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Ribosomal readthrough strategies for customized correction of premature termination codon mutations in skin proteins

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Abstract

The ribosome is a ribonucleoprotein complex that translates messenger RNA (mRNA) sequences into polypeptide chains. Ribosome biogenesis is a highly complex process with a pivotal role in many cellular processes, including proliferation, differentiation, apoptosis, development, and malignant transformation. Nonsense mutation introduces premature termination codons (PTCs), resulting in early termination of translation and synthesis of truncated proteins. Readthrough therapy aims to enhance suppression and consequently restore the production of full-length proteins. This approach has yielded considerable success over the years and has shown promising outcomes in many disorders associated with nonsense mutations; however, applying this approach to treat skin diseases remains challenging. This review summarizes current investigations on nonsense suppression strategies pertaining to epidermolysis bullosa. We focus on aminoglycosides that induce PTC readthrough, the small molecule PTC124 (ataluren), and inhibitors of nonsense-mediated mRNA decay. We also examine some emerging compounds that target the translational machinery and may become relevant for future nonsense mutation suppression therapy.

Key words: nannocystin A, eEF1A inhibition, translation elongation, ribosome stalling, anticancer macrocycles

Introduction

The ribosome serves as the primary molecular machine for the translation process. The ribonucleoprotein complex is highly conserved across all domains of life. In bacteria, the ribosomal structure comprises a 30S small subunit (21 ribosomal proteins and 16S ribosomal RNA [rRNA]) and a 50S large subunit (34 ribosomal proteins; 5S and 23S rRNAs) (Aleksashin et al. 2019; Orelle et al. 2015). In eukaryotic cells, the ribosome consists of a 40S small subunit (33 ribosomal proteins and 18S rRNA) and a 60S large subunit (49 ribosomal proteins; 5S, 5.8S, and 28S rRNAs) (Figure 1). Translation in both prokaryotes and eukaryotes is initiatedwhen the small subunit recognizes the AUG start codon on the messenger RNA (mRNA) (Missiakas et al. 1993; Sacerdot et al. 1982). The decoding of genetic code is highly accurate, with reported error rates ranging from 10^{-7} to 10^{-4}, depending on the type of mismatch (Garofalo et al. 2019; Joshi et al. 2019; Kramer et al. 2010; Manickam et al. 2014). Translation is terminated when one of the stop codons (UAA, UGA, or UAG) is introduced at the end of the open reading frame by release factors – RF1 and

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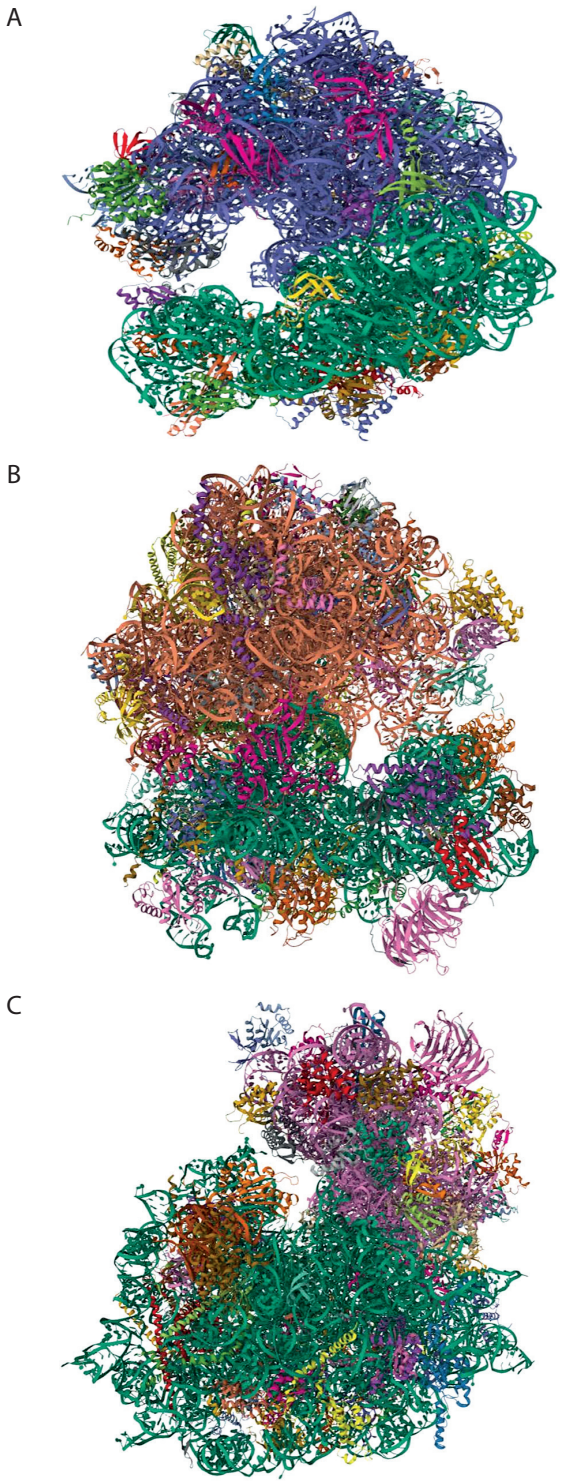

Figure 1. Ribosome construction in (**A**) bacteria (*Escherichia coli*, pdb_00004ybb), (**B**) lower eukaryote (*Saccharomyces cerevisiae*, pdb_00004v88), and (**C**) higher eukaryote (human, pdb_00008qoi)

RF2 in bacteria or eRF1 in eukaryotes. Although basal readthrough frequency is low (< 10^{-4} per stop codon) (Dabrowski et al. 2018; Schueren and Thoms 2016), it can increase up to 0.1–0.3 when stimulated by various factors such as structural elements or trans factors (Eswarappa et al. 2014; Firth et al. 2011; Namy et al. 2001). Failure to maintain decoding fidelity results in ribosomal frameshifting (+ or – direction) at low frequency (< 10^{-5}). Programmed ribosomal frameshifting refers to the mRNA signals that promote frameshifting, with an efficiency of 0.5–80% depending on the organism and sequence (Advani and Dinman 2016; Atkins et al. 2016; Caliskan et al. 2015).

Mutations that occur during translation arise from premature stop codon recognition (e.g., through base substitutions), creating premature termination codons (PTCs) that trigger nonsense-mediated decay (NMD) (Mendell and Dietz 2001). NMD degrades PTC-containing mRNAs to prevent truncated proteins, even in the context of low basal readthrough (Baradaran-Heravi et al. 2017). Approximately 11% of human genetic diseases involve NMD (Ng et al. 2018; Temaj et al. 2023). Several rare skin diseases are caused by or associated with stop codon mutations, including epidermolysis bullosa (EB), pseudoxanthoma elasticum, ichthyosis, Nagashima-type palmoplantar keratosis, Hailey-Hailey disease, xeroderma pigmentosum, hypotrichosis simplex of the scalp (Ardıçlı et al. 2019; Li et al. 2019; Peltz et al. 2013), and neurofibromatosis (Li et al. 2016).

In dermatology, both systemic and readthrough compounds suppress NMD in skin diseases. In the following sections, we focus on EB as a key example and discuss available approaches for nonsense suppression mechanisms in inherited skin conditions.

EB as a model PTC skin disease

EB serves as a useful model for studying nonsense suppression strategies in dermatology because several EB subtypes are associated with PTCs in structural skin genes (Bardhan et al. 2020). Currently, the underlying genetics and natural history of EB are relatively well defined, and initial clinical attempts to utilize pharmacological readthrough strategies have already been reported. In this section, we briefly review EB classification, highlight the burden of PTC mutations in key subtypes, and outline how these genetic insights motivate readthrough-based approaches.

EB is categorized into four major types based on mutation level and protein: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome

(KS), which vary in severity and prevalence (Has et al. 2020). In England and Wales, Petrof et al. (2022) reported 2,594 EB cases (2,361 alive), with a prevalence of 34.8 per million. The estimated subtype-specific prevalence (per million) was 17, 10.7, 1, and 0.3 for EBS, DEB, JEB, and KS, respectively (Petrof et al. 2022).

DEB

DEB is a rare disorder usually present at birth and affects the skin and nails. It includes recessive (RDEB) and dominant (DDEB) forms, with additional clinical subtypes based on phenotype (Pfendner and Lucky 1993).

RDEB is the most severe form of DEB, caused by biallelic mutations in *COL7A1*, which encodes the α1 chain of type VII collagen (C7). C7 assembles into anchoring fibrils that attach the epidermis to the dermis; absence or dysfunction of C7 results in skin fragility, blistering, scarring, morbidity, and mortality (Bardhan et al. 2020; Has et al. 2020). A Chinese cohort study reported RDEB phenotypes linked to the combinations of PTCs and glycine substitutions as well as loss of the ATG start codon, thereby expanding the known *COL7A1* mutation spectrum (Yan et al. 2018). Presently, different therapeutic strategies are being investigated, including protein replacement (Watson et al. 2020), drugs that modulate fibrosis and inflammation (Nyström et al. 2015), mesenchymal stem cell therapy (Lee et al. 2021; Rashidghamat et al. 2020), and bone marrow transplant (Wagner et al. 2010). The most attractive is gene therapy because it allows correction of *COL7A1* in autologous cells. Clinical trials using lentiviruses or retroviruses to transduce *COL7A1* into fibroblasts and keratinocytes has shown restoration of C7 in some patients previously diagnosed to have RDEB (Eichstadt et al. 2019; Lwin et al. 2019; Siprashvili et al. 2016) (NCT02493816; NCT02810951). Genome editing has also been applied in some studies. Hong et al. (2022) used adenine base editors to correct *COL7A1* PTCs or generate bypass mutations. Patient-derived skin equivalents in immunodeficient mice showed restoration of C7 deposition and anchoring fibrils.

Atanasova et al. (2017) found that amlexanox induces *COL7A1* in RDEB fibroblasts/keratinocytes. Antibiotics such as gentamicin restore functional COL7A1 in RDEB cells (Cogan et al. 2014).

Treatment with gentamicin solution significantly alleviated oral wounds. Osipowicz et al. (2021) treated four RDEB patients (genotypes: c.682+1G>A/c.5532+6T>C; c.425A>G homozygote; c.425A>G/c.7904G>A; c.425A> G/c.5884A>C) with 0.3% topical gentamicin and observed better healing of oral wounds and increased C7 expression. Mahajan et al. (2022) reported that 0.1% topical gentamicin strengthens COL7A1 expression, particularly in patients with PTC mutations.

JEB

JEB is caused by biallelic mutations in genes encoding for basement membrane anchoring proteins such as COL17A1, laminin 332 [LAMA3, LAMB3, and LAMC2], and integrin α6β4 or α3. Severe generalized JEB is lethal and is associated with PTCs that inhibit laminin 332 expression (Wimmer et al. 2024). Aminoglycosides, particularly gentamicin, promote PTC readthrough in JEB by binding to the decoding center of the eukaryotic ribosome. Previous studies indicate that gentamicin affect the conformation of nucleotides A1755 and A1756 in 18S rRNA in the small ribosomal subunit 40S (Garreau de Loubresse et al. 2014). Efficiency varies according to the stop codon and is higher for UGA than for UAG or UAA (Floquet et al. 2012).

Mutations in LAMB3, encoding β3 laminin 332 subunit, cause approximately 80% of severe JEB cases, and 95% of these alleles contains PTCs (Hammersen et al. 2016; Varki et al. 2006). In LAMB3-null keratinocytes, gentamicin-induced readthrough is reported from 2% to 27%, depending on the mutation and context (Lincoln et al. 2018).

Antibiotics such as gentamicin are shown to induce readthrough of nonsense mutations and to restore full-length protein in different rare genetic diseases. Lincoln et al. (2018) found that gentamicin can induce laminin β3 and restore laminin 332 assembly, secretion, and deposition within the dermal-epidermal junction. According to Kwong et al. (2020), 0.5% gentamicin polish on wounds increased laminin and improved wound closure.

Li et al. (2020) treated RDEB patients (COL7A1: c.426delT/c.2383C>T) with 0.3% gentamicin; their findings supported its use for nonsense mutations.

Gentamicin can reduce blistering and promote healing; however, its systemic administration is limited by nephrotoxicity and ototoxicity. Renal function and hearing should be monitored before and after treatment, and prolonged therapy should be avoided (Friesen et al. 2018).

Table 1. The aminoglycosides drugs which can bind by ribosome to suppress translation

Drugs	Place of interaction in ribosome	References
G418	40S Small subunit	(Bidou et al. 2012; Prokhorova et al. 2017)
Gentamicin	40S Small subunit	(Bidou et al. 2012; Jana et al. 2023; Prokhorova et al. 2017)
Paromomycin	40S Small subunit	(Bidou et al. 2012; Hu et al. 2022)
NB54	40S Small subunit	(Bidou et al. 2012; Goldmann et al. 2012; Rowe et al. 2011)
NB74	40S Small subunit	(Bidou et al. 2012; Nudelman et al. 2010; Temaj et al. 2022a)
NB84	40S Small subunit	(Bidou et al. 2012; Nudelman et al. 2010; Temaj et al. 2022a)

Pharmacological PTC readthrough: aminoglycosides and non-aminoglycosides

Several small molecules have been shown to promote translational readthrough at PTCs, thereby restoring partial or full-length protein expression. Among these, classical aminoglycoside antibiotics and newer non-aminoglycoside translational readthrough-inducing drugs have been most extensively studied. In this section, we review the pharmacology, mechanisms, and safety profiles of these compounds and relate them to the EB-specific examples discussed above (Table 1).

Aminoglycosides and non-aminoglycosides

Aminoglycosides are a class of antibiotics that inhibit protein synthesis by binding to the ribosome (Mingeot-Leclercq et al. 1999). The first aminoglycoside was isolated from *Streptomyces griseus* and was introduced for clinical use in 1944. Later, several other aminoglycoside members were discovered, including neomycin (from *S. fradiae*), kanamycin (from *S. kanamyceticus*), gentamicin (from *Micromonospora purpurea*), netilmicin (from *Sisomicin*), tobramycin (from *Streptoalloteichus tenebrarius*), and amikacin (derived from kanamycin) (Krause et al. 2016). The mechanism of action of aminoglycosides involves targeting the bacterial ribosome, specifically the small subunit 30S. Several studies using X-ray and nuclear magnetic resonance have shown that aminoglycosides such as neomycin bind to the aminoacyl-transfer RNA (tRNA) recognition A site and simultaneously interact with 16S rRNA. Moreover, using X-ray, other aminoglycosides such as streptomycin, spectinomycin, and paromomycin have been shown to interact with 16S rRNA at the A-site (Webster and Shepherd 2022). Although aminoglycosides have strong ability to act as a PTC readthrough therapy, this ability depends on the type of stop codon (UAG = ambre; UAA = ochre; UGA = opal (or umbre) (Schueren and Thoms 2016). Aminoglycosides play a critical role in eukaryotic translation mechanism and promotes readthrough of PTC. Aminoglycosides such as paromomycin, G418, gentamicin, and TC007 have been studied as potential therapeutic candidates (Bidou et al. 2012; Jana et al. 2023; Prokhorova et al. 2017). Prokhorova et al. (2017) showed that aminoglycosides bind to several sites on 80S ribosome and can affect both subunits.

Many studies have demonstrated that different aminoglycosides have varying nonsense mutation suppression activity (McHugh et al. 2020). For example, gentamicin is a mixture of compounds with varying effects. Among all gentamicin group compounds, Gentamicin B1 is the main group with nonsense mutation suppressor activity (Baradaran-Heravi et al. 2017; Pasmooij 2018). Other aminoglycosides such as G418, gentamicin, paromomycin, NB54 (Bidou et al. 2012; Goldmann et al. 2012; Rowe et al. 2011), NB74, and NB84 (Bidou et al. 2012; Nudelman et al. 2010; Temaj et al. 2022a) can bind to 40S small subunit. Consequently, Gentamicin B1 is more efficient when treating rare diseases such as Duchenne muscular dystrophy and baker muscular dystrophy (Bidou et al. 2012; Temaj et al. 2022b; Temaj and Gashi 2025). Despite these promising findings, aminoglycosides have limited clinical applications because of their side effects, ototoxicity, and nephrotoxicity (Dabrowski et al. 2018). This has prompted the designing of new derivatives with reduced toxicity but enhanced readthrough activity.

The best known non-aminoglycoside is Ataluren (PTC124) (Table 2) (Huang et al. 2022), which promotes

Table 2. The non-aminoglycosides drugs which can bind by ribosome to suppress translation

Drugs	Place of interaction in ribosome	References
Ataluren	TC, aa-tRNA.eEF1A.GTP (near-cognate ternary complex)	(Huang et al. 2022)but only one TRID (translation readthrough inducing drug
Negamycin	18S rNAs; 25S rRNAs	(Bidou et al. 2012; Welch et al. 2007; Temaj et al. 2022a)
RTC13	18S rNAs; 25S rRNAs	(Temaj et al. 2022a; Bidou et al. 2012; Du et al. 2009)
RTC14	18S rNAs; 25S rRNAs	(Bidou et al. 2012; Du et al. 2009)
Tylosin	18S rNAs; 25S rRNAs	(Bidou et al. 2012; Priuska and Schacht 1995)

nonsense mutation suppression (Hainrichson et al. 2008). Ataluren has chemical structure comparable to that of aminoglycosides, but it lacks toxic effects (Hirawat et al. 2007). Ataluren is tolerable when administered orally in low doses, and it can achieve a higher level of readthrough (Campofelice et al. 2019). It is approved in Phase II clinical trials (NCT00592540; NCT00803205) for over 10 years and phase 3 clinical traits (NCT01826487) for 5 years. It also exhibits good effects against several other diseases (Roy et al. 2016). Other non-aminoglycosides (negamycin [Bidou et al. 2012; Welch et al. 2007; Temaj et al. 2022a], RTC13/14 [Temaj et al. 2022a; Bidou et al. 2012; Du et al. 2009], and tylosin [Bidou et al. 2012; Priuska and Schacht 1995]) bind to 18S/25S rRNAs (Bidou et al. 2012; Ohguchi et al. 2018).

Development therapy based on aminoglycosides

EB is associated with high morbidity and high cost of care (~$300,000/year per U.S. patient) (Pearson 1962; Uitto et al. 2016). Because there is no curative treatment for RDEB, the development of new therapeutic options is receiving increasing interest. Current management approaches focus on suppression of inflammation and fibrosis and restoration of C7 for healing. Topical agents such as botulin-rich triterpenes/allantoin show better performance compared to standard care (Uitto et al. 2018). Approximately 30% of RDEB cases harbor nonsense mutations. Many aminoglycosides can induce PTC readthrough and are currently being investigated in clinical trials; they can also restore collagen 7. Gentamicin is an aminoglycoside currently in phase I/II clinical trials (NCT02698735). Aminoglycosides have negative side effects and have very limited treatment scope. In the long term, gene editing methods such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) – CRISPR-associated protein 9 (Cas9) and Transcription Activator-Like Effector Nucleases (TALENs) are likely to play a major role, as they can directly rectify the underlying mutations and offer the prospect of durable benefit (Chamorro et al. 2016).

Development therapy based on translation inhibition/translation-targeting small molecules: conceptual relevance for nonsense mutation suppression

Many newly developed small molecules have been shown to be very effective in treating different inherited

Table 3. Drugs which inhibit translation initiation

Drugs	Inhibition of translation initiation	References
Zotatifin	eIF4A	(Gerson-Gurwitz et al. 2021)
Honoharringtonine	eIF4A	(Gandhi et al. 2014)
Cycloheximide	28S rRNA	(Schneider-Poetsch et al. 2010)
Rocaglamide A	eIF4A1	(Iwasaki et al. 2016)
Silvestrol	eIF4A	(Cencic et al. 2009)
Pateamine A	eIF4A	(Low et al. 2005; Bordeleau et al. 2005)
Hippuristanol	eIF4A	(Lindqvist et al. 2008)
Ribavirin	eIF4E	(Kentsis et al. 2004)
Lactam	eIF4E	(Fan and Sharp 2021)

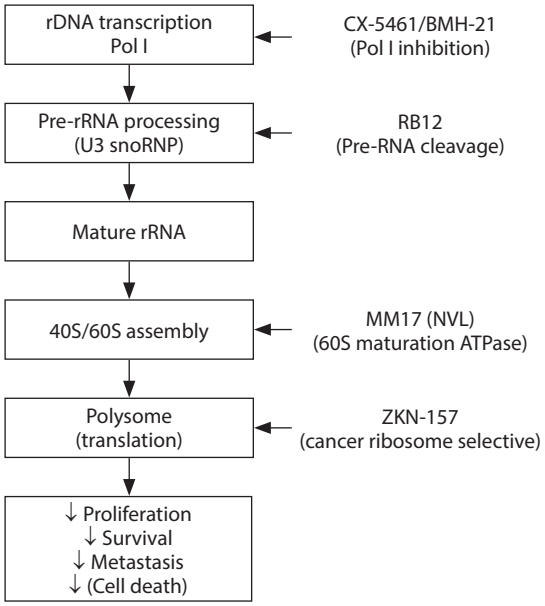

Figure 2. A linear flowchart depicting the ribosome biogenesis pathways and modulation by different small-molecule inhibitors targeting cancer cells. The processing begins with ribosomal DNA transcription (Pol I), which is inhibited by compound CX-5461/BMH-21 (Pol I inhibitors blocking ribosomal RNA [rRNA] synthesis), flowing downward to pre-rRNA processing (U3 snoRNP), which is blocked by compound RBI2 (pre-rRNA cleavage inhibitor). It then progresses to maturation of the rRNA, followed by assembly of the 40S/60S subunits (noted as an adenosine triphosphatase [ATPase]-dependent step), which is inhibited by MM17 nuclear VCP-like protein (targeting 60S maturation ATPase), finally leading to the formation of polysomes (translation), which is disrupted by compounds such as ZKN-157 (cancer ribosome-selective inhibitor)

diseases (Table 3). Several of these compounds act at the translation initiation level. For example, zotatifin and homoharringtonine (HHT) bind to eIF4A and function as selective inhibitors of translation initiation in eukaryotic cells. Cycloheximide, a classical universal inhibitor of protein synthesis, binds to a conserved site (C3993) on 28S rRNA and blocks elongation in eukaryotic cells; moreover, at higher doses, it also affects prokaryotes (Schneider-Poetsch et al. 2010). Rocaglamide A (RocA), isolated from *Aglaia elliptifolia* in 1982, exhibits antiproliferative activity against leukemia cells. RocA can block eIF4A1 and inhibit the scanning process from 43S ribosome subunit (Iwasaki et al. 2016). Silvestrol, isolated from *Aglaia foveolata*, can induce dimerization of eIF4A and RNA to inhibit protein translation (Cencic et al. 2009). Pateamine A (Low et al. 2005; Bordeleau et al. 2005), isolated from marine sponge *Mycale* sp., binds irreversibly to eIF4A and blocks the assembly of the initiation complex (Bordeleau et al. 2005; Low et al. 2005). Hippuristanol (Lindqvist et al. 2008), a polyoxygenated sterol from the coral species *Isis hippuris*, inhibits eIF4A RNA binding, helicase activity, and RNA-dependent adenosine triphosphatase (ATPase) activity (Lindqvist et al. 2008).

eIF4E is another factor with a critical role in cap-dependent translation (Pelletier and Sonenberg 2019). Ribavirin (Kentsis et al. 2004), which can bind to eIF4E, shows robust and broad-spectrum antiviral activity. Ribavirin acts as an m7G-cap mimetic, competing for direct binding to eIF4E to disrupt the eIF4E-m7G mRNA cap complex at low concentration (micromolar) (Kentsis et al. 2004). Lactam is another small molecule that bind to eIF4E and inhibits translation initiation (Fan and Sharp 2021).

Several molecules also target translation elongation. The main targets are eukaryotic elongation factor 1A (eEF1A) and the ribosome. eEF1A is a highly conserved molecule with a molecular weight of approximately 40 kDa guanosine triphosphatase and plays an essential role in protein synthesis (Abbas et al. 2015). It binds to aminoacyl-tRNAs and forms the complex eEF1A-guanosine triphosphate(GTP)-aa-tRNA (Maruyama et al. 2019). This complex interacts with the interface between the 40S and 60S ribosomal subunits and delivers the aa-tRNA to the A-site according to the codon sequence on the mRNA. After correct codon–anticodon pairing, GTP is hydrolyzed, eEF1A dissociates from the ribosome, and it is recycled for the next round

Table 4. Drugs which inhibit translation elongation

Drugs	Inhibition of translation elongation	References
Plitidepsin	eukaryotic translation elongation factor 1A (eEF1A)	(Varona et al. 2022)
Nannocystein	eEF1A	(Hou et al. 2021; Sánchez-Murcia et al. 2017)
Ternatins	eEF1A-GTP-aa-tRNA	(Carelli et al. 2015)
Narsiclasine	eEF1A	(Van Goietsenoven et al. 2010)

of peptide bond formation (Condeelis 1995). Plitidepsin (Table 4) (Varona et al. 2022), also known as dehydrodidemnin B, was first identified by Rinehart et al. (1981); it is isolated from Caribbean marine tunicate (sea squirt) and shows antiproliferative activity (Urdiales et al. 1996). Plitidepsin also exhibits antiviral activity against both DNA and RNA viruses (Peters et al. 1995). Nannocystin is a 21-membered compound isolated from *Nanocystis* sp. by Sanofi labs (Hoffmann et al. 2015). Nannocystin A (Hou et al. 2021; Sánchez-Murcia et al. 2017) inhibits fungal growth and shows antiproliferative activity in various cancers at nanomolar concentrations by binding to eEF1A (Sánchez-Murcia et al. 2017). Ternatins (Carelli et al. 2015) are a group of polyacylated anthocyanins, first isolated from the mushroom species *Cloriolis versicolor*. Mechanistic studies revealed that ternatins can bind to the ternary complex eEF1A-GTP-aa-tRNA and to pitfall EF1A on the ribosome (Carelli et al. 2015). Narciclasine (Van Goietsenoven et al. 2010) can bind to eEF1A and exhibit antiproliferative effects on cancer cells such as melanoma cells (Van Goietsenoven et al. 2010).

Small molecules with the ability to modulate the ribosome

In the last decade, many small molecules that can bind directly to the ribosome have been identified, and several of these molecules show selectivity for the eukaryotic ribosome (Gilles et al. 2020). Harringtonines (HTs) are pentacyclic alkaloid natural products isolated from *Cephalotaxus harringtonii*. The main members are cephaloxtaxine, HT, isoharringtonine, deoxypharrintonine, and HHT; all these compounds contain a pentacyclic core but differ in terms of the C3 ester. HT blocks the elongation step in the translation process by preventing binding of aa-tRNA to the A-site of the small subunit ribosome (Ingolia et al. 2011). HHT binds to the 60S large ribosome subunit in the peptidyl transferase center in a pocket comprising mostly rRNA. In this manner came to hydrogen bond interaction between the methoxy and C-3 ester carbonyl (Mikolajczak et al. 1977). HHT shows broad antiviral activity by decreasing the eIF4E level (Dong et al. 2018). Mycalamides are a group of marine natural products present within archaeal systems. Mycalamide A can bind to the ribosome at the E-site (Gürel et al. 2009). These and other ribosome-targeting compounds highlight the diversity of small molecules capable of modulating ribosomal function. Figure 2 summarizes the different sites on the ribosome that are targeted by the small-molecule inhibitors discussed in this review.

Conclusions

Currently, there is no pharmacological therapy approved for treating rare skin diseases caused by PTCs, including EB. The studies summarized in this review show that amino acid insertion at a PTC, rather than being a random event, depends on a combination of factors such as the compound used, the identity of the stop codon, the local sequence context, and the behavior of the translational machinery. These observations support the idea that drug-induced readthrough can, at least in a subset of patients, restore clinically relevant levels of the full-length protein. Aminoglycosides and non-aminoglycoside agents such as ataluren have shown that the expression of truncated proteins can be recovered *in vitro* and *in vivo*. Ataluren appears to be relatively well tolerated at optimized low doses, whereas aminoglycosides such as gentamicin have limited applicability due to dose-dependent nephrotoxicity and ototoxicity. Hence, aminoglycosides are generally restricted to short-term or local administration. In future, continued efforts to refine readthrough agents, understand genotype-specific responses, and combine pharmacological approaches with gene-based therapies are crucial to translate these concepts into durable clinical benefits for patients.

Author contributions

Y.G. and A.T. contributed to the study design and data collection. H.N. and S.B. contributed to data analysis and interpretation. D.S. and I.B. contributed to data collection and assembly. S.X. contributed to the research concept and design. N.N. and M.X. critically revised the manuscript and approved the final version. G.T. contributed to the research concept and design, data collection and assembly, data analysis and interpretation, manuscript preparation, critical revision of the manuscript, and final approval of the article. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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