfsTer17); c.145-2A>G	Pulmonary arterial hypertension	(Abou Hassan et al., 2019; Best et al., 2017; Eichstaedt et al., 2016; Hadinnapola et al., 2017; Song et al., 2016; Tenorio et al., 2015; Q. Zeng, Chen, et al., 2020; H.-S. Zhang, Liu, et al., 2019)

TABLE 5 (Continued)

Gene	Allele	Disease/ syndrome	References
	(splice acceptor variant); c.145-2A>G (splice acceptor variant); c.257 +4A>C (splice region variant & intron variant); c.3605A>T (p. His1202Leu); c.1795G>C (p.Gly599Arg); c.3097C>T (p.Gln1033Ter); c.1159_1160delCT (p.Leu387CysfsTer27); c.1795G>C (p.Gly599Arg); c.2446C>T (p.Gln816Ter); c.3218G>T (p.Arg1073Leu); c.1072_1073dupGT (p.Val359Ter); c.44C>T (p.Pro15Leu); c.2516T>C (p. Ile839Thr); c.3722A>G (p.Glu1241Gly); c.4646G>A (p.Arg1549His); c.1660G>T (p.Asp554Tyr); c.3711_3713delGAG (p.Arg1238del); c.3604C>T (p.His1202Tyr); c.220G>A (p.Asp74Asn); c.257+4A>C (splice mutation); c.1672C>T (p.Gln558Ter); c.2320-4T>G (splice mutation); c.933T>A (p.Tyr311Ter); c.4892+1G>T (splice mutation)		
EIF2AK4	c.1466T>C (p.Leu489Pro); c.3344C>T (p.Pro1115Leu)	Pulmonary hypertension	(Gómez et al., 2015)
EIF2AK4	c.1153dupG (p.Val385fs); c.860-1G>A (splice mutation); c.3766C>T (p. Arg1256Ter); c.3438C>T (p.Arg1150Ter)	Pulmonary capillary hemangiomatosis	(Best et al., 2014)

(LEUDEN) syndrome (OMIM #618877; Calame et al., 2021; Mao et al., 2020; Table 5). The primary symptoms of LEUDEN syndrome include developmental delay, white matter alterations, hypomyelination, seizures, and neurologic regression following febrile illness (Calame et al., 2021; Mao et al., 2020). LEUDEN syndrome is rare—there are only 10 reported cases to date corresponding to eight different missense variants that largely localize to the double-stranded RNA binding motifs and kinase domain of PKR (Mao et al., 2020). Three additional homozygous, heterozygous, or heterozygous de novo *EIF2AK2* missense mutations are also linked to early-onset generalized dystonia (Kuipers et al., 2021), a neurological disorder characterized by abnormal movements due to involuntary muscle contractions (Balint et al., 2018). In addition to dystonia, a subset of patients displayed neurological symptoms reminiscent of LEUDEN syndrome such as developmental delay, seizures, and dystonia onset or neurologic regression with febrile illness (Kuipers et al., 2021).

The molecular mechanisms behind a subset of the *EIF2AK2* variants linked to LEUDEN syndrome and early-onset generalized dystonia were examined. LEUDEN syndrome patient-derived fibroblasts, specifically those bearing the c.31A>C p.Met11Leu, c.398A>T p.Tyr133Phe, or c.1382C>G p.Ser461Cys mutation, presented decreased baseline protein levels of p-eIF2α and ATF4. In response to long-term poly(I:C) treatment, the c.31A>C p.Met11Leu and c.398A>T p.Tyr133Phe mutants failed to exhibit the expected increase in eIF2α phosphorylation (Mao et al., 2020). These results indicate that the mutations associated with LEUDEN syndrome are loss of function. In intriguing contrast with LEUDEN syndrome, the early-onset generalized dystonia variants appear to be gain of function. Patient-derived fibroblasts expressing the c.95A>C p.Asn32Thr or c.388G>A p.Gly130Arg variant displayed increased PKR and eIF2α phosphorylation upon extended poly(I:C) treatment compared to wild-type controls (Kuipers et al., 2021). It is interesting to note that p.Met11Leu (LEUDEN syndrome) and p.Asn32Thr (dystonia) both localize to the first double-stranded RNA binding motif of PKR, yet show opposite phenotypes, and p.Tyr133Phe (LEUDEN syndrome) and p.Gly130Arg (dystonia) both localize to the second double-stranded RNA binding motif of PKR, yet show opposite phenotypes.

As a recently described disease with a limited number of reported cases, there are several questions to address regarding LEUDEN syndrome. It will be important to determine how all of the identified *EIF2AK2* variants impact the function of PKR as this will provide the necessary information to determine effective treatment strategies (Figure 6a,c); it could be detrimental to treat a loss-of-function *EIF2AK2* mutation as a gain-of-function mutation, and vice versa. It will also be important to determine how disease-associated *EIF2AK2* variants affect cells of the central nervous system. While the ISR is activated in all cell types, cells of the central nervous system appear to be specifically affected in LEUDEN syndrome and dystonia.

6.6 | Genetic diseases of *EIF2AK3* (PERK)

Wolcott–Rallison syndrome (WRS; OMIM #226980) is a rare autosomal recessive disease that is characterized by neonatal diabetes, multiple epiphyseal dysplasia, and liver disease (Julier & Nicolino, 2010; Wolcott & Rallison, 1972). Patients with WRS may also present with renal dysfunction, intellectual disability, neutropenia, or hypothyroidism. WRS often leads to death at a young age (Julier & Nicolino, 2010). 28 years after its first description, homozygous mutations in *EIF2AK3*, the gene that encodes PERK, were identified as the cause of WRS (Delépine et al., 2000). Since then, numerous *EIF2AK3* mutations have been reported to be associated with WRS (Table 5). The reported mutations span the entire gene, and several are nonsense or frameshift mutations that produce premature stop codons and truncated protein products (Julier & Nicolino, 2010). As the kinase domain of PERK is located in the C-terminal region of the protein, it is often disrupted and is expected to result in loss of function (Figure 6a,c). In support of this, yeast expressing *EIF2AK3* missense variants localized to the kinase domain of PERK exhibit reduced or abolished eIF2 phosphorylation (Senée et al., 2004). Additionally, *Perk*$^{-/-}$ mice recapitulate the characteristic symptoms of WRS including diabetes, skeletal dysplasia, and growth retardation (H. P. Harding et al., 2001; Iida et al., 2007; Y. Li et al., 2003; J. Wei et al., 2008; P. Zhang, McGrath, Li, et al., 2002; W. Zhang et al., 2006). Thus, PERK is particularly important for proper pancreatic function and development.

EIF2AK3 variants are also associated with tauopathies, neurodegenerative diseases characterized by tau protein aggregates. Tau associates with microtubules to promote their stability and assembly and is expressed in neuronal axons (Binder et al., 1985). Genome-wide association studies revealed that the *EIF2AK3* single-nucleotide polymorphism rs7571971 is associated with the tauopathies progressive supranuclear palsy and *APOE* ε4-positive Alzheimer's disease (Höglinger et al., 2011; Q.-Y. Liu et al., 2013). Further, a patient diagnosed with WRS expressing homozygous *EIF2AK3 R902stop* alleles exhibited hallmarks of neurodegeneration including FUS-positive inclusion bodies and tau-containing

neurofibrillary tangles in the frontal cortex, and ubiquitin-positive foci in cells of the cerebellum (Bruch et al., 2015). Tauopathy-associated *EIF2AK3* alleles lead to dysfunctional ISR activity as neurons derived from patients with progressive supranuclear palsy display reduced p-eIF2α and CHOP mRNA levels, and elevated cell death in response to ER stress (Yuan et al., 2018). Thus, PERK alleles are also associated with neurodegenerative tauopathies.

6.7 | Genetic diseases of *EIF2AK4* (GCN2)

Mutations in *EIF2AK4*, the gene that encodes GCN2, are associated with different forms of pulmonary hypertension including pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and pulmonary arterial hypertension (Abou Hassan et al., 2019; Best et al., 2014, 2017; Eichstaedt et al., 2016; Eyries et al., 2014; Hadinnapola et al., 2017; Table 5). The primary symptoms of pulmonary hypertension are progressive exercise dyspnea, dyspnea on bending down, exercise-induced syncope, fatigue, and edema (Hoeper et al., 2017). GCN2 acts through the ISR and ATF4 to promote angiogenesis in response to amino acid restriction (Longchamp et al., 2018). *EIF2AK4* mutations were first linked to pulmonary veno-occlusive disease. In a study of 13 families and 20 patients affected by pulmonary veno-occlusive disease, 22 separate mutations in *EIF2AK4* were identified, largely premature stop codons or indels. The recessive, loss-of-function mutations localized to all regions of the GCN2 protein and were either homozygous or heterozygous compound mutations (Eyries et al., 2014). Next, a genomic analysis of two brothers affected by pulmonary capillary hemangiomatosis and two unrelated individuals with sporadic pulmonary capillary hemangiomatosis uncovered multiple loss-of-function *EIF2AK4* mutations. The homozygous or heterozygous compound mutations identified were autosomal recessive (Best et al., 2014). More recently, mutations in *EIF2AK4* have been linked to pulmonary arterial hypertension, albeit less commonly (Abou Hassan et al., 2019; Best et al., 2017; Eichstaedt et al., 2016; Hadinnapola et al., 2017). Pulmonary hypertension-associated *EIF2AK4* mutations are thought to be loss of function and likely prevent sufficient ISR activation (Figure 6a,c). Thus, treatments aimed at stimulating the ISR may be promising for individuals suffering from various forms of pulmonary hypertension.

6.8 | Potential therapies for diseases of the integrated stress response

Mutations in genes that encode key translation or ISR factors lead to an array of afflictions. With the exception of diseases caused by mutations in *EIF2AK4*, several manifest as neurodevelopmental disorders with endocrine system defects. Collectively, many systems are affected including the reproductive, skeletal, and circulatory systems, in addition to the nervous and endocrine systems. Because of the severity and pleiotropy of the phenotypes associated with such diseases, it is critical to identify effective therapies. One potential treatment is the small molecule called ISRIB (integrated stress response inhibitor), an ISR inhibitor that binds to and activates the eIF2 GEF eIF2B by promoting its assembly (Sekine et al., 2015; Sidrauski et al., 2013, 2015; Tsai et al., 2018; Zyryanova et al., 2018). ISRIB has been shown to rescue cognitive deficits in the Ts65Dn mouse model of Down syndrome which displays elevated p-eIF2α levels in the brain due to PKR activation (P. J. Zhu et al., 2019). In the context of MEHMO syndrome, ISRIB treatment improved many of the deficiencies exhibited by patient-derived iPSCs expressing an *EIF2S3* frameshift mutation. Consistent with ISR inhibition, ISRIB increased global translation and decreased the expression of ATF4, CHOP, and GADD34 in frameshift mutants. ISRIB also rescued ternary complex levels and enhanced the differentiation of MEHMO patient-derived iPSCs into neurons (Young-Baird et al., 2020).

Although creating therapies to combat VWM will be particularly challenging due to the abundance of causative mutations and the vast spectrum of symptom severity, ISRIB and a similar eIF2B activator have shown tremendous promise. ISRIB has been demonstrated to recover mutant eIF2B complex stability and GEF activity (Wong et al., 2018), normalize translation suppression and the expression of ISR targets (Abbink et al., 2019; Moon & Parker, 2018a), and enhance VWM mouse motor skills (Abbink et al., 2019). Similar results have also been obtained with 2BAct, a recently described eIF2B activator, also in a mouse model of VWM (Wong et al., 2019). Alternatively, inhibitors of specific eIF2α kinases may hold therapeutic promise for genetic diseases of the ISR. For example, PERK inhibitor I also rescues translation suppression defects in VWM patient cell lines upon ER stress (Axten et al., 2012; Moon & Parker, 2018a). However, these compounds can exhibit toxicity precluding their therapeutic use (Halliday et al., 2015). ISRIB may also prove to be an effective treatment for the diseases caused by mutations in the CReP-encoding gene *PPP1R15B* as it is predicted that p-eIF2α levels would be elevated, leading to chronic ISR activity.

Diseases caused by mutations in the genes that encode the ISR kinases are generally predicted to be loss of function. For instance, the *EIF2AK1* (HRI) mutation associated with LEMSPAD syndrome and *EIF2AK2* (PKR) mutations associated with LEUDEN syndrome causes decreased p-eIF2α levels, likely impairing ISR activity. Thus, LEMSPAD and LEUDEN syndrome patients may benefit from treatments that increase ISR activity like guanabenz (Pakos-Zebrucka et al., 2016; Tsaytler et al., 2011) or its derivative Sephin1 (Das et al., 2015; Pakos-Zebrucka et al., 2016), GADD34 inhibitors that were demonstrated to extend eIF2α phosphorylation and ATF4 expression as well as delay translation recovery upon stress in HeLa cells (Das et al., 2015; Tsaytler et al., 2011). Alternatively, the CReP inhibitor nelfinavir, originally a treatment for HIV, effectively induced the ISR in HeLa cells as determined by increased p-eIF2α and ATF4 levels in the absence of stress (De Gassart et al., 2016; Pakos-Zebrucka et al., 2016). The p-eIF2α dephosphorylation inhibitor salubrinal similarly activates the ISR—rat pheochromocytoma cells exhibited eIF2α phosphorylation and expression of GADD34 and CHOP upon treatment with salubrinal (Boyce et al., 2005; Pakos-Zebrucka et al., 2016). Similarly, loss-of-function mutations in *EIF2AK3* (PERK) and *EIF2AK4* (GCN2) associated with WRS and pulmonary hypertension, respectively, are also predicted to diminish ISR activity. Chemicals such as Sephin1, guanabenz, nelfinavir, or salubrinal may represent viable therapies. In contrast, *EIF2AK2* mutations associated with early-onset generalized dystonia are gain of function and likely hyperactivate the ISR. Thus, it is imperative to choose a treatment that will decrease ISR activity, such as the PKR inhibitor C16 which blocks PKR autophosphorylation (Jammi et al., 2003; Pakos-Zebrucka et al., 2016) and reduced p-eIF2α levels in mouse macrophages (Fritzlar et al., 2019).

7 | CONCLUSION

The continuous discovery of genetic disorders associated with mutant alleles of ISR factors suggests an important role in the dynamic regulation of translation in human health and development. We highlight three research areas of particular importance for future work. First, the role of the ISR in promoting the development, regeneration, and function of the nervous system must be elucidated. Human genetic diseases including VWM, LEUDEN syndrome, and WRS are associated with neuropsychological, neurodegenerative, and neurodevelopmental phenotypes, emphasizing the importance of precise regulation of the ISR in neuronal biology and health, as does recent works suggesting that targeting the ISR with small molecules such as ISRIB rescues deficits in cognitive function, myelination, and prion-mediated neurodegeneration (reviewed in Kapur et al., 2017; Moon et al., 2018). Evaluating the precise mechanisms by which ISR factors regulate neuronal health and genetic disease holds promise for uncovering novel therapeutic strategies for a wide range of neurodevelopmental and neurodegenerative conditions.

Second, in addition to its important role in human development, the impact of ISR dysregulation in aging must be determined. Altered RNP granule dynamics may contribute to aging, as stress granule- and P-body-like aggregates accumulate with age in *C. elegans* (Lechler et al., 2017; Rieckher et al., 2018). Cognitive defects associated with aging can be ameliorated by targeting the ISR with ISRIB in a mouse model (Krukowski et al., 2020). Additionally, suppressing the ISR can extend lifespan and improve memory and learning in model organisms. Furthermore, alleles of the *EIF2AK3*, *EIF2AK4*, *EIF2S2*, and *EIF2B2* homologs increased longevity in *C. elegans*, implicating the ISR in lifespan (Derisbourg et al., 2021). Thus, an important outstanding research area is determining the molecular mechanisms the ISR contributes to organismic longevity.

A third important area of research will be to determine how defects in essential ISR genes cause cell- and tissue-type specific effects. The majority of the genes that encode components of the ISR are essential, suggesting that these factors are vital for all cell types. Yet, the diverse array of phenotypes ranging from pulmonary arterial hypertension to progressive white matter loss associated with mutations in eIF2α kinases implies there may be (1) cell-type-specific genes that are induced by the ISR, (2) differential stoichiometry of ISR factors among cell types, or (3) certain cell types that rely on the precise regulation of translation in unstressed or stressed conditions due to their morphological or functional roles. A large body of work has uncovered the major players in the ISR pathway that mediate rapid changes in mRNA regulation at the transcriptional and translational levels to facilitate cell survival during stress. Uncovering the molecular mechanisms by which the ISR is activated and dysregulated in specific tissues will unlock future therapeutic strategies for a wide range of human diseases.

Dysregulation of the ISR is implicated in many other disease states including neurodegeneration and cancer and intersects with innate immune pathways. The ISR is constitutively activated in several neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's disease and ALS (reviewed in Costa-Mattioli & Walter, 2020; Moon et al., 2018; Pakos-Zebrucka et al., 2016), and inhibition of the ISR by genetic or chemical means such as

PPP1R15A (GADD34) overexpression or the PERK inhibitor GSK2606414 have been demonstrated to counteract neurodegeneration in fly and mouse models (Celardo et al., 2016; Moreno et al., 2012; Radford et al., 2015). Abnormal ISR activity has also been linked to cancer (Costa-Mattioli & Walter, 2020). For example, both oncogene-induced PERK activation and loss of PKR function promote tumorigenesis (Barber et al., 1995; Bobrovnikova-Marjon et al., 2010; Donzé et al., 1995; Hart et al., 2012; Koromilas et al., 1992; E. F. Meurs et al., 1993; Nagy et al., 2013). Finally, the ISR plays an important role in immunity (Costa-Mattioli & Walter, 2020). PKR activates the ISR to shut down global translation upon viral infection to prevent viral protein translation (Eiermann et al., 2020), and ISR induction is required for the activation of nuclear factor kappa B (NF-kB), a family of transcription factors that drive the expression of pro-inflammatory genes (Deng et al., 2004). Furthermore, HRI is required to produce pro-inflammatory cytokines upon bacterial infection via phosphorylation of eIF2α and activation of the ISR (Abdel-Nour et al., 2019). Therefore, understanding the mechanisms and outcomes of ISR activation holds promise for developing new therapeutic intervention strategies for a wide spectrum of human diseases.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Alyssa English: Conceptualization (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Katelyn Green:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Stephanie Moon:** Conceptualization (lead); funding acquisition (lead); supervision (lead); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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FURTHER READING

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