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Emerging roles of ribosome translation in stem cells and stem cell therapy - a review

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Abstract
Stem cells differ from other somatic cells in that they possess self-renewal and differentiation potential, which endows them with unique characteristics, and have great therapeutic potential. Studies have shown that the self-renewal and differentiation potential of stem cells is regulated by ribosomes during protein synthesis. In this review, we discuss the translation regulation mechanisms and ribosome biogenesis in stem cells. Protein translation levels and ribosome biogenesis change dynamically during the development and differentiation of stem cells, and hierarchical translational regulation promotes stem cell differentiation. We also demonstrate that mitochondrial protein translation plays an important role in the regulation of stem cell fate. Ribosomes not only mediate the self-renewal and differentiation of stem cells through protein synthesis. They are also a key target for stem cell therapy. Understanding the mechanism of ribosome regulation in stem cells will allow better control of stem cells for their application.

Keywords Stem cell, Ribosome, Protein translation, Mitochondrial ribosomal protein translation, Stem cell therapy

Introduction

The ability to self-renew and differentiate are the two major characteristics shared by stem cells. Embryonic stem cells (ESCs) are pluripotent stem cells derived from early embryos capable of unlimited self-replication and differentiation into various cell types. Adult stem cells are multipotent cells in mature tissues and organs that self-renew and differentiate into specific cell types for tissue repair and regeneration. Stem cells have notable prospects for application in regenerative medicine.

The self-renewal and differentiation potential of stem cells is controlled by complex genetic programs such as chromatin remodeling, mRNA transcription, processing, and stability [1, 2]. The Notch [3], Wnt [4, 5], Bmi-1 [6], Sonic hedgehog [7–9], and c-Met [10] pathways regulate the self-renewal characteristics of stem cells, and an imbalance in these pathways can lead to dysfunction. Currently, transcription is assumed to be the primary mechanism that regulates the self-renewal and differentiation of most stem cells [11, 12]. Transcription factors play crucial roles in determining stem cell fate, and protein levels in stem cells are mainly regulated at the transcriptional level [12]. Several studies have shown that ribosomal translation is important in protein synthesis [13]. In ESCs and many adult stem cells, precise regulation of ribosomal translation processes is crucial for self-renewal and differentiation. Translation regulation

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also plays a fundamental role in maintaining stem cell homeostasis and responding to environmental cues, such as differentiation signals or tissue damage, through rapid reprogramming [1].

Stem cell therapy is an innovative form of regenerative medicine that has attracted widespread attention from the global medical community. It is used to treat cancers and heart, neurodegenerative, and other diseases and can be a powerful tool for clinical medical research. By studying the biological characteristics and differentiation mechanisms of stem cells, we can better understand the processes of disease occurrence and development. This will aid in creating innovative treatment methods through technologies such as stem cell modification and gene editing to achieve better application of stem cell therapy. In this review, we discuss how the regulatory mechanism of ribosomal translation is involved in the self-renewal and differentiation potential of stem cells and its potential application in stem cell therapy.

Emerging roles of ribosome translation in stem cells

Stem cells in the quiescent phase have lower levels of protein synthesis

An increasing number of studies have shown that both embryonic and somatic stem cells are characterized by low rates of global protein synthesis [14]. Schwanhausser et al. demonstrated that translation significantly contributes to protein abundance [13]. In 2004, Raman microspectroscopy was used to monitor biochemical markers during the in vitro differentiation of mouse embryonic stem cells (mESCs), and the ratio of RNA-to-protein peak areas was used as an indicator of mRNA translation. The level of nontranslated mRNA is high in undifferentiated mESCs, and as mESCs begin to differentiate, their mRNA translation increases [15]. Investigation of the different states of protein synthesis during self-renewal and differentiation of mESCs has shown that protein synthesis is parsimonious during the mESC self-renewal phase. Most mRNAs are insufficiently bound to ribosomes in undifferentiated mESCs; therefore, these cells lack polyribosomes and have low polyribosome content. During mESC differentiation into embryoid bodies (EBs), an "anabolic switch" is triggered, resulting in significant increases in global mRNA levels, ribosome transcript loading, polyribosome content, and global protein synthesis [16]. Polysome profiling experiments have demonstrated a global rise in the overall translational activity of early mESCs during differentiation. Additionally, ribosomal protein (RP) expression is moderately upregulated during the early stages of mESC differentiation, indicating an increase in the number of RPs involved in ribosome assembly and protein synthesis. This is consistent with the results of the polyribosome analysis, further confirming that protein translation probably plays an essential role in ESC differentiation [17]. Analysis of mESCs using ribosome profiling revealed more than a thousand significant translation pause sites that may function as key regulatory locations [17]. Therefore, we postulate that this may also be a reason for the low level of stem cell translation and that it may stem from the inherent necessity of totipotent cells to sustain their undifferentiated state and exhibit high plasticity. Human embryonic stem cells (hESCs) have lower levels of global protein translation and limited p70 ribosomal protein S6 kinase (p70 S6K) activation than their differentiated progenies. Easley et al. used drugs such as ether amine or purinomycin to block global translation activity in hESCs for 24–36 h, resulting in cell death. This suggests that the low level of translation observed in hESCs is essential for the survival of pluripotent stem cells [18]. Translation levels were measured during the induction of hESCs into forebrain neurons and they showed that the mechanistic target of the rapamycin complex 1 (mTORC1) signaling pathway drives a high level of translation of translation-related genes during the differentiation of hESCs into neural progenitor cells (NPCs). By comparing the regulation of translation across three distinct cell types, hESCs, NPCs, and early neuronal cultured cells, the translation levels of many RPs were found to increase during differentiation from NPCs to early neuronal cells, suggesting that mTORC1 signaling may enhance translation efficiency during early neuronal development, thereby affecting downstream biological processes related to ribosomal protein synthesis [19]. This implies that altered translation efficiency is a primary mechanism involved in the early stages of hESCs differentiation.

Signer et al. used a fluorogenic assay with O-propargyl-puromycin to measure protein synthesis in hematopoietic stem cells (HSCs), which are typical somatic stem cells. The protein synthesis rate of HSCs in vivo is significantly lower than that of most other hematopoietic progenitor cells. In the resting phase (G_0/G_1) or mitotic phase ($S/G_2/M$), the induced proliferation of HSCs shows a lower rate of protein synthesis than that of hematopoietic progenitor cells [20]. Jarzebowski et al. used the RiboPuromycylation method to determine that mouse hematopoietic stem cells (mHSCs) have lower puromycin uptake and, therefore, lower protein translation activity than other more mature progenitor populations. They also confirmed that to maintain their self-renewal ability and long-term function, mHSCs might have conserved mechanisms for metabolic activities, such as reducing the rate of protein synthesis [21]. Robert et al. also found that the rate of protein synthesis in HSCs was lower than that in other hematopoietic progenitor cells and had no significant correlation with the cell cycle, total RNA, or mRNA content [22]. Other adult stem cells, including

neural [23], skeletal muscle [24], hair follicles [25], and *Drosophila* germline stem cells(GSCs) [26], have been shown to have a lower rate of protein synthesis than progenitors in the same tissue. When genetic changes increase the rate of protein synthesis in these stem cells, their numbers are depleted, suggesting that reduced protein synthesis rates may be a common feature of a wide range of adult stem cell populations. Skin stem cells synthesize fewer proteins than their immediate progenitors in vivo under normal conditions or when forced to proliferate. Therefore, an increased translation rate correlates with lineage commitment and differentiation processes in stem cells rather than their proliferation [25]. Similarly, stem and progenitor cells within tumors synthesize fewer proteins than committed progeny that differentiate and specialize into multiple tumor cell types [25]. Previous studies have revealed the importance of post-transcriptional translational regulation in differentiating neural stem cells (NSCs) into neurons. Protein synthesis is very low in quiescent ventricle-contacting NSCs; however, it is significantly increased in active NSCs, decreases upon reaching late neuroblasts through neural progenitor cells and early neuroblasts, and decreases gradually in mature neurons [27]. Single-cell transcriptomics has further confirmed that dormant NSCs have an extremely low rate of protein synthesis and undergo an intermediate phase after activation, during which the cell increases its protein synthesis machinery [23]. Muscle stem cells, also known as satellite cells, maintain low levels of protein synthesis by phosphorylating eukaryotic initiation factor 2 subunit alpha (eIF2α), essential for maintaining their resting state and ability to self-renew [24]. The balance between the self-renewal and differentiation of GSCs is susceptible to changes in ribosome biosynthesis and the rate of intracellular protein synthesis. In the *Drosophila* GSC system, the transition between self-renewal and differentiation depends on ribosome biogenesis (the process of ribosome synthesis) and the regulation of protein synthesis. To achieve morphological and functional transformation of stem cells into specific cell types during differentiation, cells must synthesize a series of proteins appropriate for their new roles, resulting in a significant increase in global protein synthesis [26]. The overall protein translation rate in *Drosophila* intestinal stem cells (ISCs) is exceptionally high. Upon differentiation into daughter cells, they immediately become post-mitotic yet do not exhibit the usual increase in translation rate. The high translation rate in ISCs represents a unique biological phenomenon that may reflect the specialized requirements of these cells for maintaining intestinal function, which is not commonly observed in other types of stem cells [28–30].

Functional considerations of parsimonious protein translation in stem cells

Although ESCs contain numerous free ribosomes, they primarily exist as monosomes or subunits, indicating that the translation potential of ribosomes is not completely utilized [16]. After observing that stem cells maintain low levels of protein translation, researchers have further analyzed and investigated the underlying reasons for this parsimonious protein translation in stem cells. A prevailing perspective suggests that low protein synthesis rates minimize unnecessary wear and tear of stem cells, thereby playing a crucial role in maintaining their self-renewal and longevity. This translation mode may restrict the expression of specific genes to ensure that stem cells do not initiate specific differentiation pathways prematurely or incorrectly while maintaining stability during self-renewal. Before ESCs differentiate into specific cell types, inappropriate protein expression is prevented by restricting their translational activity [16]. In HSCs and other types of somatic stem cells, the low rate of protein synthesis helps maintain metabolic homeostasis. Reduced protein synthesis limits protein misfolding and negatively affects stem cell function. Therefore, reducing protein synthesis in somatic cells may help maintain a stable state and prolong cell survival [20]. Stem and progenitor cells generally need to maintain low metabolic and protein expression levels to retain their undifferentiated state and potential proliferative capacity [25]. Low levels of protein synthesis within stem cells help prevent excessive cell division and deplete their ability to self-renew, thereby ensuring the long-term stability and regenerative potential of the population [27]. However, one study showed that mouse blastocyst-derived ESCs treated with the translation inhibitor cycloheximide showed little increase in their in vitro lifespan, whereas inhibition of the mTOR signaling pathway significantly increased their lifespan [31]. There may be other reasons for the parsimonious protein translation in stem cells. Some researchers have speculated that maintaining low protein levels in stem cells facilitates rapid proteomic remodeling during differentiation. High proteasomal activity is a recognized contributor to the function and viability of ESCs and induced pluripotent stem cells [32, 33]. In summary, parsimonious translation and hierarchical translational regulation in ESCs may play essential roles in quality control during pluripotency and differentiation. The key question is whether the differences in ribosomal protein translation during stem cell self-renewal and differentiation are consequences of stem cell fate decisions or act as active regulators that influence these processes.

Mechanism to maintain low protein levels in quiescent stem cells

mTORC1 signaling pathway mediates selective translational regulation in quiescent stem cells

hESCs strictly regulate mTORC1-p70 S6K-mediated low-protein translation to maintain pluripotency. In undifferentiated hESCs, the activity of the mTORC1 signaling pathway was relatively low compared to that in the differentiated progeny cells. hESCs showed lower p70 S6K activity and higher TSC1 (Tuberous sclerosis 1)-TSC2-mTORC1 inhibitory complex, which may reflect the molecular basis of their ability to maintain an undifferentiated state and self-renew. Moderate inhibition of this signaling pathway in stem cells helps maintain pluripotency and an undifferentiated state. If the activity of the mTORC1 signaling pathway increases, the pluripotency of stem cells can be altered, possibly leading to a bias in the stem cell differentiation of specific lineages. Activation of p70 S6K expression or enhanced mTORC1 activity promotes hESCs differentiation [18]. mTORC1 also regulates the delicate balance between self-renewal and differentiation during NSC differentiation by regulating downstream molecules such as eukaryotic initiation factor 4E binding protein (4E-BP) and S6K1/S6K2. The overactive mTORC1 signaling pathway affects the self-renewal ability of NSCs by inhibiting the action of the 4E-BP2 protein and activating cap-dependent translation mechanisms. Hartman et al. showed that a genetic reduction in mTORC1 activity prevents cell differentiation in neonatal mouse NSCs, thereby reducing lineage and neuronal generation. Activation of the translation inhibitor 4E-BP1 produces a similar effect, preventing NSC differentiation induced by mTORC1 overactivation and promoting self-renewal [34]. The TOR signaling pathway also plays a vital role in the maintenance and differentiation of GSCs. The Tel2-Tti1-TOR complex in *Drosophila melanogaster* promotes the expression of ribosome assembly factors and is essential for germline differentiation [35]. HSCs contain more non-phosphorylated 4E-BP1 and 4E-BP2, which inhibit translation initiation and decrease protein synthesis [22]. Knockout of 4E-BP1 and 4E-BP2 significantly increased global protein synthesis in HSCs and impaired their ability to reconstitute activity, revealing a mechanism for maintaining HSCs function by inhibiting protein synthesis. HSCs lacking 4E-BP1 and 4E-BP2 are less able to maintain their numbers and produce blood cells in the long term than normal stem cells [22]. Morita et al. [36] and Tahmasebi et al. [37] showed that activated 4E-BP selectively inhibits the translation of certain types of mRNA. The lower protein translation rate in HSCs is not primarily mediated by reduced ribosome supply but by the upregulation of translation inhibition mechanisms and the influence of specific tRNA-derived small RNAs [21]. This indicates that not all mRNA translations are affected to the same degree; however, those closely related to specific physiological or pathological processes are significantly inhibited. This selective translational regulatory mechanism is important for cells to adapt to different environmental conditions, maintain normal physiological functions, and cope with disease.

Regulation of low translation activity of stem cells by translation initiation

One study used mouse skeletal muscle stem cells as a model to identify a universal mechanism of translation inhibition that maintains the resting state of stem cells by phosphorylation of eIF2α (p-eIF2α) at serine 51. The activity of phosphorylated eIF2α was inhibited, thereby reducing the formation of the translation initiation complex and the overall protein synthesis rate. p-eIF2α partly ensures a robust translational silencing of accumulating mRNA, which is necessary to prevent the activation of muscle stem cells. In addition, p-eIF2α-dependent mRNA translation regulated by upstream open reading frames also constitutes a molecular feature of stem cell characterization. Zismanov et al. revealed that the absence of phosphorylation on eIF2α induced satellite cells to transition from a quiescent state to an activated myogenic program. Drug-induced inhibition of eIF2α dephosphorylation enhanced the self-renewal and regeneration ability of skeletal muscle stem cells [24]. One mechanism regulating protein synthesis in HSCs involves the control of 4E-BP phosphorylation. Phosphorylated 4E-BP binds to eukaryotic initiation factor 4E (eIF4E) and prevents it from participating in mRNA translation [20, 38]. The transcription factor Yin Yang 2 (YY2) plays a crucial regulatory role in self-renewal and lineage differentiation of mESCs (Fig. 1). The expression of YY2 is inhibited by the translation of 4E-BP and influenced by polypyrimidine tract binding protein 1 (PTBP1)-mediated splicing. In mESCs lacking *Eif4ebp1* and *Eif4ebp2* (4E-BP1 and 4E-BP2), the expression of mESC markers such as octamer-binding protein 4 (Oct4) and sex-determining region Y-box 2 (SOX2) is inhibited. Moderate increases or decreases in Oct4 or SOX2 protein levels can impair the self-renewal of ESCs and trigger their differentiation. YY2 affects cell self-renewal and differentiation by controlling key pluripotent factors, such as Oct4 and estrogen-related receptor-β (Esrrb), and its overexpression guides mESCs to differentiate into cardiovascular lineages [39]. The methyltransferase-like (METTL) 16 protein interacts with eIF3α/β and participates in the translation initiation mechanism in the cytoplasm, thereby regulating the translation initiation of mRNA. METTL16-mediated translation initiation maintains tumor plasticity and cell characteristics in liver cancer stem cells (CSCs) [40].

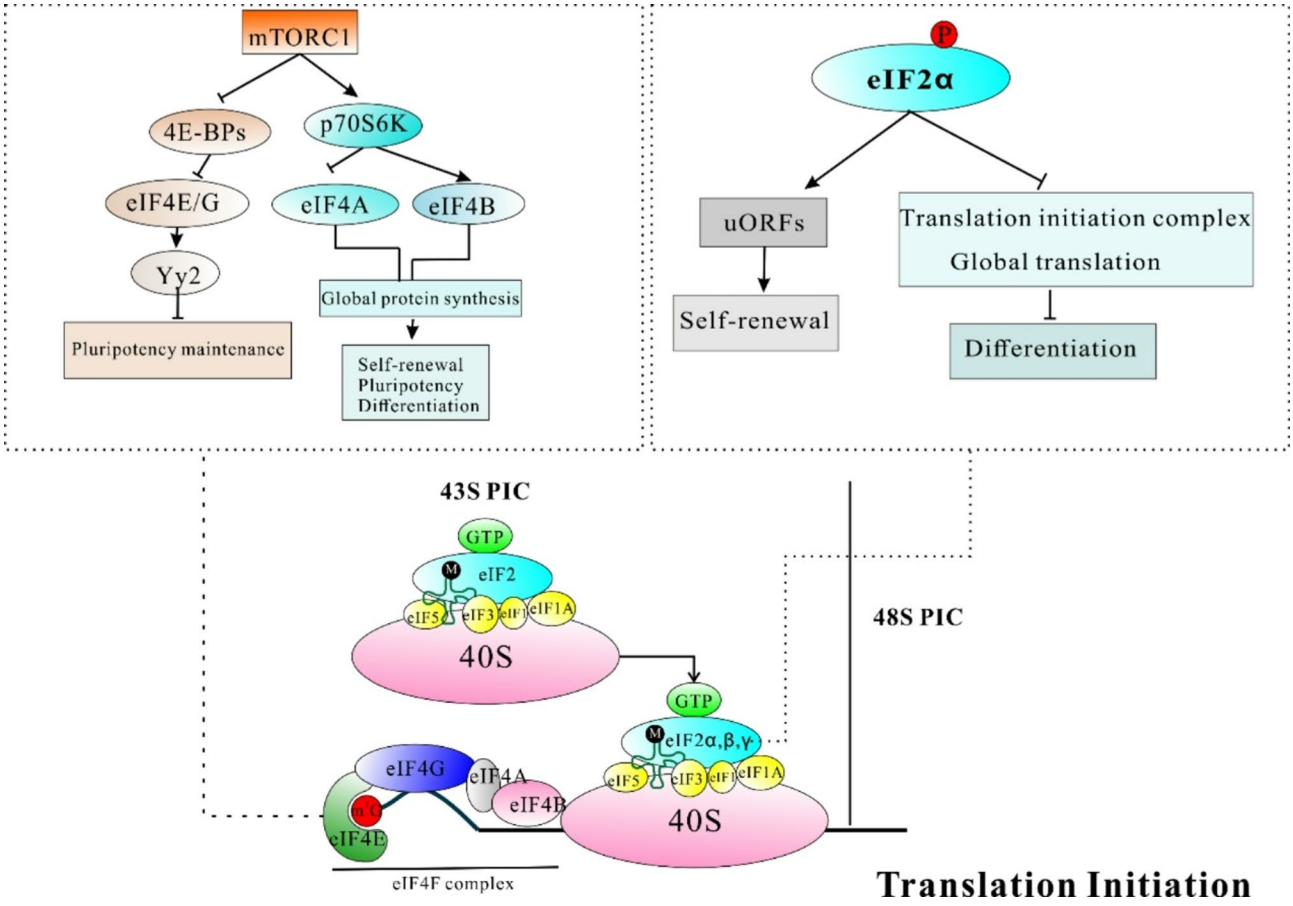

Fig. 1 Regulation of low translation activity of stem cells by translation initiation. At the beginning of eukaryotic translation, eIF1, eIF1A, eIF2-tRNAiMet-GTP, eIF3, eIF5 and 40 S ribosomal subunits formed 43 S preinitiation complex (PIC). The mRNA cap binding complex eIF4F recruits 43 S PIC to mRNA to form 48 S PIC. The 48 S PIC scans mRNA until it encounters an AUG initiation codon, at which point GTP is hydrolyzed on eIF2 to form a complete 80 S ribosome, and the translation of the open reading frame begins. mTORC1 controls protein synthesis through two key targets: 4E-BP and p70S6K. mTORC1 phosphorylates 4E-BP, phosphorylated 4E-BP binds to eIF4E and prevents it from participating in mRNA translation. The expression of YY2 is inhibited by the translation of 4E-BP. YY2 affects self-renewal and differentiation of stem cell. Phosphorylation of p70S6K activates multiple effectors, facilitating global translation via downstream eIF4B and eIF4A. Global translation inhibition is caused by eIF2α phosphorylation while promoting selective translation of mRNA, thereby promoting self-renewal via upstream open reading frames (uORFs). The activity of phosphorylated eIF2α was inhibited, thereby reducing the formation of the translation initiation complex and inhibition of differentiation. eIF1, eukaryotic initiation factor 1; eIF1A, eukaryotic initiation factor 1 A subunit; eIF3, eukaryotic initiation factor 3; eIF4A, eukaryotic initiation factor 4 A; eIF4B, eukaryotic initiation factor 4B; eIF5, eukaryotic initiation factor 5; mTORC1, mechanistic target of rapamycin complex 1; 4E-BP, eukaryotic initiation factor 4E binding protein; p70S6K, p70 ribosomal protein S6 kinase; YY2, Yin Yang 2

Stem cells are characterized by high ribosomal biogenesis despite low levels of protein synthesis

Functional analysis of low protein synthesis but high ribosomal biogenesis in stem cells

Stem cells maintain their characteristics by balancing two seemingly contradictory conditions: low translational activity and high ribosome biogenesis. The number of ribosomes in stem cells does not directly correspond to the translation rate, and maintaining a large ribosomal reserve enables a rapid increase in translation speed when needed. Stem cells require high ribosome levels to maintain their differentiation potential [14]. The ribosome concentration model suggests that changes in intracellular ribosome concentrations can affect global and mRNA-specific translational control [41]. Sufficient quantity and activity of ribosomes are fundamental to ensure that stem cells effectively perform their functions, including self-renewal and differentiation. Impairment of ribosome biogenesis can lead to defects in stem cell function, affect tissue regeneration and repair, and may even contribute to the onset of diseases such as cancer. Ribosomal biogenesis is a highly regulated process, particularly in stem cells. Because stem cells require low metabolic activity to preserve their undifferentiated state, they must respond swiftly to differentiation signals for proliferation and differentiation. This indicated that ribosome biogenesis can adapt promptly and precisely to these alterations. The regulation of ribosome biogenesis

ensures that cells can appropriately adjust the rate of protein synthesis in response to various conditions such as growth, differentiation, and stress. As these cells differentiate into proliferative precursor cells, the activities of both processes are altered to varying degrees. This shift reflects different protein requirements across cellular states, with translation programs and ribosome biogenesis regulating stem cell function and fate. The fate of stem cells depends on the balance between these processes, and an imbalance can lead to an age-related decline in stem cell function. Age-associated alterations include aberrant up- or downregulation of rRNA and protein synthesis, which can result in enhanced proliferative capacity, diminished differentiation potential in stem cells, or induction of a senescent state [42]. However, this raises the question of maintaining the balance between low protein translation levels and high ribosome biogenesis in stem cells. How does high ribosomal biogenesis ensure that ribosomes do not undergo protein synthesis? These issues require further investigation.

Regulation of ribosome biogenesis in stem cells

Ribosomal DNA (rDNA) transcription in stem cells The nucleolus plays a crucial role in maintaining the stem cell characteristics of ESCs. In ESCs, the nucleolus is hyperactive and characterized by the absence of silenced rRNA genes and heightened ribosome biogenesis. As ESCs exit their pluripotent state, a portion of these rRNA genes is epigenetically silenced, reducing ribosome biogenesis [43]. Ribosome biogenesis is a highly coordinated multistep process that primarily occurs in the nucleolus, with additional stages occurring in the nucleoplasm and cytoplasm. This process requires three RNA polymerases (RNA Pols), 75 small nucleolar RNAs (snoRNAs), and more than 250 ribosome biogenesis factors (RBFs) for regulation and completion (Fig. 2). rDNA transcription refers to the process in the cell nucleus where the rDNA sequence is transcribed into RNA by RNA Pols. In stem cells, rDNA transcription is precisely regulated by modulating its rate, which influences stem cell fate. The high rDNA transcription rate is a characteristic feature of stem cells. Stem cells, such as mESCs, exhibit higher rDNA transcription rates than differentiated cells. Despite their high nucleolar activity and elevated rDNA transcription compared to differentiated cells, ESCs exhibit lower protein synthesis rates. This suggests that a high transcriptional level of rDNA supports self-renewal, whereas the inhibition of rRNA synthesis can promote differentiation [43]. The transcription of rDNA in GSCs is performed by a complex regulated by RNA Polymerase I (Pol I), which comprises three components: TATA Box Binding Protein (TBP)-Associated Factor (TAF1B), TATA box-binding protein-associated factor, RNA polymerase I subunit C (TAF1C), and an under-specified polymerase I cofactor (UDD). UDD stimulates rRNA transcription in GSCs and is highly expressed in GSCs compared to their immediate descendant cells. The proliferative capacity of GSCs decreased when the transcriptional activity of Pol I was inhibited. Stem cells undergo asymmetric cell division, resulting in an unequal distribution of certain components between the two daughter cells. For instance, wicked UDD and the U3 small nucleolar RNA complex wicked (Wcd) tend to be retained to a greater extent in stem cells following division than in their differentiating progeny [44, 45]. This indicates that normal Pol I activity is essential for stem cells to maintain their self-renewal abilities. Elevated transcriptional activity of Pol I leads to a reduction in stem cell progeny and delays cyst differentiation in vivo [44]. High rates of rDNA transcription in stem cells are potentially regulated by specific transcription factors such as Oct4 and upstream binding factor 1(UBF1) and are associated with the maintenance of pluripotency. Interference with ribosome biogenesis through the suppression of rRNA maturation or transcription is accompanied by a decrease in the expression of stem cell pluripotency-related mRNAs, such as Oct4, Sox2, and Nanog [46–48]. Stem cells and their differentiated progenies possess distinct physiological functions and metabolic requirements; therefore, their transcriptional regulation varies. Reducing rRNA transcription levels triggers cell differentiation in Drosophila germline stem cells and mouse hematopoietic progenitor cells [44, 49]. This effect is not achieved through global translation inhibition or cell cycle arrest [49, 50]. During the differentiation of ESCs into endoderm cells, the transcription rate of rRNA decreases by approximately 50% within a few hours owing to the disassociation of the transcription factor UBF1 from the rRNA gene promoter. The synthesis of rRNA decreases, and translation processes can become imbalanced in aged stem cells, which may contribute to a decline in stem cell functionality [51, 52].

Hypertranscription of rRNA genes is not directly associated with increased protein synthesis; instead, it may contribute to preserving free ribosomes that respond to differentiation signals. A high rate of rDNA transcription is crucial for stem cell survival. ESCs and GSCs exhibit higher levels of rRNA expression than their differentiated counterparts. In contrast, HSCs display reduced levels of pre-rRNA and mature 18 S and 28 S rRNAs, which are significantly lower than those found in differentiated hematopoietic progenitor cells [49]. Differences in rDNA transcription rates among various stem cell populations may be attributed to multiple factors, including the cell proliferation state, microenvironment, in vitro growth conditions, and cell-specific molecular regulatory networks. In mouse HSCs, the silencing of rDNA genes and downregulation of ribosome biogenesis

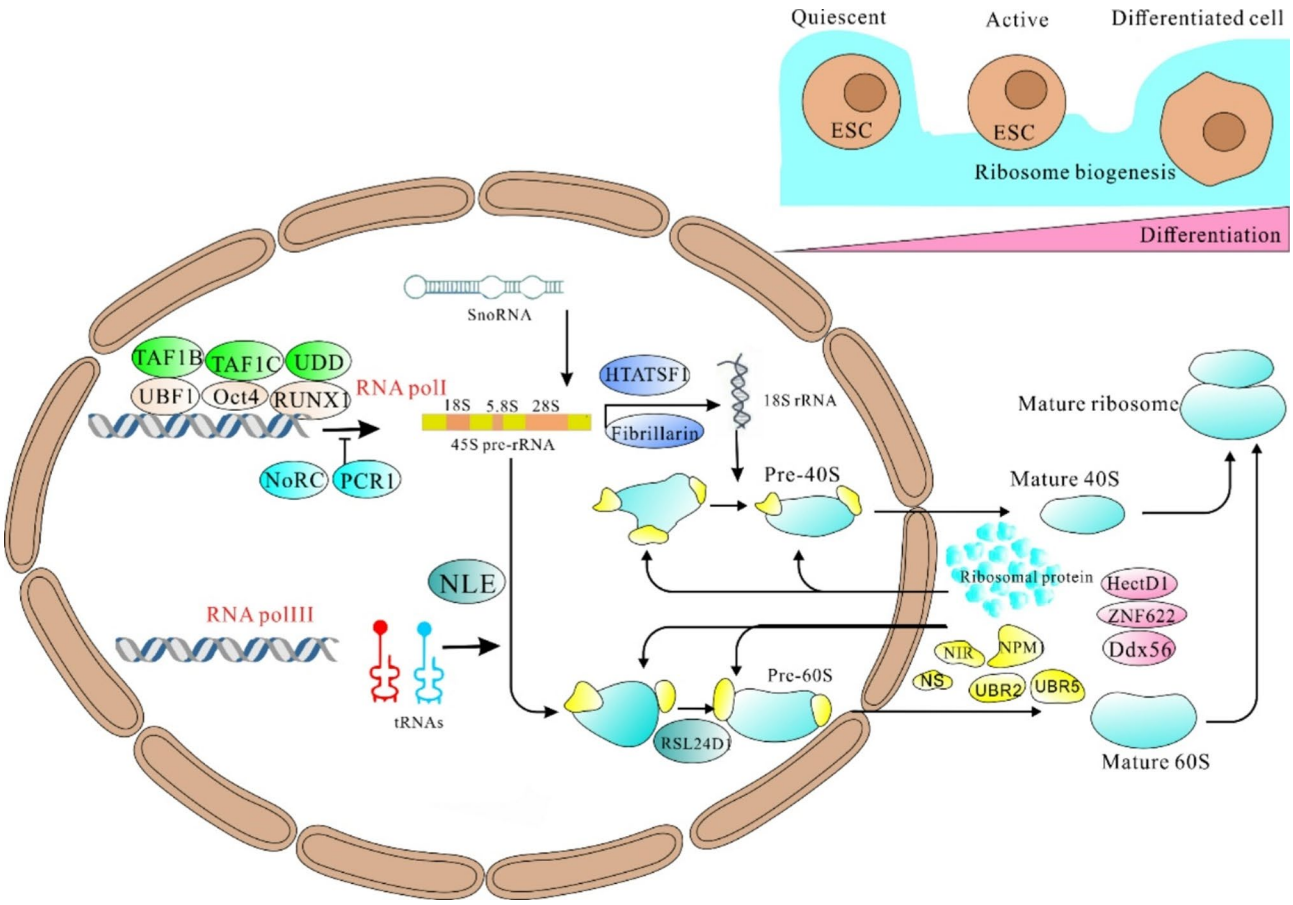

Fig. 2 Ribosome biogenesis in stem cells. Top: Ribosome biogenesis tend to be higher in stem cells than in differentiated cells. During differentiation, ribosome biogenesis is tightly and dynamically regulated in accordance with the needs of the differentiating cell. Ribosome biogenesis activity is high in the quiescent state but decline in active stem cell, which are primed to differentiate. Ribosome biogenesis begins in the nucleolar with the synthesis of pre-ribosomal RNA (pre-RNAs) via RNA polymerase I (Pol I) and RNA Pol III. Ribosome biogenesis factors and ribosomal proteins were transported into the nucleus and nucleolus, pre-rRNA was folded and processed, and ribosomal proteins were added to form pre-40 S and pre-60 S particles. These particles are assembled into mature ribosomes in the cytoplasm with the help of ribosome assembly factors. Multiple factors support ribosome biogenesis in stem cells by promoting transcription of rRNA through RNA Pol I, including TAF1B, TAF1C, UDD, UBF1, Oct4 and RUNX1. Polycomb repressive complex 1(PRC1) and nucleosome remodeling complex (NoRC) repress transcription of rDNA. NLE is involved in pre- rRNA processing and maturation. RNA Pol II transcribes mRNA of ribosomal proteins and ribosome biogenesis factors, as well as small nucleolar RNAs (snoRNAs). snoRNAs play a role in rRNA processing. rRNA methyltransferase fibrillarin, RNA-binding protein HIV-Tat-specific factor 1(HTATSF1) involved in 18 S rRNA processing. Ribosomal L24 domain containing 1(RSL24D1) is highly expressed in stem cells and involved in the maturation of the 60 S large ribosomal subunit. Ribosome biogenesis factors: NIR, NPM1, NS, UBR2, UBR5. Ribosome assembly factors: HectD1, ZNF622, Ddx56. UDD, under-specified polymerase I cofactor; UBF1, upstream binding factor 1; Oct4, Octamer-binding protein 4; RUNX1, runt-related transcription factor; NLE, notchless. NIR, neural inhibitory nuclear factor; NPM1, Nucleophosmin; NS, nucleostemin; UBR2, ubiquitin protein ligase E3 component n-recognin 2; UBR5, ubiquitin-protein ligase E3 component n-recognin 5; HectD1, HECT domain E3 ubiquitin ligase 1; ZNF622, zinc finger protein 622; Ddx 56, DEAD-Box Helicase 56

are associated with stem cell aging. Despite the high rate of rDNA transcription in stem cells, a lower level of protein translation was observed, indicating that stem cells maintain their identity by strictly controlling the rate of protein synthesis, independent of rDNA transcription rates. The disparity in rDNA transcription rates between stem cells and differentiated cells is predominantly determined by distinct protein factors that bind to the rDNA loci. When stem cells begin to differentiate into specific cell types, the downregulation of specific phenotypic transcription factors inhibits rDNA activity, thereby reducing rRNA synthesis. Studies have identified 17 pluripotency-associated factors that bind to rDNA sites in mESCs and potentially regulate rRNA synthesis and maintain stem cell pluripotency. Other factors involved in rRNA regulation include histone variants, chromatin regulators, and transcription factors. mESCs express high levels of the histone variant H2A.X, which is abundant in the promoter regions of rDNA and recruits the nucleosome-remodeling complex, a transcriptional repressor factor, thereby inhibiting rDNA transcription [53]. Polycomb repressive complex 1 is a protein complex in which the chromobox (CBX4) protein plays a role by recruiting Kruppel-associated box protein 1 to repress transcription

of rDNA, preventing the accumulation of mature 18 S and 28 S rRNAs [54]. The absence of the CBX4 protein accelerates cellular senescence in mesenchymal stem cells; however, it has minimal impact on the phenotype of ESCs or NSCs.

Hayashi et al. demonstrated that transcription initiation factor I knockdown induces differentiation of HSCs, suggesting that rRNA synthesis is essential for stem cell maintenance [49]. The runt-related transcription factor (RUNX1) directly binds to repetitive sequences within the rDNA promoter region, ensuring appropriate levels of rRNA expression and biosynthesis in HSCs [55]. Mutations in RUNX1 are frequently observed in myelodysplastic syndromes and leukemia. Fibrillarin (Fbl) is a methyltransferase that enhances ribosomal DNA transcription and ribosome biogenesis by methylating immature rRNA and histone H2A. It is highly expressed in mouse mESCs and neuroepithelial-like progenitor cells of the zebrafish midbrain [56]. Watanabe-Susaki et al. revealed that overexpression of Fbl can maintain the pluripotency of stem cells, even in the absence of leukemia inhibitory factor [56].

Stem cell RBFs Despite their lower translational activity compared to differentiated cells, ESCs exhibit higher expression of RBFs and RPs. ESC pluripotency relies on various ribosome biogenesis factors, including the rRNA methyltransferase fibrillarin, the RNA-binding protein HIV-Tat-specific factor 1, and several factors involved in 18 S rRNA processing [46, 56, 57]. This suggests that they must accumulate sufficient ribosomes to accommodate rapid proteomic changes in response to environmental cues and the timely initiation of differentiation programs. Stem cells may globally regulate the expression levels of RBFs or finely tune the stoichiometry of specific RBFs to ensure precision and efficiency of ribosome assembly, thereby adapting to the needs of stem cell function. Single-cell analysis of zebrafish hematopoietic lineages showed upregulation of multiple RBFs, such as nucleostemin (NS), Fbl, Nucleolar protein 5, nucleolar protein 10, nucleolin (NCL), diazaborine resistance gene 1, and nucleolar protein 5 A [58]. Several multifunctional RBFs, such as NS, NCL, Nucleophosmin (NPM1), Fragile X mental retardation protein (FMRP), and the ubiquitin-protein ligase E3 component n-recognin 5 (UBR5), are involved in diverse processes, including the DNA damage response, transcription, RNA transport, and protein degradation, all of which are intricately linked to the regulation of gene expression in stem cells [58]. NS is a prospective RBF expressed in early mouse embryos, ESCs, MSCs, NSCs, HSCs, hematopoietic progenitor cells, and spermatogonia [59–63]. Ribosome biogenesis proteins, ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), and UBR5 play crucial roles in rRNA modification. UBR2 is highly expressed in zebrafish hematopoietic stem cells, whereas UBR5 is highly expressed in human and mouse ESCs. UBR5 interacts with box H/ACA small nucleolar ribonucleoproteins, and its absence affects ribosome maturation in mESCs. UBR5 absence leads to reduced proliferation of ESCs, which are dependent on the p53 pathway [64]. Neural inhibitory nuclear factor (NIR) accumulates in the nucleoli of glioma stem cells, where it interacts with the nuclear proteins NCL and NPM1 to activate rDNA transcription and promote self-renewal and tumor progression. NIR knockdown significantly inhibited the proliferation, self-renewal capacity, and tumor growth of glioma stem cells. Studies have revealed high NIR expression in glioblastoma multiforme (GBM), which is inversely correlated with patient survival rates [65]. RP expression is also tightly regulated in NSCs, HSCs, and ESCs. Fortier et al. [66] revealed that insufficient RP expression can influence ESC differentiation.

Specific RBFs are preferentially expressed and selectively enriched in stem cells. For example, a phosphorylated adaptor for RNA export (PHAX) is an RBF involved in the intracellular transport of small nucleolar ribonucleoproteins whose expression is regulated during the differentiation of hESCs into HSCs [67]. Certain key RBFs are expressed at higher levels in ESCs than in their differentiated progenies and are crucial for maintaining their self-renewal capacity. Ribosomal L24 domain-containing 1(RSL24D1) is highly expressed in stem cells and is involved in the maturation of the 60 S large ribosomal subunit. Loss of RSL24D1 results in reduced assembly of the 60 S subunit, leading to decreased global translation efficiency, particularly affecting the translation of key pluripotency transcription factors and components of the polycomb repressive complex 2. This, in turn, impairs the self-renewal capacity of ESCs; however, it has less impact on differentiation. Downregulation of RSL24D1 leads to a decrease in H3K27me3 modification, which may cause aberrant activation of developmental genes [68]. In human HSCs and common myeloid or granulocyte progenitors, pre-ribosome-associated RBFs and RPs exhibit higher coexpression levels than differentiated monocytes [69]. Rehn et al. have shown that the absence of PTBP1 leads to a condition similar to ribosomopathy. Lack of PTBP1 is associated with decreased self-renewal ability, reduced red blood cell differentiation, and decreased protein synthesis in HSCs. This is because the lack of PTBP1 is related to significant defects in ribosome biosynthesis and selectively reduces the translation of mRNA encoding ribosomal proteins [70]. Upregulation of RBF genes in progenitor cells may be a conserved mechanism. Despite the lack of evidence for the upregulation of global ribosome biogenesis in stem cells, the individual regulation of key RBFs is essential for maintaining stem cell characteristics, including those of adult stem cells and ESCs [71].

This implies that the expression levels of these specific factors are crucial for stem cells to maintain their undifferentiated state and self-renewal capacity.

rRNA modifications and maturation of stem cells The expression levels and post-transcriptional modifications of rRNA play crucial roles in regulating stem cell proliferation, differentiation, and fate. During stem cell differentiation, not only does the expression of rRNA change, but the regulators controlling rRNA maturation, such as the DEAD-box-containing RNA helicase 27 (DDX27) protein, are also altered. For instance, in zebrafish muscle stem cells (MuSCs) and proliferating myoblasts, the DDX27 gene is actively expressed; however, its expression decreases as the cells ultimately differentiate [72]. Studies have shown that the survival and proliferation of adult stem cells such as HSCs, ISCs, and MuSCs rely on the ribosome maturation factor notchless (NLE) [73–75]. NLE is a crucial factor in the maturation of the ribosomal 60 S subunit and is enriched in mature HSCs compared to less mature progenitor cells and bone marrow cells [73]. It is also highly expressed in the intestinal stem and progenitor cells of mice [74], and its expression increases upon the activation of quiescent MuSCs [75]. It is essential for maintaining HSCs and the proliferation of muscle satellite cells. Decreased NLE levels in HSCs lead to the rapid depletion and loss of both HSCs and immature precursor cells. Unlike HSCs, activated MuSCs undergo proliferative arrest without NLE activity. NLE inactivation leads to accumulating pre-28 S rRNA intermediates in both HSCs and MuSCs, concurrently activating the p53 pathway. In HSCs, there is a significant reduction in 60 S subunits and 80 S ribosomes [73–75].

Two primary rRNA modifications, 2'-O-methylation (2'-O-me) and pseudouridination, are essential for ribosome function and are finely regulated in stem cells [76, 77]. These modifications can influence rRNA functionality and subsequently affect protein synthesis. Pseudouridylation is the most abundant and widespread epigenetic modification of RNA in living organisms. The 2'-O-me of rRNA is an essential source of ribosomal heterogeneity, and changes in the 2'-O-me of rRNA affect neural differentiation. NPM1 and Dyskerin (DKC1) [78] are also involved in rRNA modification, encompassing 2'-O-Me and pseudouridination. Ly-1 antibody-reactive clone (LYAR) is a zinc-finger nucleolar protein expressed at higher levels in mESCs than in differentiated cells. Reduced LYAR expression in mESCs leads to cell proliferation arrest and increased apoptosis. The absence of LYAR not only affects cellular survival but also impairs ESC differentiation [79]. This indicates that stem cells have specific requirements for rRNA-modifying enzymes such as DKC1 and LYAR, which differ from their differentiated descendants. snoRNAs play crucial roles in rRNA modification, and studies have revealed an association between NPM1 and numerous box H/ACA and box C/D snoRNAs. In MEFs with NPM1 deletion, the levels of 2'-O-me at five sites within the 28 S rRNA were significantly reduced; however, pseudouridine levels remained unchanged. Mice with NPM1 mutations exhibit highly penetrant hematopoietic abnormalities reminiscent of features observed in ribosomopathies, which are characterized by excessive proliferation and impaired differentiation of HSCs [80]. In ESCs, NPM1 and DKC1 can form complexes with pluripotency factors Oct4 and Nanog, which may be implicated in the maintenance and differentiation of these cells [80–82]. In Drosophila, FMRP directly binds to the 60 S ribosomal subunit and inhibits translation by interacting with RPL5 [83]. In hESCs and hNPCs, FMRP interacts with several box C/D snoRNAs and mediates 2'-O-Me at 12 sites on 18 S and 28 S rRNAs [84]. The "writer" PUS7 (pseudouridine synthase 7) modifies and activates a new tRNA-derived small fragment network, targeting the translation initiation complex. PUS7 inactivation in ESCs impairs tRNA-derived small fragment-mediated translation regulation, increasing protein biosynthesis. It plays a key role in guiding stem cell translation and is important in disease development [77]. KDM2B (Lysine-demethylase 2B) is a lysine demethylase containing a JmjC domain that promotes ribosomal biosynthesis by stimulating the transcription of genes encoding ribosomal biosynthesis factors and proteins, particularly those involved in 40 S ribosomal subunit biosynthesis. Decreased KDM2B expression affects the assembly of small and large subunit process bodies, manifesting as defects in pre-ribosomal RNA processing. KDM2B indirectly promotes the self-renewal of cancer stem cells [85]. During the differentiation of GSCs in Drosophila, the absence of either pre-40 S or -60 S ribosome biogenesis factors, along with a specific box H/AC snoRNP responsible for rRNA pseudouridylation, triggers the initiation of GSC differentiation [26].

Ribosome assembly in stem cells Correct ribosome biosynthesis and assembly can ensure the efficiency and accuracy of protein translation, which is crucial for normal development and prevention of diseases such as cancer. Large-scale, unbiased, in vivo RNA interference screening of female Drosophila GSCs demonstrated that genes influencing germ cell differentiation were enriched in ribosome assembly factors, suggesting that the complete detachment of daughter cells during germline division requires the participation of ribosome assembly factors and specific translation initiation factors [26]. The transition of GSCs from self-renewal to differentiation relies on enhanced ribosome biogenesis and increased protein synthesis. Ribosome assembly and specific translation initiation factors are crucial for GSC daughter cell

abscission. A reduction in ribosomal assembly components and translation initiators such as eIF4E leads to the formation of undifferentiated interconnected cells [26]. HECT domain E3 ubiquitin ligase 1 (HectD1) affects ribosomal assembly via ubiquitination and degradation of the 60 S subunit assembly factor ZNF622 (zinc finger protein 622). The absence of HectD1 leads to the accumulation of ZNF622 and eIF6, which in turn affects the binding of the 60 S/40S subunits and the regenerative ability of HSCs. Depletion of ZNF622 in HectD1-deficient HSCs restores ribosomal assembly, protein synthesis, and HSC reconstruction abilities [86]. Shwachman–Diamond syndrome is related to ribosomal dysfunction and is usually caused by mutations in ribosomal assembly factors [87, 88]. In patients with Shwachman Diamond syndrome, germline mutations have been found in three genes, SBDS, DNAJC21, and EFL1, all involved in the maturation and assembly of the 60 S subunit [89–92]. These mutations lead to ribosomal subunit binding defects and a decrease in the rate of protein synthesis [91, 93–95]. This indicates that HSCs are particularly sensitive to disturbances in the ribosome assembly. Gene knockout and overexpression studies have shown that DEAD-Box Helicase 56 (DDX 56) is involved in ribosome assembly and that its deletion can lead to growth defects and cell death in mESCs. Additionally, Ddx56 maintains mESC proliferation by interacting with the Oct4/Sox2 complex [96].

Precise and dynamic regulation of protein synthesis is essential for stem cell differentiation

Translation rates increase during the activation of quiescent stem cells into proliferative progenitors. High protein synthesis rates throughout maturation are maintained until the cell eventually differentiates into a nondividing cell, at which point translation rates decline [71]. In EBs, cell differentiation is a highly energy-intensive metabolic process during which cells synthesize numerous proteins to support changes in form and function [66]. As differentiation progresses, a series of translation regulatory factors selectively promote the translation of mRNA related to cell differentiation, thereby ensuring the accuracy and reliability of the entire differentiation process. ESC differentiation is accompanied by a significant increase in the rate of protein synthesis and the development of associated organelles, which leads to a rise in the homeostatic protein content of each cell and corresponding adaptive changes in the cell structure. The rate of protein synthesis doubles during the differentiation of ESCs into other cell types [16].

Dormant NSCs are characterized by high glycolysis and lipid metabolism and transition to high protein synthesis and differentiation readiness when activated [23]. Neurons maintain a portion of their mRNA through translational silencing. This efficient and energy-saving biological strategy ensures they can respond quickly and accurately to external stimuli while avoiding energy waste caused by excessive protein production [27]. The binding ability of O-propargyl-puromycin to newly synthesized polypeptide chains was used to quantitatively measure the overall rate of protein synthesis within the cellular environment. The results revealed more pronounced labeling signals in the suprabasal layers of the interfollicular epidermis than in the basal layer, indicating enhanced global protein synthesis during epithelial differentiation. This observation aligns with the requirement for substantial production of novel proteins during cell differentiation to fulfill functional adaptations [97].

Hierarchical translational regulation during differentiation of stem cells

Modulation of the translation rate is governed by various regulatory factors, including mRNA stability, promoter activity, and availability of translation initiation complexes. These elements are intricately regulated during stem cell activation and differentiation to ensure cells adapt to new biological states. Ribosome-associated mRNA quality control may be crucial in stem cells with high plasticity and critical functions [97]. In the early differentiation of hESCs, alteration of translation efficiency is one of the main mechanisms, and RNA-binding proteins such as LIN28 play an important regulatory role. LIN28 enhances translation by recruiting RNA helicase A to polyribosomes, allowing the ribosomes to read and synthesize the corresponding proteins more efficiently. In ESCs, mRNAs with LIN28-enhanced translation are critical for cell growth and development [98]. Sampath et al. used translation state array analysis to reveal changes in translation efficiency during ESC differentiation and observed increased mRNA and ribosome loading in differentiated cells. In EBs, the polyribosomal portion of the cytoplasmic lysate significantly increased by approximately 60%. During differentiation, ESCs form a polysome profile similar to highly metabolically active cells, such as HeLa or activated T cells [16].

Stem cell differentiation is a hierarchical translational regulation process. As stem cells transition from an undifferentiated state to a specialized cell type, the translation of different genes is activated or suppressed sequentially and hierarchically. In ESCs, a translational regulatory cascade has been identified from the mTOR pathway to 4EBP1, deleted in azoospermia-like (DAZL) and guanine-rich sequence binding factor 1 (GRSF1). As a target of the mTOR pathway, the reduced translation efficiency of DAZL leads to decreased protein levels and participation in the translation regulatory cascade [99]. Certain types of ribosomes specialize in translating particular mRNA molecules so that specific gene expression can be achieved preferentially or efficiently. This is also

called ribosome specialization [100–102]. The subunit composition of ribosomes is crucial for achieving specificity and precise regulation of gene expression, which may directly impact the determination and function of stem cells. In mESCs, the ratio of monosome to polysome ribosomal subunits is distinct and associated with different mRNAs [103]. This suggests that ribosome composition influences the translation of specific mRNAs. Certain ribosomal proteins can directly guide specific translation processes through mechanisms dependent on internal ribosomal entry sites [104]. Transcript-specific translation pathways rely on eIF3 to initiate and control the translation of specific mRNA [105]. hESCs may separate the translation of different types of mRNA through ribosome specialization and transcription-specific translation pathways, thus ensuring the precise regulation of proteins required for cell development and differentiation. Preferential translation of translation-related genes occurs in hESCs; however, the molecular mechanisms involved require further exploration. Under varying environmental conditions or physiological states, certain mRNAs in stem cells exhibit higher or lower translational efficiencies than others do. Differential translation efficiency and its impact on stem cell differentiation, the relationship between global translation alterations, the translation of key transcripts, and their specific roles in the differentiation process warrant further investigation.

Studies have shown that the RNA helicase DDX6 (DEAD-box helicase 6) is crucial for guiding pluripotent stem cells, such as mESCs and human pluripotent stem cells (hPSCs), to lose their pluripotency and enter the differentiation pathway. When DDX6 proteins bind to specific mRNAs, these mRNAs are directed to P-bodies, and the translation process of DDX6-bound mRNAs is inhibited. Once DDX6 activity is lost, the processing body (P-body) dissolves and releases mRNA-encoding transcription and chromatin factors, re-entering the ribosome pool for translation. DDX6 silencing inhibits P-body assembly, allowing cells to maintain high levels of pluripotency marker expression and thus resist differentiation. DDX6 inhibition also prompts cells to acquire an "ultra-pluripotent" state similar to that in early embryos [106].

Lee et al. found that conditioned deletion of phosphatase and tensin homolog (PTEN) genes in HSCs leads to abnormal activation of the mTORC1 signaling pathway, resulting in increased phosphorylation of 4E-BP and protein synthesis, ultimately leading to accelerated HSCs depletion [107]. By reducing 4E-BP2 expression, Hartman et al. increased protein synthesis in neural precursor cells, leading to premature neuronal differentiation [34]. Similarly, Yang et al. found that if the levels of eIF4E1, another key factor involved in the initiation of protein translation, were reduced in neural precursor cells, a similar effect was induced, enhancing protein synthesis and promoting early neural differentiation [108].

In germline stem cells, the overactivity of ribosome biogenesis, such as rapid nucleolar synthesis of ribosomes, promotes stem cell growth. This is because more ribosomes can accelerate protein synthesis within cells, thus meeting the need for rapid proliferation and self-renewal of stem cells [26]. In the early stages of ESC differentiation, RP expression was moderately upregulated; therefore, the number of RPs involved in ribosome construction and protein synthesis increased. This finding is consistent with the results of previous polyribosome analyses. Moreover, the translation efficiencies of different mRNA molecules vary greatly. Studies have shown that RPL38 can selectively control the translation of some genes, including *Homeobox (Hox)* [102]. Therefore, different RPs may regulate specific gene translation types, affecting the functional properties of different cells [17]. Signals are issues worthy of in-depth studies on how the protein synthesis machinery perceives signals that trigger stem cell differentiation and the mechanisms by which protein synthesis signaling pathways communicate with stem cell differentiation.

Mitochondrial ribosome translation in stem cell fate

The self-renewal and rapid proliferation of ESCs are highly dependent on glycolysis [109]. ESCs undergo significant metabolic reprogramming during differentiation, shifting glycolysis towards mitochondrial oxidative phosphorylation (OXPHOS) [110]. To meet the demand for increased OXPHOS during this process, a series of mitochondrial changes occur, including an increase in mitochondrial number, electron transfer chain density, tricarboxylic acid cycle activation, and adenosine triphosphate production [111–114]. Mitochondrial ribosomes translate the key core proteins of the electron transfer chain that are essential for their function. Several studies have indicated that mitochondrial ribosomal protein translation is important in stem cell self-renewal and differentiation.

Methylation and other modifications of rRNA and tRNA are crucial for mitochondrial biogenesis and efficient and accurate protein translation [115]. The METTL family of proteins is involved in mRNA stability and translation efficiency. In the Mettl family, Mettl17 is a mitochondrial protein associated with chromosome 4 open reading frame 14 (C4orf14), a mitoribosome-interacting GTPase [116] that is crucial for the stability of mitochondrial small subunit complexes, ribosome assembly, and protein translation. The absence of Mettl17 led to a reduction of approximately 50–70% in the modification of 12S rRNA (m4C840 and m5C842), significantly reducing mitochondrial oxidative phosphorylation and delaying mESC differentiation [117] (Fig. 3). Mettl8

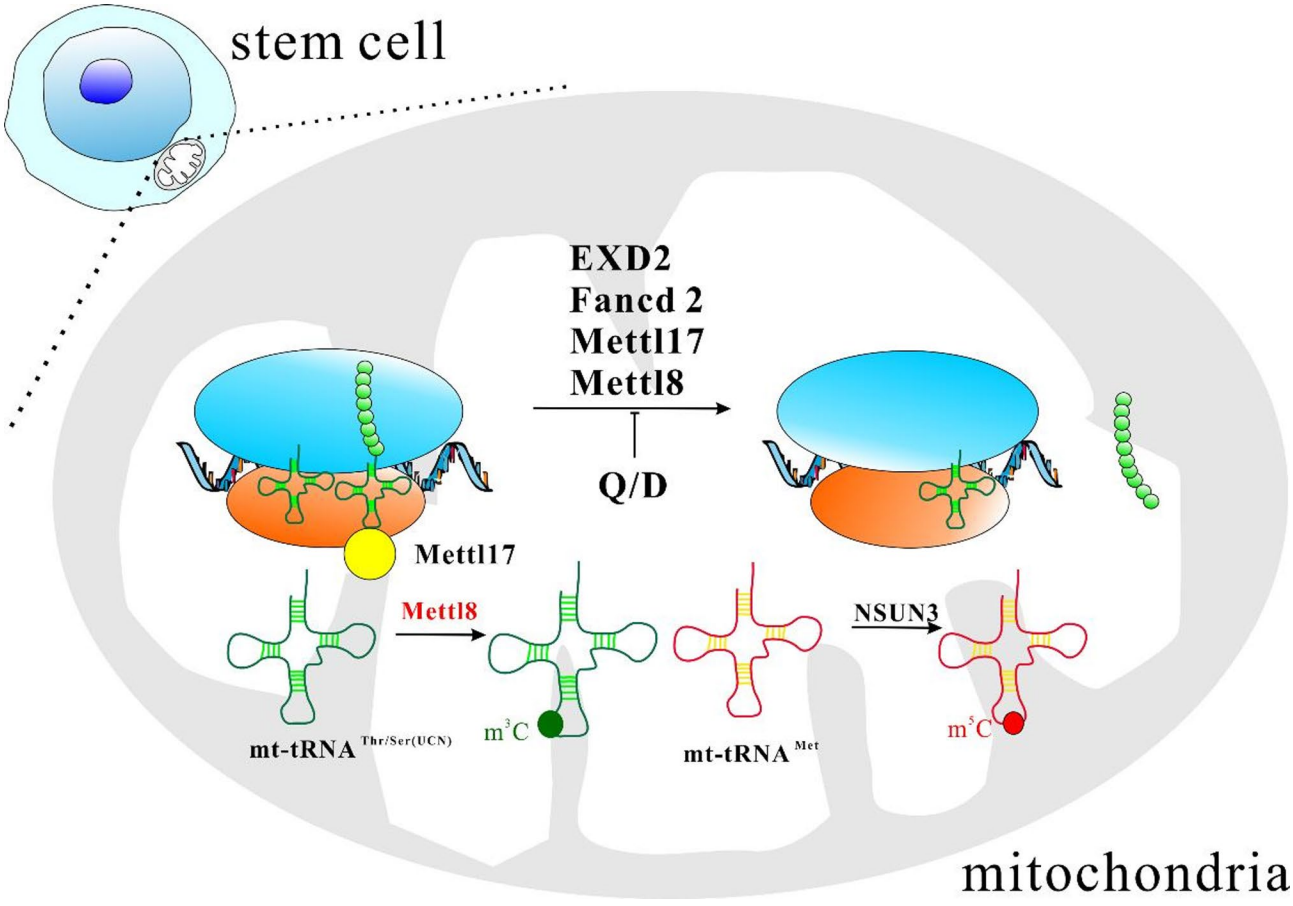

Fig. 3 Mitochondrial ribosome translation and stem cell fate. Stem cell mitochondrial proteins, EXD2, Fancd2, Mettl17 and Mettl8, regulate mitochondrial protein synthesis. Mettl8 is an mt-tRNA m3C methyltransferase. Deletion of Mettl8 in stem cell leads to reduced m3C modification of mt-tRNA Thr/Ser, decreased mitochondrial protein translation. NSUN3 is an RNA cytosine methyltransferase that catalyzes the generation of 5-methylcytosine in the anticodon loop of mitochondrial $tRNA^{Met}$ in stem cells. The bacterial antibiotic quinolopristine/dafopristine (Q/D) binds to the mitochondrial ribosome subunit and inhibits the translation of mitochondrial proteins, leading to OXPHOS dysregulation and glioblastoma stem cells growth inhibition. EXD2, Exonuclease 3'-5' domain-containing 2; Fancd 2, FA group D2 protein; Mettl8, methyltransferase-like 8; Mettl17, methyltransferase-like 17; NSUN3, NOP2/Sun RNA methyltransferase 3

is an mt-tRNA m3C methyltransferase that regulates mitochondrial protein translation and activity, particularly in immortalized and cancer cells. Deletion of Mettl8 in mouse embryonic cortical NSCs led to reduced m3C modification of mt-tRNA Thr/Ser, decreased mitochondrial protein translation, and impaired mitochondrial function. The conditional knockout of Mettl8 in mice resulted in impaired maintenance of embryonic cortical neural stem cells in vivo; however, this effect was reversed by enhancing mitochondrial function through pharmacological methods. Mettl8 also promotes mitochondrial protein expression and neural stem cell maintenance in human cortical organoids. The absence of Mettl8 leads to the impaired maintenance of cortical neural stem cells in human forebrain organoids, accompanied by increased neural differentiation [118]. Exonuclease 3'-5' domain-containing 2 (EXD2) is a protein encoded by the nucleus and located in the mitochondria that prevents the abnormal binding of mRNA to mitochondrial ribosomes. Its deficiency leads to defects in mitochondrial translation, decreased respiration, decreased adenosine triphosphate production, increased oxygen species (ROS) levels, and decreased mtDNA levels. In a *Drosophila* model, the absence of EXD2 accelerated the depletion of reproductive stem cells, affected *Drosophila* development, and prolonged the lifespan [119]. The bacterial antibiotics quinolopristine/dafopristine have been found to effectively inhibit glioblastoma stem cell growth. It binds to the mitochondrial ribosome subunit and inhibits the translation of mitochondrial proteins, leading to OXPHOS dysregulation and glioblastoma stem cell growth inhibition, demonstrating its potential therapeutic effects. Therefore, targeting mitochondrial translation may be a promising approach for treating glioblastoma stem cells and GBM [120]. NOP2/Sun RNA methyltransferase 3 (NSUN3) is an RNA cytosine methyltransferase

that catalyzes the synthesis of 5-methylcytosine in the anticodon loop of mitochondrial $tRNA^{Met}$ in human cells. This modification is crucial for normal mitochondrial translation and functioning. Stem cells with NSUN3 mutations show a significant reduction in mt-$tRNA^{Met}$ methylation and formylation, as well as decreased mitochondrial translation and respiration. NSUN3 mutations lead to mitochondrial dysfunction, which, in turn, affects cell differentiation. The differentiation of ESCs tends towards the mesodermal and endodermal lineages, whereas differentiation of the neuroectoderm is impaired in stem cells with NSUN3 mutations. This indicates that the catalytic inactivation of NSUN3 affects the self-renewal and differentiation potential of mESCs [121]. mTORC1 regulates translation initiation through eIF4F mainly by targeting cytoplasmic and mitochondrial ribosomes [122]. The specific mitochondrial translation inhibitor chloramphenicol directly suppresses mitochondrial translation, which reduces ROS, mitochondrial mass, and mtDNA content and prevents the self-renewal of mESCs. This indicates that the inhibition of mTORC1 or mitochondrial translation successfully induces a pluripotent state while maintaining the differentiation potential of mESCs [122]. Studies have shown that the increased mitochondrial protein synthesis observed in FA group D2 protein (Fancd 2)-knockout mouse hematopoietic stem and progenitor cells is directly related to the enhancement of mitochondrial translation. Hematopoietic stem and progenitor cells with Fancd 2 deficiency are particularly sensitive to inhibition of mitochondrial translation and rely on enhanced mitochondrial translation for survival and proliferation. These results indicate that Fancd 2 limits mitochondrial activity by regulating mitochondrial translation and that enhanced mitochondrial translation and respiration may play a role in HSC deficiency and bone marrow failure in patients with Fanconi anemia [123].

Ribosome-based stem cell therapy

Stem cell therapy is a powerful tool in clinical medical research that promotes the development of personalized medicine. Patients can be treated using stem cells extracted from their bodies to avoid immune rejection reactions and other risks, thereby achieving the goal of personalized clinical treatment. Stem cell ribosomes possess unique characteristics that confer advantages to stem cell therapy.

Ribosomal heterogeneity and stem cell therapy

Due to the heterogeneity of ribosomes, their composition and function may vary across different cell types and physiological states. This variation offers a new approach to stem cell-targeted therapy. Personalized treatment plans can be developed by adjusting the composition and function of ribosomes according to the patient's condition and cell type. For example, modulating the ribosome composition and function for specific types of tumor stem cells can enhance their ability to synthesize tumor-related proteins, thereby improving their therapeutic efficacy. Ribosome heterogeneity provides novel targets for drug design and screening. Ribosomal heterogeneity may also play a role in the self-renewal and differentiation of stem cells. Dynamic changes in 2′-O-methylation of rRNA regulate the in vivo activity of acute myeloid leukemia stem cells (LSCs). The rRNA 2′-O-methylation pattern is closely associated with the stages of acute myeloid leukemia (AML) development and the gene expression characteristics of LSCs. Forced expression of the 2′-O-methyltransferase Fbl induces an AML stem cell phenotype and enables non-LSC leukemia cells to engraft in NSG mice. Dynamic 2′-O-methylation at specific sites on rRNA alters translational preferences and controls the self-renewal of AML LSCs [124]. Understanding this heterogeneity can facilitate or inhibit stem cell self-renewal and differentiation by modulating ribosomal function and protein translation, thereby providing new strategies for stem cell therapy.

Ribosome translation and biosynthesis as new therapeutic strategies in stem cell therapy

Ribosomal protein translation plays a crucial role in stem cell differentiation. By regulating this process, the direction and speed of stem cell differentiation can be influenced, thereby playing a significant role in disease treatment. For example, by modulating the synthesis of specific proteins, stem cells can be induced to differentiate into specific cell types to treat certain diseases. Stem cells isolated from deciduous teeth (SHED) have low immunogenicity, no ethical issues, and are easily accessible. They are derived from the neural crest and have potential for use in cell therapy. Xing et al. cultured SHED in vitro and injected them into mice via the tail vein. SHED migrated mainly to the liver, spleen, and lungs of mice. Six months of continuous SHED injection significantly alleviated the aging of the liver, downregulated most ribosomal proteins, and upregulated the ribosomal biosynthesis proteins Rpsa (promoting the degradation of the installed proteins) and Rplp0 (an indicative part of the transition elongation complex) [125].

CSCs are the major driving force for tumor recurrence and metastasis, and their rapid growth and mutation rates make targeting CSCs challenging. Several studies have targeted abundant ribosomes in CSCs for photodynamic therapy. Wang et al. coassembled the amino acid porphyrin with a short peptide to form nanoparticles (NPs) that carry a positive charge in the acidic tumor microenvironment. NPs target the nucleus and interact with ribosomes. The NPs produced a large amount

of ROS upon light irradiation, significantly damaging ribosomes. This led to cell apoptosis and reduced CSC markers CD44 and CD133 expression, demonstrating inhibitory effects on CSCs [126]. During the proliferative phase of regeneration in zebrafish, axolotls, and planarians, mTOR is activated and stimulates quiescent stem cells [127–129] participating in the repair process [130]. The regulatory mechanisms that maintain low protein synthesis rates and selective translation in stem cells may be exploited by cancer cells to promote undifferentiated tumors with aggressive and poor prognoses. If drugs that interfere with low protein synthesis in stem cells are screened, synthetic biology can synthesize ribosomes and optimize ribosomal proteins; disrupting low protein synthesis and selective translation in cancer stem cells could potentially promote tumor differentiation. Therefore, targeted drugs can be designed based on ribosomal translation to specifically inhibit the synthesis of proteins that act on stem cell ribosomes. This strategy offers new possibilities and directions for targeted stem cell therapies.

Certain diseases are associated with the abnormal expression or dysfunction of specific proteins. Disease intervention and treatment can be achieved by modulating protein synthesis. Using stem cell technology to regulate ribosomal protein translation may lead to the development of more effective treatments. For instance, specific genes can be knocked out or overexpressed to influence ribosomal protein translation through gene editing techniques, ultimately achieving therapeutic goals. Glioblastoma stem cells are a major cause of glioblastoma recurrence and treatment failure. Therefore, treatment strategies that target glioblastoma stem cells may significantly improve GBM prognosis. WDR12 (WD Repeat Domain 12) is highly expressed in glioblastoma stem cells and is a member of the Pes1-Bop1 complex (PeBoW), is highly expressed in glioblastoma stem cells and is essential for maintaining ribosomal biogenesis in the PeBoW complex and glioblastoma stem cells. The inhibition of WDR12 can lead to the degradation of PeBoW complex components, prevent the maturation of 28 S rRNA, and inhibit ribosomal biosynthesis in glioblastoma stem cells. Reduced WDR12 expression hindered glioblastoma stem cell proliferation, inhibited glioblastoma stem cell-derived in situ tumor growth, and prolonged survival. Therefore, targeting WDR12 to inhibit ribosome biogenesis may be a promising strategy for GBM therapy [131].

Ribosome have "extra-ribosome function" involved in the occurrence and development of various diseases

An increasing number of studies have shown that ribosomes not only have translation functions but also have "extra-ribosome function" involved in the occurrence and development of various diseases, including cancer. Previous studies have shown that ribosome incorporation induces stem cell-like characteristics and multidirectional differentiation of somatic cells [132]. Ribosomal protein S6 promotes GSC characteristics in glioblastoma cells; therefore, it may play a key role in acquiring stem cell-like characteristics and therapeutic resistance in glioblastoma cells. The functional role of ribosomes as in vitro de-differentiation factors is a novel discovery in cellular reprogramming. Exogenous ribosome incorporation can reverse somatic and cancer cells into a multipotent state [132–134]. This process involves the possible interaction between ribosomal proteins and transcription factors, possibly leading to the abnormal expression of stem cell-specific transcription factors such as Oct4, Nanog, and Sox2. Ribosome-mediated reprogramming does not rely on the translational activity of exogenous ribosomes. However, during pluripotency induction, ribosome incorporation is often accompanied by senescence-like states and cellular stress responses. Ribosome-incorporated cell clusters possess certain stem cell-like characteristics; however, they may not have the ability to self-renew, and instead tend to remain quiescent and differentiate. This ribosome-induced characteristic has potential applications in regenerative medicine and cancer treatments. These findings indicate that ribosomes are important targets for stem cell therapies. Despite the enormous potential of stem cell therapy, its application carries certain risks, such as immune reactions, heterologous infections, and tumor formation.

Conclusions and perspectives

Long noncoding RNAs are also found to be involved in translational regulation [17, 135]. They can sometimes be translated into functional peptide chains or regulate self-renewal and differentiation via other mechanisms. Translation of chromatin modifications maintains the open chromatin state in ESCs; however, the functional and mechanistic connections between transcription and translation require further investigation. Moreover, the communication mechanism between ribosomal translation and self-renewal and differentiation signals in stem cells, that is, how stem cells perceive their differentiation status through specific pathways to regulate ribosome biogenesis and translation, thereby playing a functional role in stem cell differentiation and self-renewal. In the next decade, we will gain a deeper understanding of these processes in stem cells and discover novel mechanisms that remain unelucidated.

Human pluripotent stem cells have an enormous potential for cell therapy and other applications. Over 14 cell therapies for diseases and injuries have entered or are about to enter clinical trials. Therefore, in-depth research into the characteristics of stem cells and their utilization in stem cell therapy is of great significance. The

control of ribosomal translation plays a crucial role in the self-renewal, differentiation, implantation, and tumor-suppressive functions of stem cells. Ribosomal translation not only precisely maintains the specific proteome necessary to maintain undifferentiated cell identity and stem cell pluripotency but also rapidly reprograms gene expression in response to fate change signals or environmental stimuli. We propose that ribosomal translation is a key factor in regulating gene expression in stem cells. We believe that future advancements in omics technology will reveal new paradigms in ribosomal protein synthesis in stem cells. New technologies in ribosome research, such as single-cell RNA sequencing and single-cell proteomics, have enabled precise studies on mRNA translational regulation over time and space, which are crucial for understanding stem cell function and differentiation. Methods such as synthetic biology may also offer a viable approach using small molecules to synthesize ribosomes. Current proteomic technologies have advanced to accurately compare the abundance of specific ribosomal proteins during active translation and measure protein levels within non-denatured ribosomes. This provides novel and powerful drug-targeting pathways for ribosomal heterogeneity. Such ribosome-targeted therapies may not be limited to specific ribosomopathies but can also enhance the efficacy of other drugs by targeting ribosomal features unique to diseased cells, particularly cancer cells or activated immune cells, or by impairing the production of new proteins in target tissues. We may also better leverage the potential power of ribosomal diversity and specialization to tailor synthetic biology for the production of pharmaceutical proteins.

Abbreviations

2′-O-me	2′-O-methylation
4E-BP	Eukaryotic initiation factor 4E binding protein
DAZL	Azoospermia-like
CBX4	Chromobox
C4orf14	Chromosome 4 open reading frame 14
CSCs	Cancer stem cells
DDX6	DEAD-box helicase 6
DDX27	DEAD-box containing RNA helicase 27
DDX 56	DEAD-Box Helicase 56
DKC1	Dyskerin
EBs	Embryoid bodies
ESCs	Embryonic stem cells
eIF2α	Eukaryotic initiation factor 2 subunit alpha
Esrrb	Estrogen related receptor-β
eIF4E	Eukaryotic initiation factor 4E
EXD2	Exonuclease 3′-5′ domain-containing 2
Fancd 2	FA group D2 protein
Fbl	Fibrillarin
FMRP	Fragile X mental retardation protein
GRSF1	Guanine-rich sequence binding factor 1
GBM	Glioblastoma multiforme
GSCs	Germline stem cells
hESCs	Human embryonic stem cells
hPSCs	Human pluripotent stem cells
HectD1	HECT domain E3 ubiquitin ligase 1
Hox	Homeobox
HSCs	Hematopoietic stem cells
ISCs	Intestinal stem cells
mESCs	Mouse embryonic stem cells
LYAR	Ly-1 antibody-reactive clone
mTORC1	Mechanistic target of rapamycin complex 1
Mettl	Methyltransferase-like
mHSCs	Mouse hematopoietic stem cells
MuSCs	Muscle stem cells
NCL	Nucleolin
NIR	Neural inhibitory nuclear factor
NLE	Notchless
NSUN3	NOP2/Sun RNA methyltransferase 3
NPCs	Neural progenitor
NPs	Nanoparticles
NPM1	Nucleophosmin
NS	Nucleostemin
NSCs	Neuronal stem cells
Oct4	Octamer-binding protein 4
OXPHOS	Oxidative phosphorylation
p70 S6K	p70 ribosomal protein S6 kinase
P-body	Processing body
PTEN	Phosphatase and tensin homolog
PUS7	Pseudouridine synthase 7
KDM2B	Lysine-demethylase 2B
PeBoW	Pes1-Bop1 complex
PTBP1	Polypyrimidine tract binding protein 1
RBFs	Ribosome biogenesis factors
RSL24D1	Ribosomal L24 domain containing 1
RUNX1	Runt-related transcription factor
SOX2	Sex-determining region Y-box 2
rDNA	Ribosomal DNA
RNA Pols	RNA polymerases
ROS	Reactive oxygen species
RP	Ribosomal protein
snoRNAs	Small nucleolar RNAs
SHED	Stem cells isolated from deciduous teeth
TSC1	Tuberous sclerosis 1
UBR2	Ubiquitin protein ligase E3 component n-recognin 2
UBR5	Ubiquitin-protein ligase E3 component n-recognin 5
UDD	Under-specified polymerase I cofactor
UBF1	Upstream binding factor 1
Wcd	Wicked
WDR12	WD Repeat Domain 12
YY2	Yin Yang 2
ZNF622	Zinc finger protein 622

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Yanyan Gao: Conceptualization, Funding acquisition, Investigation, Supervision, Writing-original draft, Writing-review and editing. Linlin Guo: Writing-original draft, Writing-review and editing. Gaoxiang Shi: Investigation, Resources, Writing-review and editing. Ruifang Wang: Investigation, Resources, Writing-review and editing. Xu'an Wang: Methodology, Investigation, Writing–review & editing. Jizhong Lou: Conceptualization, Funding acquisition, Investigation, Supervision, Writing-review and editing.

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References

1. Gabut M, Bourdelais F, Durand S. Ribosome and translational control in stem cells. Cells-Basel 9(2) (2020).
2. Driskill JH, Pan DJ. Control of stem cell renewal and fate by YAP and TAZ. Nat Rev Mol Cell Bio. 2023;24(12):895–911.
3. Mizutani K, Yoon K, Dang L, Tokunaga A, Gaiano N. Differential Notch signalling distinguishes neural stem cells from intermediate progenitors. Nature. 2007;449(7160):351–5.
4. Miki T, Yasuda S-y, Kahn M. Wnt/β-catenin signaling in embryonic stem cell Self-renewal and somatic cell reprogramming. Stem Cell Reviews Rep. 2011;7(4):836–46.
5. Reya T, Duncan AW, Ailles L, Domen J, Scherer DC, Willert K, Hintz L, Nusse R, Weissman IL. A role for Wnt signalling in self-renewal of Haematopoietic stem cells. Nature. 2003;423(6938):409–14.
6. Molofsky AV, He S, Bydon M, Morrison SJ, Pardal R. Bmi-1 promotes neural stem cell self-renewal and neural development but not mouse growth and survival by repressing the p16Ink4a and p19Arf senescence pathways. Gene Dev. 2005;19(12):1432–7.
7. Wu SM, Choo ABH, Yap MGS, Chan KKK. Role of Sonic Hedgehog signaling and the expression of its components in human embryonic stem cells. Stem Cell Res. 2010;4(1):38–49.
8. Yang H, Liu CC, Fan H, Chen B, Huang DG, Zhang LL, Zhang Q, An J, Zhao JJ, Wang Y, Hao DJ. Sonic Hedgehog effectively improves Oct4-Mediated reprogramming of astrocytes into neural stem cells. Mol Ther. 2019;27(8):1467–82.
9. Pethe PS, Dumasia NP, Bhartiya D. Effect of Sonic Hedgehog pathway Inhibition on PDX1 expression during pancreatic differentiation of human embryonic stem cells. Mol Biol Rep. 2021;48(2):1615–23.
10. Huh CG, Factor VM, Sánchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/signaling pathway is required for efficient liver regeneration and repair. P Natl Acad Sci USA. 2004;101(13):4477–82.
11. Theunissen TW, Jaenisch R. Mechanisms of gene regulation in human embryos and pluripotent stem cells. Development. 2017;144(24):4496–509.
12. Young RA. Control Embryonic Stem Cell State Cell. 2011;144(6):940–54.
13. Schwanhäusser B, Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J, Chen W, Selbach M. Global quantification of mammalian gene expression control. Nature. 2011;473(7347):337–42.
14. Saba JA, Liakath-Ali K, Green R, Watt FM. Translational control of stem cell function. Nat Rev Mol Cell Bio. 2021;22(10):671–90.
15. Notingher I, Bisson I, Bishop AE, Randle WL, Polak JMP, Hench LL. In situ spectral monitoring of mRNA translation in embryonic stem cells during differentiation in vitro. Anal Chem. 2004;76(11):3185–93.
16. Sampath P, Pritchard DK, Pabon L, Reinecke H, Schwartz SM, Morris DR, Murry CE. A hierarchical network controls protein translation during murine embryonic stem cell self-renewal and differentiation. Cell Stem Cell. 2008;2(5):448–60.
17. Ingolia NT, Lareau LF, Weissman JS. Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of mammalian proteomes. Cell. 2011;147(4):789–802.
18. Easley CA, Ben-Yehudah A, Redinger CJ, Oliver SL, Varum ST, Eisinger VM, Carlisle DL, Donovan PJ, Schatten GP. mTOR-Mediated activation of p70 S6K induces differentiation of pluripotent human embryonic stem cells. Cell Reprogram. 2010;12(3):263–73.
19. Blair JD, Hockemeyer D, Doudna JA, Bateup HS, Floor SN. Widespread translational remodeling during human neuronal differentiation. Cell Rep. 2017;21(7):2005–16.
20. Signer RAJ, Magee JA, Salic A, Morrison SJ. Haematopoietic stem cells require a highly regulated protein synthesis rate. Nature. 2014;509(7498):49–54.
21. Jarzebowski L, Le Bouteiller M, Coqueran S, Raveux A, Vandormael-Pournin S, David A, Cumano A, Cohen-Tannoudji M. Mouse adult hematopoietic stem cells actively synthesize ribosomal RNA. RNA. 2018;24(12):1803–12.
22. Signer RAJ, Qi L, Zhao ZY, Thompson D, Sigova AA, Fan ZP, DeMartino GN, Young RA, Sonenberg N, Morrison SJ. The rate of protein synthesis in hematopoietic stem cells is limited partly by 4E-BPs. Gene Dev. 2016;30(15):1698–703.
23. Llorens-Bobadilla E, Zhao S, Baser A, Saiz-Castro G, Zwadlo K, Martin-Villalba A. Single-Cell transcriptomics reveals a population of dormant neural stem cells that become activated upon brain injury. Cell Stem Cell. 2015;17(3):329–40.
24. Zismanov V, Chichkov V, Colangelo V, Jamet S, Wang S, Syme A, Koromilas AE, Crist C. Phosphorylation of eIF2α is a translational control mechanism regulating muscle stem cell quiescence and Self-Renewal. Cell Stem Cell. 2016;18(1):79–90.
25. Blanco S, Bandiera R, Popis M, Hussain S, Lombard P, Aleksic J, Sajini A, Tanna H, Cortés-Garrido R, Gkatza N, Dietmann S, Frye M. Stem cell function and stress response are controlled by protein synthesis. Nature. 2016;534(7607):335–40.
26. Sanchez CG, Teixeira FK, Czech B, Preall JB, Zamparini AL, Seifert JRK, Malone CD, Hannon GJ, Lehmann R. Regulation of ribosome biogenesis and protein synthesis controls germline stem cell differentiation. Cell Stem Cell. 2016;18(2):276–90.
27. Baser A, Skabkin M, Kleber S, Dang YL, Balta GSG, Kalamakis G, Göpferich M, Ibañez DC, Schefzik R, Lopez AS, Bobadilla EL, Schultz C, Fischer B. Martin-Villalba. Onset of differentiation is post-transcriptionally controlled in adult neural stem cells. Nature. 2019;566(7742):100–4.
28. Micchelli CA, Perrimon N. Evidence that stem cells reside in the adult midgut epithelium. Nature. 2006;439(7075):475–9.
29. Ohlstein B, Spradling A. The adult posterior midgut is maintained by pluripotent stem cells. Nature. 2006;439(7075):470–4.
30. Obata F, Tsuda-Sakurai K, Yamazaki T, Nishio R, Nishimura K, Kimura M, Funakoshi M, Miura M. Nutritional control of stem cell division through S-Adenosylmethionine in intestine. Dev Cell. 2018;44(6):741–51.
31. Bulut-Karslioglu A, Biechele S, Jin H, Macrae TA, Hejna M, Gertsenstein M, Song JS, Ramalho-Santos M. Inhibition of mTOR induces a paused pluripotent state. Nature. 2016;540(7631):119–23.
32. Vilchez D, Boyer L, Morantte I, Lutz M, Merkwirth C, Joyce D, Spencer B, Page L, Masliah E, Berggren WT, Gage FH, Dillin A. Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature. 2012;489(7415):304–8.
33. Noormohammadi A, Calculli G, Gutierrez-Garcia R, Khodakarami A, Koyuncu S, Vilchez D. Mechanisms of protein homeostasis (proteostasis) maintain stem cell identity in mammalian pluripotent stem cells. Cell Mol Life Sci. 2018;75(2):275–90.
34. Hartman NW, Lin TV, Zhang LB, Paquelet GE, Feliciano DM, Bordey A. mTORC1 targets the translational repressor 4E-BP2, but not S6 kinase 1/2, to regulate neural stem cell Self-Renewal in vivo. Cell Rep. 2013;5(2):433–44.
35. Glatter T, Schittenhelm RB, Rinner O, Roguska K, Wepf A, Jünger MA, Köhler K, Jevtov I, Choi H, Schmidt A, Nesvizhskii AI, Stocker H, Hafen E, Aebersold R, Gstaiger M. Modularity and hormone sensitivity of the insulin receptor/target of Rapamycin interaction proteome. Mol Syst Biol. 2011;7:547.
36. Morita M, Gravel SP, Chénard V, Sikström K, Zheng L, Alain T, Gandin V, Avizonis D, Arguello M, Zakaria C, McLaughlan S, Nouet Y, Pause A, Pollak M, Gottlieb E, Larsson O, St-Pierre J, Topisirovic I, Sonenberg N. mTORC1 controls mitochondrial activity and biogenesis through 4E-BP-Dependent translational regulation. Cell Metab. 2013;18(5):698–711.
37. Tahmasebi S, Alain T, Rajasekhar VK, Zhang JP, Prager-Khoutorsky M, Khoutorsky A, Dogan Y, Gkogkas CG, Petroulakis E, Sylvestre A, Ghorbani M, Assadian S, Yamanaka Y, Vinagolu-Baur JR, Teodoro JG, Kim K, Yang XJ, Sonenberg N. Multifaceted regulation of somatic cell reprogramming by mRNA translational control. Cell Stem Cell. 2014;14(5):606–16.
38. Barna M, Ruggero D. Tailor made protein synthesis for HSCs. Cell Stem Cell. 2014;14(4):423–4.
39. Tahmasebi S, Jafarnejad SM, Tam IS, Gonatopoulos-Pournatzis T, Matta-Camacho E, Tsukumo Y, Yanagiya A, Li WC, Atlasi Y, Caron M, Braunschweig U, Pearl D, Khoutorsky A, Gkogkas CG, Nadon R, Bourque G, Yang XJ, Tian B, Stunnenberg HG, Yamanaka Y, Blencowe BJ, Giguère V, Sonenberg N. Control of embryonic stem cell self-renewal and differentiation via

coordinated alternative splicing and translation of YY2. P Natl Acad Sci USA. 2016;113(44):12360–7.
40. Xue ML, Dong L, Zhang HH, Li YC, Qiu KQ, Zhao ZC, Gao M, Han L, Chan AKN, Li W, Leung K, Wang KTY, Pokharel SP, Qing Y, Liu W, Wang XE, Ren LL, Bi HJ, Yang L, Shen C, Chen ZH, Melstrom L, Li HZ, Timchenko N, Deng XL, Huang WD, Rosen ST, Tian JY, Xu L, Diao JJ, Chen CW, Chen JJ, Shen BY, Chen H, Su R. METTL16 promotes liver cancer stem cell self-renewal via controlling ribosome biogenesis and mRNA translation. J Hematol Oncol 17(1) (2024).
41. Mills EW, Green R. Ribosomopathies: there's strength in numbers. Science 358(6363) (2017).
42. Sharifi S, da Costa HFR, Bierhoff H. The circuitry between ribosome biogenesis and translation in stem cell function and ageing. Mech Ageing Dev 189 (2020).
43. Gupta S, Santoro R. Regulation and roles of the nucleolus in embryonic stem cells: from ribosome biogenesis to genome organization. Stem Cell Rep. 2020;15(6):1206–19.
44. Zhang Q, Shalaby NA, Buszczak M. Changes in rRNA transcription influence proliferation and cell fate within a stem cell lineage. Science. 2014;343(6168):298–301.
45. Fichelson P, Huynh JR. Asymetric growth in drosophila stem cells is related to ribosomal biogenesis. M S-Med Sci. 2009;25(10):780–1.
46. You KT, Park J, Kim VN. Role of the small subunit processome in the maintenance of pluripotent stem cells. Gene Dev. 2015;29(19):2004–9.
47. Woolnough JL, Atwood BL, Liu Z, Zhao R, Giles KE. The regulation of rRNA gene transcription during directed differentiation of human embryonic stem cells. PLoS ONE 11(6) (2016).
48. Zhang H, Wu ZY, Lu YY, Huang B, Zhou HW, Xie W, Wang JL, Shen XH. DEAD-Box helicase 18 counteracts PRC2 to safeguard ribosomal DNA in pluripotency regulation. Cell Rep. 2020;30(1):81–97.
49. Hayashi Y, Kuroda T, Kishimoto H, Wang CS, Iwama A, Kimura K. Downregulation of rRNA transcription triggers cell differentiation. PLoS ONE 9(5) (2014).
50. Pilz RB, Van den Berghe G, Boss GR. Adenosine dialdehyde and nitrous oxide induce HL-60 differentiation. Blood. 1987;70(4):1161–4.
51. Sharifi S, Bierhoff H. Regulation of RNA polymerase I transcription in development, disease, and aging. Annu Rev Biochem. 2018;87:51–73.
52. Tiku V, Antebi A. Nucleolar function in lifespan regulation. Trends Cell Biol. 2018;28(8):662–72.
53. Eleuteri B, Aranda S, Ernfors P. NoRC recruitment by H2A.X deposition at rRNA gene promoter limits embryonic stem cell proliferation. Cell Rep. 2018;23(6):1853–66.
54. Ren XQ, Hu BQ, Song MS, Ding ZC, Dang YJ, Liu ZP, Zhang WQ, Ji QZ, Ren RT, Ding JJ, Chan P, Jiang CT, Ye KQ, Qu J, Tang FC, Liu GH. Maintenance of nucleolar homeostasis by CBX4 alleviates senescence and osteoarthritis. Cell Rep. 2019;26(13):3643–56.
55. Cai XW, Gao L, Teng L, Ge JP, Oo ZM, Kumar AR, Gilliland DG, Mason PJ, Tan K, Speck NA. Runx1 deficiency decreases ribosome biogenesis and confers stress resistance to hematopoietic stem and progenitor cells. Cell Stem Cell. 2015;17(2):165–77.
56. Watanabe-Susaki K, Takada H, Enomoto K, Miwata K, Ishimine H, Intoh A, Ohtaka M, Nakanishi M, Sugino H, Asashima M, Kurisaki A. Biosynthesis of ribosomal RNA in nucleoli regulates pluripotency and differentiation ability of pluripotent stem cells. Stem Cells. 2014;32(12):3099–111.
57. Obernier K, Cebrian-Silla A, Thomson M, Parraguez JI, Anderson R, Guinto C, Rodriguez JR, Garcia-Verdugo JM, Alvarez-Buylla A. Adult neurogenesis is sustained by symmetric Self-Renewal and differentiation. Cell Stem Cell. 2018;22(2):221–34.
58. Athanasiadis EI, Botthof JG, Andres H, Ferreira L, Lio P, Cvejic A. Single-cell RNA-sequencing uncovers transcriptional States and fate decisions in haematopoiesis. Nat Commun 8 (2017).
59. Baddoo M, Hill K, Wilkinson R, Gaupp D, Hughes C, Kopen GC, Phinney DG. Characterization of mesenchymal stem cells isolated from murine bone marrow by negative selection. J Cell Biochem. 2003;89(6):1235–49.
60. Ohmura M, Naka K, Hoshii T, Muraguchi T, Shugo H, Tamase A, Uema N, Ooshio T, Arai F, Takubo K, Nagamatsu G, Hamaguchi I, Takagi M, Ishihara M, Sakurada K, Miyaji H, Suda T, Hirao A. Identification of stem cells during prepubertal spermatogenesis via monitoring of nucleostemin promoter activity. Stem Cells. 2008;26(12):3237–46.
61. Qu J, Bishop JM. Nucleostemin maintains self-renewal of embryonic stem cells and promotes reprogramming of somatic cells to pluripotency. J Cell Biol. 2012;197(6):731–45.
62. Tsai RYL, McKay RDG. A nucleolar mechanism controlling cell proliferation in stem cells and cancer cells. Gene Dev. 2002;16(23):2991–3003.
63. Yamashita M, Nitta E, Nagamatsu G, Ikushima YM, Hosokawa K, Arai F, Suda T. Nucleostemin is indispensable for the maintenance and genetic stability of hematopoietic stem cells. Biochem Bioph Res Co. 2013;441(1):196–201.
64. Saez I, Gerbracht JV, Koyuncu S, Lee HJ, Horn M, Kroef V, Denzel MS, Dieterich C, Gehring NH, Vilchez D. The E3 ubiquitin ligase UBR5 interacts with the H/ACA ribonucleoprotein complex and regulates ribosomal RNA biogenesis in embryonic stem cells. Febs Lett. 2020;594(1):175–88.
65. Tao WW, Lei H, Luo WL, Huang Z, Ling P, Guo MY, Wan LH, Zhai K, Huang Q, Wu QL, Xu ST, Zeng L, Wang XX, Dong ZQ, Rich JN, Bao SD. Novel INHAT repressor drives glioblastoma growth by promoting ribosomal DNA transcription in glioma stem cells. Neurooncology. 2023;25(8):1428–40.
66. Fortier S, MacRae T, Bilodeau M, Sargeant T, Sauvageau G. Haploinsufficiency screen highlights two distinct groups of ribosomal protein genes essential for embryonic stem cell fate. P Natl Acad Sci USA. 2015;112(7):2127–32.
67. Li PF, Wu MY, Lin QW, Wang S, Chen T, Jiang H. Key genes and integrated modules in hematopoietic differentiation of human embryonic stem cells: a comprehensive bioinformatic analysis. Stem Cell Res Ther 9 (2018).
68. Durand S, Bruelle M, Bourdelais F, Bennychen B, Blin-Gonthier J, Isaac C, Huyghe A, Martel S, Seyve A, Vanbelle C, Adrait A, Coute Y, Meyronet D, Catez F, Diaz JJ, Lavial F, Ricci EP, Ducray F, Gabut M. RSL24D1 sustains steady-state ribosome biogenesis and pluripotency translational programs in embryonic stem cells. Nat Commun 14(1) (2023).
69. Saha S, Murmu KC, Biswas M, Chakraborty S, Basu J, Madhulika S, Kolapalli SP, Chauhan S, Sengupta A, Prasad P. Transcriptomic analysis identifies RNA binding proteins as putative regulators of myelopoiesis and leukemia. Front Oncol 9 (2019).
70. Rehn M, Wenzel A, Frank AK, Schuster MB, Pundhir S, Jorgensen N, Vitting-Seerup K, Ge Y, Jendholm J, Michaut M, Schoof EM, Jensen TL, Rapin N, Sapio RT, Andersen KL, Lund AH, Solimena M, Holzenberger M, Pestov DG, Porse BT. PTBP1 promotes hematopoietic stem cell maintenance and red blood cell development by ensuring sufficient availability of ribosomal constituents. Cell Rep 39(6) (2022).
71. Wang RX, Amoyel M. mRNA translation is dynamically regulated to instruct stem cell fate. Front Mol Biosci 9 (2022).
72. Bennett AH, O'Donohue MF, Gundry SR, Chan AT, Widrick J, Drapers I, Chakraborty A, Zhou Y, Zon LI, Gleizes PE, Beggs AH, Gupta VA. RNA helicase, DDX27 regulates skeletal muscle growth and regeneration by modulation of translational processes. Plos Genet 14(3) (2018).
73. Le Bouteiller M, Souilhol C, Beck-Cormier S, Stedman A, Burlen-Defranoux O, Vandormael-Pournin S, Bernex F, Cumano A, Cohen-Tannoudji M. Notchless-dependent ribosome synthesis is required for the maintenance of adult hematopoietic stem cells. J Exp Med. 2013;210(11):2351–69.
74. Stedman A, Beck-Cormier S, Le Bouteiller M, Raveux A, Vandormael-Pournin S, Coqueran S, Lejour V, Jarzebowski L, Toledo F, Robine S, Cohen-Tannoudji M. Ribosome biogenesis dysfunction leads to p53-mediated apoptosis and goblet cell differentiation of mouse intestinal stem/progenitor cells. Cell Death Differ. 2015;22(11):1865–76.
75. Gayraud-Morel B, Le Bouteiller M, Commere PH, Cohen-Tannoudji M, Tajbakhsh S. Notchless defines a stage-specific requirement for ribosome biogenesis during lineage progression in adult skeletal myogenesis. Development 145(23) (2018).
76. Häfner SJ, Jansson MD, Altinel K, Andersen KL, Abay-Norgaard Z, Menard P, Fontenas M, Sorensen DM, Gay DM, Arendrup FS, Tehler D, Krogh N, Nielsen H, Kraushar ML, Kirkeby A, Lund AH. Ribosomal RNA 2'-O-methylation dynamics impact cell fate decisions. Dev Cell 2023;58(17): 1593-1609.
77. Guzzi N, Ciesla M, Ngoc PCT, Lang S, Arora S, Dimitriou M, Pimková K, Sommarin MNE, Munita R, Lubas M, Lim Y, Okuyama K, Soneji S, Karlsson G, Hansson J, Jönsson G, Lund AH, Sigvardsson M, Hellström-Lindberg E, Hsieh AC, Bellodi C. Pseudouridylation of tRNA-Derived fragments steers translational control in stem cells. Cell. 2018;173(5):1204–16.
78. Balogh E, Chandler JC, Varga M, Tahoun M, Menyhárd DK, Schay G, Goncalves T, Hamar R, Légrádi R, Szekeres A, Gribouval O, Kleta R, Stanescu H, Bockenhauer D, Kerti A, Williams H, Kinsler V, Di WL, Curtis D, Kolatsi-Joannou M, Hammid H, Szöcs A, Perczel K, Maka E, Toldi G, Sava F, Arrondel C, Kardos M, Fintha A, Hossain A, D'Arco F, Kaliakatsos M, Koeglmeier J, Mifsud W, Moosajee M, Faro A, Jávorszky E, Rudas G, Saied MH, Marzouk S, Kelen K, Götze J, Reusz G, Tulassay T, Dragon F, Mollet G, Motameny S, Thiele H, Dorval G, Nürnberg P, Perczel A, Szabó AJ, Long DA, Tomita K, Antignac C, Waters AM, Tory K. Pseudouridylation defect due to and mutations causes nephrotic syndrome with cataracts, hearing impairment, and Enterocolitis. P Natl Acad Sci USA. 2020;117(26):15137–47.

79. Li H, Wang BB, Yang A, Lu R, Wang WC, Zhou Y, Shi GL, Kwon SW, Zhao YM, Jin Y. Ly-1 antibody reactive clone is an important nucleolar protein for control of Self-Renewal and differentiation in embryonic stem cells. Stem Cells. 2009;27(6):1244–54.
80. Nachmani D, Bothmer AH, Grisendi S, Mele A, Bothmer D, Lee JD, Monteleone E, Cheng K, Zhang Y, Bester AC, Guzzetti A, Mitchell CA, Mendez LM, Pozdnyakova O, Sportoletti P, Martelli MP, Vulliamy TJ, Safra M, Schwartz S, Luzzatto L, Bluteau O, Soulier J, Darnell RB, Falini B, Dokal I, Ito K, Clohessy JG, Pandolfi PP. Germline mutations lead to altered rRNA 2′-O-methylation and cause dyskeratosis congenita. Nat Genet. 2019;51(10):1518–29.
81. Fong YW, Ho JJ, Inouye C, Tjian R. The dyskerin ribonucleoprotein complex as an OCT4/SOX2 coactivator in embryonic stem cells. Elife 3 (2014).
82. Johansson H, Simonsson S. Core transcription factors, Oct4, Sox2 and Nanog, individually form complexes with nucleophosmin (Npm1) to control embryonic stem (ES) cell fate determination. Aging-Us. 2010;2(11):815–22.
83. Chen E, Sharma MR, Shi XY, Agrawal RK, Joseph S. Fragile X mental retardation protein regulates translation by binding directly to the ribosome. Mol Cell. 2014;54(3):407–17.
84. Kim TH, Tsang B, Vernon RM, Sonenberg N, Kay LE, Forman-Kay JD. Phosphodependent phase separation of FMRP and CAPRIN1 recapitulates regulation of translation and deadenylation. Science. 2019;365(6455):825–9.
85. Kottakis F, Foltopoulou P, Sanidas I, Keller P, Wronski A, Dake BT, Ezell SA, Shen Z, Naber SP, Hinds PW, McNiel E, Kuperwasser C, Tsichlis PN. NDY1/KDM2B functions as a master regulator of polycomb complexes and controls Self-Renewal of breast Cancer stem cells. Cancer Res. 2014;74(14):3935–46.
86. Lv KS, Gong CJ, Antony C, Han X, Ren JG, Donaghy R, Cheng Y, Pellegrino S, Warren AJ, Paralkar VR, Tong W. HectD1 controls hematopoietic stem cell regeneration by coordinating ribosome assembly and protein synthesis. Cell Stem Cell. 2021;28(7):1275–90.
87. Warren AJ. Molecular basis of the human ribosomopathy Shwachman-Diamond syndrome. Adv Biol Regul. 2018;67:109–27.
88. Woloszynek JR, Rothbaum RJ, Rawls AS, Minx PJ, Wilson RK, Mason PJ, Bessler M, Link DC. Mutations of the gene are present in most patients with Shwachman-Diamond syndrome. Blood. 2004;104(12):3588–90.
89. Boocock GRB, Morrison JA, Popovic M, Richards N, Ellis L, Durie PR, Rommens JM. Mutations in SBDS are associated with Shwachman-Diamond syndrome. Nat Genet. 2003;33(1):97–101.
90. Dhanraj S, Matveev A, Li HB, Lauhasurayotin S, Jardine L, Cada M, Zlateska B, Tailor CS, Zhou J, Mendoza-Londono R, Vincent A, Durie PR, Scherer SW, Rommens JM, Heon E. Dror. Biallelic mutations in DNAJC21 cause Shwachman-Diamond syndrome. Blood. 2017;129(11):1557–62.
91. Tan SJ, Kermasson L, Hoslin A, Jaako P, Faille A, Acevedo-Arozena A, Lengline E, Ranta D, Poirée M, Fenneteau O, le Pointe HD, Fumagalli S, Beaupain B, Nitschké P, Bôle-Feysot C, de Villartay JP, Bellanné-Chantelot C, Donadieu J, Kannengiesser C, Warren AJ, Revy P. EFL1 mutations impair eIF6 release to cause Shwachman-Diamond syndrome. Blood. 2019;134(3):277–90.
92. Tummala H, Walne AJ, Williams M, Bockett N, Collopy L, Cardoso S, Ellison A, Wynn R, Leblanc T, Fitzgibbon J, Kelsell DP, van Heel DA, Payne E, Plagnol V, Dokal I, Vulliamy T. Mutations link a Cancer-Prone bone marrow failure syndrome to corruption in 60S ribosome subunit maturation. Am J Hum Genet. 2016;99(1):115–24.
93. Finch AJ, Hilcenko C, Basse N, Drynan LF, Goyenechea B, Menne TF, Fernández AG, Simpson P, D'Santos CS, Arends MJ, Donadieu J, Bellanné-Chantelot C, Costanzo M, Boone C, McKenzie AN, Freund SMV, Warren AJ. Uncoupling of GTP hydrolysis from eIF6 release on the ribosome causes Shwachman-Diamond syndrome. Gene Dev. 2011;25(9):917–29.
94. Menne TF, Goyenechea B, Sánchez-Puig N, Wong CC, Tonkin LM, Ancliff PJ, Brost RL, Costanzo M, Boone C, Warren AJ. The Shwachman-Bodian-Diamond syndrome protein mediates translational activation of ribosomes in yeast. Nat Genet. 2007;39(4):486–95.
95. Wong CC, Traynor D, Basse N, Kay RR, Warren AJ. Defective ribosome assembly in Shwachman-Diamond syndrome. Blood. 2011;118(16):4305–12.
96. Wang JW, Liu JH, Ye MM, Liu F, Wu S, Huang JJ, Shi G. Ddx56 maintains proliferation of mouse embryonic stem cells via ribosome assembly and interaction with the Oct4/Sox2 complex. Stem Cell Res Ther 11(1) (2020).
97. Liakath-Ali K, Mills EW, Sequeira I, Lichtenberger BM, Pisco AO, Sipilä KH, Mishra A, Yoshikawa H, Wu CCC, Ly T, Lamond AI, Adham IM, Green R, Watt FM. An evolutionarily conserved ribosome-rescue pathway maintains epidermal homeostasis. Nature. 2018;556(7701):376–80.
98. Tan SM, Altschuler G, Zhao TY, Ang HS, Yang H, Lim B, Vardy L, Hide W, Thomson AM, Lareu RR. Divergent LIN28-mRNA associations result in translational suppression upon the initiation of differentiation. Nucleic Acids Res. 2014;42(12):7997–8007.
99. Chang WY, Stanford WL. Translational control: A new dimension in embryonic stem cell network analysis. Cell Stem Cell. 2008;2(5):410–2.
100. Komili S, Farny NG, Roth FP, Silver PA. Functional specificity among ribosomal proteins regulates gene expression. Cell. 2007;131(3):557–71.
101. Shi Z, Barna M, Regulons RNA, Proteins RNA-B. Annu Rev Cell Dev Biol. 2015;31(1):31–54.
102. Xue S, Tian S, Fujii K, Kladwang W, Das R, Barna M. RNA Regulons in hox 5′ UTRs confer ribosome specificity to gene regulation. Nature. 2014;517(7532):33–8.
103. Shi Z, Fujii K, Kovary KM, Genuth NR, Röst HL, Teruel MN, Barna M. Heterogeneous ribosomes preferentially translate distinct subpools of mRNAs Genome-wide. Mol Cell. 2017;67(1):71–83.
104. Genuth NR, Barna M. The discovery of ribosome heterogeneity and its implications for gene regulation and organismal life. Mol Cell. 2018;71(3):364–74.
105. Lee ASY, Kranzusch PJ, Cate JHD. eIF3 targets cell-proliferation messenger RNAs for translational activation or repression. Nature. 2015;522(7554):111–4.
106. Di Stefano B, Luo EC, Haggerty C, Aigner S, Charlton J, Brumbaugh J, Ji F, Jiménez IR, Clowers KJ, Huebner AJ, Clement K, Lipchina I, de Kort MAC, Anselmo A, Pulice J, Gerli MFM, Gu HC, Gygi SP, Sadreyev RI, Meissner A, Yeo GW. Hochedlinger. The RNA helicase DDX6 controls cellular plasticity by modulating P-Body homeostasis. Cell Stem Cell. 2019;25(5):622–38.
107. Lee JY, Nakada D, Yilmaz OH, Tothova Z, Joseph NM, Lim MS, Gilliland DG, Morrison SJ. mTOR activation induces tumor suppressors that inhibit leukemogenesis and deplete hematopoietic stem cells after deletion. Cell Stem Cell. 2010;7(5):593–605.
108. Yang G, Smibert CA, Kaplan DR, Miller FD. An eIF4E1/4E-T complex determines the genesis of neurons from precursors by translationally repressing a proneurogenic transcription program. Neuron. 2014;84(4):723–39.
109. Kondoh H, Lleonart ME, Nakashima Y, Yokode M, Tanaka M, Bernard D, Gil J, Beach D. A high glycolytic flux supports the proliferative potential of murine embryonic stem cells. Antioxid Redox Sign. 2007;9(3):293–9.
110. Hwang I-Y, Kwak S, Lee S, Kim H, Lee SE, Kim J-H, Kim YA, Yoon K, Jeon DH, Chung X, Jin S, Park H, Jang E-J, Cho H-D. Youn. Psat1-Dependent fluctuations in α-Ketoglutarate affect the timing of ESC differentiation. Cell Metab. 2016;24(3):494–501.
111. Xu XL, Duan SL, Yi F, Ocampo A, Liu GH, Belmonte JCI. Mitochondrial regulation in pluripotent stem cells. Cell Metab. 2013;18(3):325–32.
112. Chung S, Arrell DK, Faustino RS, Terzic A, Dzeja PP. Glycolytic network restructuring integral to the energetics of embryonic stem cell cardiac differentiation. J Mol Cell Cardiol. 2010;48(4):725–34.
113. Facucho-Oliveira JM, Alderson J, Spikings EC, Egginton S, John JCS. Mitochondrial DNA replication during differentiation of murine embryonic stem cells. J Cell Sci. 2007;120(22):4025–34.
114. Klymkowsky M, Suhr ST, Chang EA, Tjong J, Alcasid N, Perkins GA, Goissis MD, Ellisman MH, Perez GI, Cibelli JB. Mitochondrial Rejuvenation after Induced Pluripotency. Plos One 5(11) (2010).
115. Bohnsack MT, Sloan KE. The mitochondrial epitranscriptome: the roles of RNA modifications in mitochondrial translation and human disease. Cell Mol Life Sci. 2018;75(2):241–60.
116. He J, Cooper HM, Reyes A, Di Re M, Kazak L, Wood SR, Mao CC, Fearnley IM, Walker JE, Holt IJ. Human C4orf14 interacts with the mitochondrial nucleoid and is involved in the biogenesis of the small mitochondrial ribosomal subunit. Nucleic Acids Res. 2012;40(13):6097–108.
117. Shi ZN, Xu SY, Xing SH, Yao K, Zhang L, Xue LX, Zhou P, Wang M, Yan GQ, Yang PY, Liu J, Hu ZP, Lan F. Mettl17, a regulator of mitochondrial ribosomal RNA modifications, is required for the translation of mitochondrial coding genes. Faseb J. 2019;33(11):13040–50.
118. Zhang F, Yoon K, Zhang DY, Kim NS, Ming GL, Song HJ. Epitranscriptomic regulation of cortical neurogenesis via Mettl8-dependent mitochondrial tRNA m3C modification. Cell Stem Cell. 2023;30(3):300–11.
119. Silva J, Aivio S, Knobel PA, Bailey LJ, Casali A, Vinaixa M, Garcia-Cao I, Coyaud É, Jourdain AA, Pérez-Ferreros P, Rojas AM, Antolin-Fontes A, Samino-Gené S, Raught B, González-Reyes A, de Pouplana LR, Doherty AJ, Yanes O, Stracker TH. EXD2 governs germ stem cell homeostasis and lifespan by promoting mitoribosome integrity and translation. Nat Cell Biol. 2018;20(2):162–74.
120. Sighel D, Notarangelo M, Aibara S, Re A, Ricci G, Guida M, Soldano A, Adami V, Ambrosini C, Broso F, Rosatti EF, Longhi S, Buccarelli M, D'Alessandris QG, Giannetti S, Pacioni S, Ricci-Vitiani L, Rorbach J, Pallini R, Roulland S, Amunts A, Mancini I, Modelska A, Quattrone A. Inhibition of mitochondrial translation suppresses glioblastoma stem cell growth. Cell Rep 35(4) (2021).

121. Trixl L, Amort T, Wille A, Zinni M, Ebner S, Hechenberger C, Eichin F, Gabriel H, Schoberleitner I, Huang AM, Piatti P, Nat R, Troppmair J, Lusser A. RNA cytosine methyltransferase Nsun3 regulates embryonic stem cell differentiation by promoting mitochondrial activity. Cell Mol Life Sci. 2018;75(8):1483–97.
122. Xu XT, Ahmed T, Wang LL, Cao XT, Zhang ZY, Wang M, Lv Y, Kanwal S, Tariq M, Lin RX, Zhang H, Huang YH, Peng H, Lin DN, Shi X, Geng DD, Liu BH, Zhang XF, Yi W, Qin Y, Esteban MA, Qin BM. The mTORC1-eIF4F axis controls paused pluripotency. Embo Rep 23(2) (2022).
123. Chatla S, Du W, Wilson AF, Meetei AR, Pang QS. Fancd2-deficient hematopoietic stem and progenitor cells depend on augmented mitochondrial translation for survival and proliferation. Stem Cell Res 40 (2019).
124. Zhou FB, Aroua N, Liu Y, Rohde C, Cheng JD, Wirth AK, Fijalkowska D, Göllner S, Lotze M, Yun HY, Yu XB, Pabst C, Sauer T, Oellerich T, Serve H, Röllig C, Bornhäuser M, Thiede C, Baldus C, Frye M, Raffel S, Krijgsveld J, Jeremias I, Beckmann R, Trumpp A. Müller-Tidow. A dynamic rRNA ribomethylome drives stemness in acute myeloid leukemia. Cancer Discov. 2023;13(2):332–47.
125. Xing CC, Hang ZC, Guo WH, Li YX, Shah RS, Zhao YH, Zeng ZH, Du HW. Stem cells from human exfoliated deciduous teeth rejuvenate the liver in naturally aged mice by improving ribosomal and mitochondrial proteins. Cytotherapy. 2023;25(12):1285–92.
126. Wang J, Yang BC, Lv CF, Chen TC, Sun LX, Sun L, Hao JF, Ding F, Wang TY, Jiang JZ, Qin Y. Amino porphyrin-peptide assemblies induce ribosome damage and cancer stem cell Inhibition for an enhanced photodynamic therapy. Biomaterials 289 (2022).
127. Rodgers JT, King KY, Brett JO, Cromie MJ, Charville GW, Maguire KK, Brunson C, Mastey N, Liu L, Tsai CR, Goodell MA, Rando TA. mTORC1 controls the adaptive transition of quiescent stem cells from G to G. Nature. 2014;510(7505):393–6.
128. Hirose K, Shiomi T, Hozumi S, Kikuchi Y. Mechanistic target of Rapamycin complex 1 signaling regulates cell proliferation, cell survival, and differentiation in regenerating zebrafish fins. Bmc Dev Biol 14 (2014).
129. González-Estévez C, Felix DA, Smith MD, Paps J, Morley SJ, James V, Sharp TV, Aboobaker AA. SMG-1 and mTORC1 act antagonistically to regulate response to injury and growth in planarians. Plos Genet 8(3) (2012).
130. Johnson K, Bateman J, DiTommaso T, Wong AY, Whited JL. Systemic cell cycle activation is induced following complex tissue injury in Axolotl. Dev Biol. 2018;433(2):461–72.
131. Mi LJ, Qi QH, Ran HW, Chen LS, Li D, Xiao DK, Wu JQ, Cai Y, Zhang SY, Li YY, Li BH, Xie J, Huang HH, Li T, Zhou T, Li AL, Qi J, Li FY, Man JH. Suppression of ribosome biogenesis by targeting WD repeat domain 12 (WDR12) inhibits glioma Stem-Like cell growth. Front Oncol 11 (2021).
132. Ito N, Katoh K, Kushige H, Saito Y, Umemoto T, Matsuzaki Y, Kiyonari H, Kobayashi D, Soga M, Era T, Araki N, Furuta Y, Suda T, Kida Y, Ohta K. Ribosome incorporation into somatic cells promotes lineage transdifferentiation towards multipotency. Sci Rep-Uk 8 (2018).
133. Ito N, Anam MB, Ahmad SAI, Ohta K. Transdifferentiation of human somatic cells by ribosome. Dev Growth Differ. 2018;60(5):241–7.
134. Kudo M, Anam MB, Istiaq A, Ahmad SAI, Ito N, Ohta K. Ribosome incorporation induces EMT-like phenomenon with cell cycle arrest in human breast Cancer cell. Cells Tissues Organs. 2022;211(2):212–21.
135. Guttman M, Donaghey J, Carey BW, Garber M, Grenier JK, Munson G, Young G, Lucas AB, Ach R, Bruhn L, Yang XP, Amit I, Meissner A, Regev A, Rinn JL, Root DE. Lander. LincRNAs act in the circuitry controlling pluripotency and differentiation. Nature. 2011;477(7364):295–300.

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