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Review paper

Potentials of ribosomopathy gene as pharmaceutical targets for cancer treatment

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ABSTRACT

Ribosomopathies encompass a spectrum of disorders arising from impaired ribosome biogenesis and reduced functionality. Mutation or dysexpression of the genes that disturb any finely regulated steps of ribosome biogenesis can result in different types of ribosomopathies in clinic, collectively known as ribosomopathy genes. Emerging data suggest that ribosomopathy patients exhibit a significantly heightened susceptibility to cancer. Abnormal ribosome biogenesis and dysregulation of some ribosomopathy genes have also been found to be intimately associated with cancer development. The correlation between ribosome biogenesis or ribosomopathy and the development of malignancies has been well established. This work aims to review the recent advances in the research of ribosomopathy genes among human cancers and meanwhile, to excavate the potential role of these genes, which have not or rarely been reported in cancer, in the disease development across cancers. We plan to establish a theoretical framework between the ribosomopathy gene and cancer development, to further facilitate the potential of these genes as diagnostic biomarker as well as pharmaceutical targets for cancer treatment.

1. Introduction

Ribosomes are known as the most essential machine that provide energy and functional macromolecules in an organism and are responsible for translating mRNA into proteins within living cells. Ribosome biogenesis (Ribi) is a multistep process that synthesizes the mature ribosome and plays a critical role in supporting cell proliferation, differentiation, development, and transformation [1]. Malignant growth and expansion of cancer cells characterized by uncontrolled cell proliferation and metastasis require heightened protein synthesis to sustain elevated cell mitosis rates, therefore leading to increased demand for ribosome provision [2]. Over the past decade, causal relationships between dysregulated Ribi and increased cancer risk have been established. Abnormal Ribi is now also recognized as an important hallmark of cancer cells. Moreover, emerged studies have demonstrated that tumor suppressors, oncogenes, and proto-oncogenes can regulate the malignant progression of cancer by altering Ribi [3]. Consequently, increasing attention has been given to the study of Ribi and tumor development, including but not limited to molecular regulatory mechanisms and cancer treatment strategies.

Ribosomopathy is a class of clinical diseases caused by defects in Ribi, including Diamond-Blackfan anemia (DBA), Schwachman-

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Diamond syndrome (SDS), dyskeratosis congenita (DC), cartilage hair hypoplasia (CHH), 5q-syndrome (5q), Treacher Collins syndrome (TCS), and others [4]. The etiology of most of these diseases can be attributed to mutations in the genes that encode multiple ribosomal proteins (RPs) or ribosome assembly factors, and further result in impaired Ribi. In addition to TCS, the common features of patients suffering from ribosomopathy comprise defects in erythropoiesis, bone marrow failure, and varied growth and developmental disorders [5]. More notably, emerged evidence has shown the heightened susceptibility to cancer in ribosomopathy patients, as compared to the general population. As early as 2008, MacInnes et al. [6] found that individual carrying more than a dozen different heterozygous mutations in RPs had a high incidence of malignant peripheral nerve sheath tumors in a zebrafish model. The incidence of cancer is approximately 11-fold higher in individuals with DC, and the relative risk of cancer is 13.7-fold higher in DBA patients [7,8]. This implied that ribosomopathy genes may play a key role in developing malignancies. Although some of these genes have been found to participate in the cancer regulation network, the systematic and in-depth value of ribosomopathy genes in cancer development as well as cancer diagnosis has not been well discussed.

Recent studies have highlighted that Ribi is a promising target for cancer treatment. Numerous anti-cancer drugs have been found to work in part by interfering with Ribi. Examples include oxaliplatin and actinomycin D, which inhibit ribosomal DNA (rDNA) transcription, as well as 5-fluorouracil (5-Fu) and camptothecin, which target ribosomal RNA (rRNA) processing [9]. In recent years, RNA polymerase I (RNA Pol I) inhibitors, such as CX-5461 and CX-3543, have emerged as potential therapeutics [10]. These findings seem to provide a more direct strategy for supporting the viability of targeting Ribi in cancer treatment. However, these drugs possess resistance, adverse effects, low specificity, and mediocre efficacy. This calls for further exploration of more precise and specific targets to facilitate the development of improved therapeutic agents.

In this study, we conducted a comprehensive overview of ribosomopathy genes in cancer development. We highlighted the potential of these ribosomopathy genes which can function as the promising pharmaceutical targets in cancer treatment, and provided a new perspective and possibility for Ribi-based cancer treatment strategies.

2. Ribi and dysregulated Ribi in cancer

As shown in Fig. S1 [11], eukaryotic Ribi is mainly carried out in the cell nucleolus and involves the biogenesis, processing, and modification of precursor rRNA, assembly of RPs, and incorporation of additional assembling factors. First, 47S pre-rRNA is transcribed from rDNA in the presence of RNA Pol I and transcription initiation factors, and then cleaved into 28S, 18S, and 5.8S rRNA. Subsequently, 47 distinct RPs (known as RPLs, e.g., RPL5 and RPL11) associate with 28S, 5.8S, 5S rRNA to form the ribosome precursor 60S (pre-60S subunit), and 33 distinct RPs (known as RPSs, e.g., RPS3 and RPS23) bind to 18S rRNA to form the ribosome precursor 40S (pre-40S subunit). These ribosomal particles are then transported to the cytoplasm for further assembly and maturation. A mature 80S ribosome with translational activity consists of the 40S small subunit and the 60S large subunit. The 40S small subunit decodes genetic information, while the 60S large subunit catalyzes of peptide bond formation. Together, the coordinated action of these subunits render the formation of an active and mature molecular machine that can be capable of efficient protein synthesis. Eukaryotes are regulated by “cotranscriptional” events, and contrary to what might be initially thought, much of the processing does not occur after transcription has terminated, but rather during transcription. It's worth noting that rRNA transcription does not usually exist in a “naked form”, and that the correct folding of pre-rRNA in both large and small ribosomal subunits requires the deposition of a large number of RPs and their accurate localization and binding, e.g., RPL3 binds very early in pre-60S biogenesis. In addition, Ribi factors can also participate in the rRNA assembly and processing process, together to complete this highly complex, dynamic assembly process [12].

As compared to normal cells, cancer cells harbor a dysregulated Ribi that embodies hyperactived RNA Pol I, up-regulated rRNA transcription, abnormal modifications of rRNA and cancer-driven translation. All of these disturbances implicate the abnormal Ribi in increased cancer risk and poor prognosis [13]. Qualitative modifications of the ribosome can exert oncogenic potential, including destabilization of rDNAs and modifications and mutations of rRNAs and RPs. For example, instability of the rDNA locus may lead to malignant transformation of cells and its methylation is a key factor in carcinogenesis [14]. Heterozygous mutations in the *RP* gene cause an increased incidence of colon adenocarcinoma (COAD) and osteosarcoma. In addition to translation, the functions of RPs in development, differentiation, and tumorigenesis are also known as “extra-ribosomal functions”. Some of these studies showed that knockdown of certain RPs induced G1-phase cell cycle arrest [15]. As a highly dynamic structure, the nucleolus regulates cell growth according to external stimuli, and its size, shape, and number change to some extent after stimulation [16]. Nucleolus size is directly correlated with the degree of cancer malignancy and is a parameter that predicts the clinical outcome of the disease [17]. A study has since found that in neuroblastoma, the higher the Ribi activity is, the worse the prognosis, which corroborates the above view to some extent [18]. These observations suggest the significance of Ribi in cancer.

3. Ribosomopathy and its causative genes

3.1. Common ribosomopathies

The common human ribosomopathies in the clinic include DBA, SDS, DC, CHH, 5q, and TCS. The zebrafish, murine, or human disease models of DBA, SDS, 5q, DC, and TCS are well-established and have shown that these diseases are linked to different causative genes that affect distinct steps in Ribi, ultimately leading to ribosome defects and disease occurrence. Specifically, DBA is caused by multiple *RPs* gene mutations, and deficiency of any of the *RPs* gene impairs the occurrence of pre-40S and pre-60S, ultimately affecting the production of mature ribosome. SDS is caused by mutations in Shwachman-Bodian-Diamond syndrome (*SBDS*) gene and further leads to the obstacle in eukaryotic initiation factor 6 (eIF6) releasing from pre-60S, and thus cannot participate in late 60S maturation in the cytoplasm. DC is caused by mutations in the *DKC1* gene, which encodes dyskerin, an enzyme that performs pseudouridination of rRNA. *DKC1* mutations impair the processing and modification of the 47S precursor and prevent the formation of mature rRNA. CHH is caused by mutations in *RMRP* gene, encoding the RNA component of the mitochondrial RNA processing complex, which can restrict the function of the cleavage precursor rRNA and impair 5.8S rRNA maturation at the 5′ end. 5q is related to haploinsufficiency of small ribosomal subunit protein 14 (*RPS14*). Deletion of *RPS14* allows the failure of pre-40S synthesis, which ultimately leads to a reduction in 80S ribosome. TCS was caused by mutations in *POLR1C* and *POLR1D*, encoding the Pol I and Pol III subunits, and *TCOF1*, encoding the protein Treacle, which can result in reduced transcription of 47S pre-rRNA (Fig. 1 [11]). However, these diseases share a common feature of being associated with abnormalities in Ribi and function, and presenting disrupted cellular

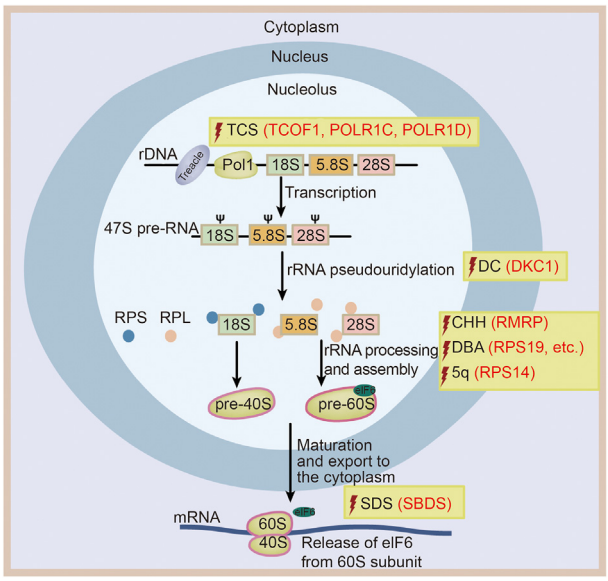

Fig. 1. Association between ribosomopathy and gene mutations in abnormal ribosome biogenesis. Various mutated genes in the different steps of ribosome biogenesis were shown, including *POLR1C*, *POLR1D*, *TCOF1* genes (related to the Treacher Collins syndrome (TCS)), *DKC1* gene (related to the dyskeratosis congenita (DC)), *RMRP* gene (related to the cartilage hair hypoplasia (CHH)), multiple ribosomal protein genes (related to the Diamond-Blackfan anemia (DBA)), *RPS14* gene (related to the 5q syndrome (5q)), and Shwachman-Bodian-Diamond syndrome (*SBDS*) gene (related to the Schwachman-Diamond syndrome (SDS)). rDNA: ribosomal DNA; Pol: polymerase; RPS: small ribosomal subunit protein; RPL: large ribosomal subunit protein; eIF6: eukaryotic initiation factor 6. Reprinted from Ref. [11] with permission.

proliferation, differentiation, and regulation. Most importantly, they exhibit a higher susceptibility to various types of cancers (Table 1 [19–25]). This further underscores the important role of ribosomes in cancer development. The molecular basis of ribosomopathies is mainly associated with nucleolar stress activation and abnormal mRNA translation. Studies in a zebrafish model of DBA were the first to show that p53 activation/nucleolar stress played a critical role in ribosomopathies [26]. Recasens-Alvarez et al. [27] modeled human ribosomopathies in Drosophila and found that ribosomopathy-associated mutations cause proteotoxic stress that is alleviated by target of rapamycin (TOR) inhibition. Herein, we focus on the ribosomopathy genes in each disease. The function of each ribosomopathy gene in Ribi was summarized in Table S1. The association between dysregulated genes in common ribosomopathies and cancer progression are summarized in Tables 2 [28–47] and S2 [48–82].

3.1.1. DBA

DBA is the first described human ribosomopathy and the most prevalent type of ribosomopathy. DBA represents a rare congenital bone marrow failure syndrome. The primary characteristic of DBA is the disruption in the production of red blood cells, thus resulting in insufficient hemoglobin levels necessary for normal growth and development. This condition typically manifests in infancy, with symptoms including pale skin, weakness, lethargy, neuromotor learning difficulty, and severe anemia [19]. Additionally, individuals with DBA may exhibit various physical structural abnormalities, such as short stature, craniofacial dysmorphism, urinary and reproductive abnormalities, cardiac defects, and an increased susceptibility to cancer [83,84]. Classical DBA was found to be associated with 20 types of *RP* gene mutations, which lead to defect in rRNA maturation and further result in nucleolar stress that activates the p53 pathway and its targets, thereby inducing cell cycle arrest and apoptosis. In addition, an alternative or potentially complementary hypothesis was reported in which impaired maturation of ribosome subunits can lead to delayed translation of globin, resulting in inadequate proliferation of blood cells. The classical ribosomopathy genes of DBA include *RPL5*, *RPL11*, *RPL35A*, R*PS24*, *RPS7*, *RPS10*, *RPS19*, and *RPS26*, etc., which are either mutated or haploinsufficient [85–88]. Among these genes, *RPS19* is not only the first gene to be identified but also the most commonly mutated gene, primarily in a heterozygous state [89]. *RPS19*, *RPS17*, *RPS7*, and other *RPs* are involved in the maturation of 18S rRNA, and their deletion leads to a reduction in the population of free 40S small subunits. Depletion of *RPL5*, *RPL11*, and *RPL35A* proteins results in decreased

Table 1
Ribosomopathy gene defects and clinical features and cancer risk.

Ribosomopathy	Clinical features	Incidence	Cancer risk	Treatment	Refs.
DBA	Anemia; Growth and stunting; Malformations of the head, genitourinary tract, heart and limbs	7/1,000,000 (France)	MDS; AML	Glucocorticoids; HSCT; Chronic red blood cell transfusions with iron chelation	[19]
SDS	Pancreatic exocrine deficiency; Bone marrow failure	1/168,000 (Italy)	MDS; AML; Myeloid malignancy	Pancreatic enzyme supplementation; Nutritional support; Blood transfusion; HSCT	[20,21]
DC	Reticular hyperpigmentation; Nail dystrophy and white spots; Bone marrow failure	1/1,000,000	Tongue cancer; Squamous cell skin cancer; Anogenital, gastric esophageal and lymphoma AML	Androgen; Blood transfusion; HSCT	[22]
CHH	Short limbs; Stunted hair growth; Impaired cell-mediated immunity and erythropoiesis	1/23,000 (Finland)	Basal cell carcinoma; Squamous cell carcinoma; Non-Hodgkin's lymphoma	HSCT; Surgical correction (children with severe skeletal abnormalities)	[23]
5q	Macrocytic anemia	NA	AML	Blood transfusion; HSCT; Immunosuppressants; Immunomodulators; Chemotherapy	[24]
TCS	Mandibulofacial dysplasia	1/50,000	NA	Bone and soft tissue reconstruction	[25]

DBA: Diamond-Blackfan anemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; SDS: Schwachman-Diamond syndrome; DC: dyskeratosis congenita; CHH: cartilage hair hypoplasia; 5q: 5q syndrome; NA: not available; TCS: Treacher Collins syndrome.

Table 2
The dysregulated ribosomopathy genes of Diamond-Blackfan anemia are associated with cancer progression.

Related genes	Cancer types	Altered expression level	Functional alterations	Related signal pathway	Refs.
RPS19	BRCA	Up-regulation	Promotion of tumor growth;	Complement C5a receptor 1	[28,29]
	OV		Suppressing anti-tumor immune responses	NA	
	Squamous skin cancer	Up-regulation	Promoting the migration and invasion ability of tumor; Regulation of EMT marker expression	Akt/mTOR/c-Myc signaling pathway	[30]
	PRAD	Up-regulation	Associated with elevated Gleason grade	NA	[31]
RPS17	NA	NA	NA	NA	
RPS24	COAD	NA	Promoting tumor proliferation, migration; Regulating cell cycle	NA	[32]
		Up-regulation	Promoting tumor angiogenesis	RPS24c/MVIH/PGK1 pathway	[33]
	HCC	Up-regulation	Promoting tumor growth and proliferation; Associated with poor prognosis	NA	[34]
	PRAD	Up-regulation	Associated with high Gleason grade	NA	[31]
	LUAD	Up-regulation	Promoting tumor proliferation, migration, and invasion	NA	[35]
RPL5	BRCA	Down-regulation	Associated with tumor proliferation, G1-S cell cycle transition and apoptosis	Inhibiting P53 degradation by binding to MDM2	[36]
	COAD	Up-regulation	Promoting tumor proliferation and migration	MAPK/ERK signaling pathway	[37]
	MM	Down-regulation	Associated with shorter overall survival	NA	[38]
RPS7	LUAD	Up-regulation	Associated with worse survival outcomes	NA	[39]
	OV	NA	Inhibiting tumor proliferation, migration, and invasion, slows cell cycle progression; Slightly increasing apoptosis and response to cisplatin treatment	PI3K/AKT and MAPK signaling pathways	[40]
RPS15	ESCC	Up-regulation	Promoting proliferation and metastasis; Associated with poor prognosis.	P38 MAPK pathway	[41]
RPL35A	GC	Up-regulation	Promoting cell proliferation and migration; Inhibiting apoptosis and cell cycle	NA	[42]
RPS26	NA	NA	NA	NA	
RPL26	PAAD	NA	Promoting tumor proliferation	NA	[43]
RPS10	NA	NA	NA	NA	
RPL11	BRCA	Down-regulation	Inhibiting tumor proliferation and G1-S cell cycle transition, and induces apoptosis; Associated with overall survival	Binding to MDM2 to inhibit P53 degradation	[36]
RPL36	HCC	Up-regulation	Associated with length of survival	NA	[44]
	Glioma	Up-regulation	Promoting tumor proliferation and G1/S cell cycle progression	NA	[45]
RPS27A	LUAD	Up-regulation	Associated with LUAD progression and poorer prognosis	Enhancing the binding of RPL11 and MDM2	[46]
	Cervical cancer	Up-regulation	Associated with poor prognosis	NA	[47]

BRCA: breast invasive carcinoma; OV: ovarian serous cystadenocarcinoma; NA; not available; EMT: epithelial-mesenchymal transition; PRAD: prostate adenocarcinoma; COAD: colon adenocarcinoma; HCC: hepatocellular carcinoma; LUAD: lung adenocarcinoma; MM: multiple myeloma; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; PAAD: pancreatic adenocarcinoma.

numbers of 60S large subunits, ultimately leading to a significant decrease in mature 80S ribosomes. Despite the highly conserved expression of RPs across organisms, *RP* mutations cause a reduction in mature 80S ribosomes, leading to a cascade of detrimental consequences for the cell and the organism. Some DBA patients also exhibit non-RP mutated genes (*GATA1*, *EPO*, *TSR2*, and *ADA2*), and we do not include them in the ribosomopathy gene category here.

3.1.2. SDS

SDS is an autosomal recessive disorder and another type of congenital bone marrow failure syndrome. It is characterized by severe impairment of pancreatic exocrine secretion, malnutrition, neutropenia observed in blood work, and epiphyseal dysplasia in approximately half of affected children [21,90]. Approximately 90% of SDS patients harbor heterozygous nonsense mutations in the *SBDS* gene located on chromosome 7, leading to a significant decrease in *SBDS* protein expression. Decreased $CD34^{+}$ cells and impaired hematopoietic stem cell colony formation were found in these patients [91]. In addition to *SBDS*, mutations in *EFL1* and *DNAJC21* have also been identified in SDS cases [92,93]. Mutations in *SBDS* and *EFL1* impede the release of eukaryotic initiation factor 6 (eIF6) from pre-60S, thereby affecting late-stage 60S ribosome maturation. This results in impaired translational activity in nascent 80S ribosomes, consequently affecting erythropoiesis [94,95]. SDS is also associated with an increased risk of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and pancreatic adenocarcinoma (PAAD) [96,97].

3.1.3. DC

DC is one of the major types of congenital aplastic anemia and a rare genetic skin disease, with a higher incidence in males than in females [22]. The cutaneous mucosal triad represents the most prominent and characteristic clinical manifestation of DC. It is characterized by reticulopigmentation of the skin, finger (toe) nail dystrophy, and oral mucosal leukoplakia, although these features may not occur simultaneously [98]. DC can be transmitted in three forms, including autosomal dominant manner or autosomal recessive or X-linked pattern. Approximately 19 mutated genes are reported to be associated with DC, and the highest number was found in *DKC1* at Xq28. Most of these genes are telomerase associated genes, and mutation in these genes affect the telomerase components or telomere-stabilizing components and further disturb enzyme function. A significant short can be observed in DC patients. Mutations in *DKC1* lead to X-linked recessive DC. The *DKC1* gene encodes the dyskerin protein, a component of the telomerase complex. In addition, mutation in the RNA component of telomerase, specifically the *TERT* gene, encoding telomere-specific reverse transcriptase and *TERC* gene, encoding an internal RNA template strand and *PARN*, which is involved in telomere maintenance, result in autosomal dominant DC [99]. Mutations in *NOP10*, *NHP2*, *TCAB1*,

and *C16orf57* were associated with autosomal recessive DC. Patients with mutations in *NOP10* have reduced telomere length and reduced *TERC* levels. In general, X-linked DC (XL-DC) is more severe than the other two forms [100,101]. Apart from the heightened susceptibility to progressive bone marrow hematopoietic failure, individuals with DC often face complications such as malignancies, including both hematologic and solid tumors. The most common malignancy observed in DC is squamous cell carcinoma of the head and neck, along with occurrences in the skin, rectum, and cervix [7]. The increased vulnerability to malignancy in DC is primarily attributed to impaired telomerase function rather than impaired Ribi [102,103]. Abnormal telomere shortening renders cells susceptible to premature cell death and tissue damage, thereby contributing to the range of pathological signs and symptoms observed in DC. However, DC is not completely unrelated to Ribi, and there is multiple evidence that it is associated with altered rRNA modifications [104].

3.1.4. CHH

In 1965, McKusick et al. [105] first reported CHH, an autosomal recessive syndrome that exhibits a higher prevalence in the Amish and Finnish populations. The characteristic features of CHH include bone marrow failure, thin and sparse hair, abnormal epiphyseal cartilage development, short limbs, immune dysfunction, and increased susceptibility to malignancies [106]. Among the different types of cancer, basal cell carcinoma, squamous cell carcinoma, and non-Hodgkin's lymphoma are the most commonly observed in individuals with CHH, and they are associated with a generally poor prognosis [107]. CHH is caused by heterozygous mutations in *RMRP*, resulting in low expression levels of RMRP RNA in patients with CHH [108]. Furthermore, *RMRP*, a long noncoding RNA (lncRNA) component, has been found to be upregulated in various cancer types, such as glioma [109], esophageal squamous cell carcinoma (ESCC) [110], and colorectal cancer (CRC) [75], in several studies examining their progression.

3.1.5. 5q

5q syndrome is a separate subtype of MDS caused by mutations in an allele of *RPS14* located on the long arm of chromosome 5 [111]. Haploinsufficiency of *RPS14* leads to impaired processing of 18S rRNA and compromised synthesis of the 40S ribosomal subunit, leading to defective ribosome function [112]. In contrast to other types, 5q syndrome typically manifests in older individuals and generally carries a more favorable prognosis. It is characterized by macrocytic anemia and may also exhibit an increased platelet count. The progression rate to AML in patients with 5q syndrome is approximately 10% [24,113]. Similar to the mechanism of carcinogenesis in patients with DBA, patients with 5q have impaired Ribi synthesis due to *RPS14* haploinsufficiency, which leads to activation of p53, which promotes AML and tumorigenesis.

3.1.6. TCS

TCS was initially described in full in 1900 by an English physician, Treacher Collins [114], as a congenital craniofacial anomaly inherited in an autosomal dominant manner. The key features of this syndrome include hypoplasia of the mandible and zygoma, as well as narrowing of the airways. Generally, individuals with TCS have normal intelligence, although conductive deafness may be present [115]. To date, the genes reported to be mutated in TCS are *TCOF1*, encoding the protein Treacle, and *POLR1C, POLR1D*, encoding both common subunits of RNA Pol I and RNA Pol III, leading to decreased transcription of 47S pre-rRNA. Among patients with TCS, approximately 93% exhibit heterozygous mutations in the *TCOF1* gene [116]. Mutations in *POLR1C*, *POLR1D*, and *TOCF1* cause decreased RNA Pol I activity and rRNA levels, which in turn cause deficiencies in Ribi and p53 activation. Although the regulatory mechanisms involved in TCS and DBA or 5q pathogenesis are strikingly similar, TCS causes ribosome assembly to start by reducing the nascent 47S pre-rRNA transcript, whereas DBA and 5q cause ribosome assembly to start by interfering with the maturation of partially assembled pre-ribosomes. This might help to explain why TCS is the only well-characterized ribosomopathy known to date that does not manifest bone marrow failure and an increased cancer risk. This observation raises intriguing prospects for further investigation. It has been noted by Aspesi and Ellis [11] that TCS somehow avoids bone marrow failure and the increased cancer incidence, implying that inhibiting the upstream steps of Ribi might be a means to treat some bone marrow failure syndromes and reduce cancer predisposition.

3.2. Suspected ribosomopathies

Several previously unrecognized ribosomopathies were gradually identified, including *LTV1*-associated inflammatory poikiloderma with hair abnormalities and acral keratoses (LIPHAK), disorders/differences of sex development, Bowen-Conradi syndrome, progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy syndrome, alopecia, neurological defects and endocrinopathy syndrome, and others. Most of the identified causative genes (Table S3 [117–138]) in these suspected ribosomopathies are associated with ribosome assembly and translation processes. Mutations in these genes disrupt the formation of the appropriate number and proper assembly of functional ribosomes, which can potentially contribute to the development of cancer to some extent.

4. Recent advances in ribosomopathy genes in cancer pathogenesis

4.1. RPL5

RPL5, encoding the ribosomal protein L5, participates in the synthesis of the 60S large subunit in Ribi. Heterozygous *RPL5* mutations or deletions have now been found in various human cancers. Analysis of The Cancer Genome Atlas (TCGA)/International Cancer Genome Consortium (ICGC) pan-cancer dataset, which includes 19,000 cancer samples from 49 cancer types, identified 139 mutations associated with *RPL5* cancers [139]. *RPL5* is a recurrent target of congenital mutations in DBA. It is found that 2% of T-cell acute lymphoblastic leukemia, 11% of glioblastoma (GBM), 28% of melanoma, 34% of breast carcinoma (BRCA), and $\geq$40% of multiple myeloma (MM) cases exhibit *RPL5* deletions or mutations [140]. Research by Dai and Lu [141] demonstrated that *RPL5* inhibits MDM2-mediated p53 ubiquitination, leading to p53 signal activation, cell cycle arrest, and apoptosis. Furthermore, studies have shown that *RPL5* can act as a tumor suppressor in hepatocellular carcinoma (HCC) [142]. In MM, approximately 20%–40% of cases exhibit under-expression of *RPL5*. Lowly-expressed *RPL5* is associated with worse patient survival rates in newly diagnosed cases. Notably, patients with low *RPL5* expression who were treated with bortezomib, a proteasome inhibitor, showed a significant improvement in their progression-free survival. Consequently, *RPL5* expression has emerged as a novel biomarker associated with therapeutic response in myeloma [143,144].

4.2. RPS19

Approximately 25% of DBA patients exhibit mutations in *RPS19*, one of the 33 RP types that, along with 18S rRNA, constitute the small 40S ribosomal subunit. *RPS19* encodes the ribosomal protein

S19, whose deficiency can disrupt the maturation of the 40S ribosomal subunit [89,145,146]. In triple-negative breast cancer (TNBC) progression, ribosomal protein S19 acts as an endogenous ligand that interacts with C5a receptor 1 (C5aR1), which is expressed on tumor-infiltrating myeloid-derived suppressor cells to produce the cytokines transforming growth factor β (TGF-β) and interleukin-10 (IL-10) and induce regulatory T cells. These immune responses promote the recruitment of myeloid-derived suppressor cells into tumors, creating an environment that supports tumor growth and progression [28]. Furthermore, Chen et al. [30] found that the high expression of *RPS19* in A431-III cells may be associated with the aggressiveness of A431-III cells.

4.3. RPS14

RPS14 encodes the ribosomal protein S14, a structural protein that is involved in 40S ribosomal subunit production, along with 18S rRNA and other RPs. In the context of 5q, haploinsufficiency of *RPS14* leads to impaired processing of 18S rRNA, resulting in reduced levels of 40S subunits and dysfunctional ribosomes, consequently leading to the failure of erythropoiesis. Studies have indicated that RPS14 is mainly associated with cell cycle progression. Overexpression of *RPS14* can indirectly induce cell cycle arrest and senescence [147,148]. Recent evidence demonstrates that *RPS14* is highly expressed in rectum adenocarcinoma (READ), glioma, and BRCA, promoting cancer cell proliferation, metastasis, and correlating with poor prognosis [48–50]. However, it is worth mentioning that some researchers, based on bioinformatic analysis, have reported low expression of *RPS14* in TNBC cells, suggesting an association with poor overall survival (OS) in BRCA patients [149]. The contradictory findings regarding *RPS14* expression in BRCA warrant further exploration and investigation to elucidate the underlying mechanisms and potential implications for cancer progression and patient outcomes.

4.4. DKC1

DKC1 mutations are the main cause of XL-DC [150]. *DKC1*, encoding dyskerin pseudouridine synthase 1, plays the role of encoding dyskerin and is highly conserved. It protects telomere integrity by binding to telomerase RNA and catalyzing the pseudouridylation of rRNA. Notably, *DKC1* overexpression is a characteristic feature observed in many aggressive sporadic cancers [102,151].

Mutations in the *DKC1* gene can lead to alterations in the translation of mRNAs encoding tumor suppressor proteins, such as p27 and p53 [152,153]. Studies have shown that mice with *DKC1* mutations exhibit impaired rRNA processing and ribosomal dysfunction even before the onset of telomerase activity defects, displaying phenotypes similar to those observed in humans with the disease [154]. *DKC1* mutation carriers have a higher risk of developing solid tumors, with an overall cancer rate of 40% [102]. More significantly, *DKC1* overexpression has been associated with tumor aggressiveness and drug resistance, indicating a poor prognosis [155]. Dysregulated expression of *DKC1* has been reported in various human cancer types, affecting cancer cell growth, metastasis, and patient prognosis [57,58,156].

4.5. RMRP

The mutation in CHH is found in the *RMRP* gene which encodes the untranslated RNA component of the mitochondrial RNA processing ribonuclease (RNase MRP). This ribonuclease is localized to both the nucleolus and mitochondria [157,158]. The activity of RNase MRP in humans is essential for the cleavage of 5.8S rRNA and Cyclin B, thereby affecting both Ribi and cell cycle regulation [159]. Chen et al. [75] found that *RMRP* is highly-expressed in CRC and is associated with a poor prognosis. Loss of *RMRP* activates the p53 pathway. Moreover, *RMRP* also promotes the growth and proliferation of CRC both *in vitro* and *in vivo* in a p53-dependent manner. Overexpression of *RMRP* has been found in many types of cancers, such as bladder urothelial carcinoma (BLCA), lung adenocarcinoma (LUAD), BRCA, and gastric cancer (GC). It interacts with a variety of microRNAs (miRNAs) to exert oncogenic effects and is significantly associated with poor prognosis. In non-cancer diseases, such as ischemic stroke and depression, *RMRP* expression levels are also altered [159].

4.6. TCOF1

TCOF1, the first pathogenic factor found to be associated with TCS, is a nucleolar factor that regulates rDNA transcription in the nucleolus [160]. Mutations in *TCOF1* which encodes the treacle protein will result in reduced transcription of 47S pre-rRNA [80]. *TCOF1* has been reported to play a key role in several processes, including Ribi, the DNA damage response, mitotic regulation, and telomere integrity [161]. Although, TCS patients do not show an increased cancer incidence, its ribosomopathy gene, *TCOF1*, was found to be involved in multiple cancers. Highly-expressed *TOCF1* was observed in TNBC and liver hepatocellular carcinoma (LIHC). Wu et al. [81] also found that silencing *TCOF1* in HCC inhibited cell proliferation, migration, and invasion while inducing cell cycle arrest and apoptosis. Moreover, *TCOF1* silencing was associated with HCC progression, unfavorable outcomes, and the regulation of *KRAS*-activated genes and epithelial-mesenchymal transition genes in HCC. Recent studies have shown that *TCOF1* mediates the recruitment of glioma-associated oncogene 1 to the nucleolus and induces its binding to RNA Pol I subunit A, and ultimately promoting the activity of RNA Pol I and Ribi [162].

4.7. SBDS

As the predominant pathogenic factor of SDS, *SBDS* encoding the SBDS ribosome maturation factor plays a crucial role in the generation of the 60S large subunit. Mutations in *SBDS* result in a decrease in the maturation of 80S ribosomes. Hao et al. [163] found that *SBDS* is overexpressed in various human cancer types, and its high expression is significantly correlated with unfavorable prognosis. In contrast, *SBDS* knockdown activates p53 through the ribosomal stress RPL5/RPL11-MDM2 pathway, thereby inhibiting cancer cell proliferation and invasion.

4.8. DHX37

DHX37 is a ribosomal assembly factor involved in early pre-rRNA processing steps, which are essential for the production of 18S rRNA and its small subunit [164]. *DHX37* absence in HeLa cells was found to disrupt the maturation process of the 18S rRNA, leading to reduced levels of both mature 18S rRNA and 40S subunits. Moreover, a lack of *DHX37* in these cells triggers a surveillance pathway that leads to the degradation of pre-ribosomal particles, indicating the importance of *DHX37* in human Ribi [165]. *DHX37* can not only play a direct oncogenic role, but also affect the immune microenvironment and inhibit the anti-tumor immunity of CD8 T cells [124,166].

4.9. RPSA

RPSA is the causative gene implicated in isolated congenital asplenia, and its encoding ribosomal protein SA is a component of

ribosomal 40S [127]. During embryonic development, mutations in *RPSA* impair pre-40S rRNA processing, which in turn affects Ribi and impairs the expression of key genes involved in splenic patterning, such as *NKX2-5*, *BAPX1*, and *POD1* [167]. Furthermore, *RPSA* has been associated with tumor progression, where elevated expression of *RPSA* has been reported to enhance invasiveness, adhesion, and angiogenesis in tumor cells. Recent findings also suggest that *RPSA* can maintain cellular activity by evading apoptosis, thus retaining tumor survival and proliferation in the organism [168]. Brassart et al. [169] found that bioactive matrix fragments can bind to *RPSA* and thus participate in the process of inducing cancer cell blastogenesis and extracellular vesicle release, thereby facilitating the dissemination of cancer cells from metastatic sites to distant sites. In PAAD, overexpression of *RPSA* is associated with high aggressiveness and poor prognosis, suggesting its potential utility as a marker for certain tumors.

5. Pan-cancer analysis of ribosomopathy genes

As mentioned above, the roles of several ribosomopathy genes (e.g., *RPL5* and *RPS19*) in cancer were well-studied. However, there are some ribosomopathy genes that have not been well reported to be associated with cancer, including *BMS1*, *CIRHIN*, *DNAJC21*, *EMG1*, *LTV1*, *NOL11*, *RPL10*, *RBM28*, *RPS20*, *RPS23*, *RPSA*, and *ZNHIT3*. To further explore the potential role of these genes in human cancer, we used the bioinformatic approaches to analyze the expression patterns of these genes in cancer development as well as its prognostic value in cancer patients in 33 types of human cancers, including adrenocortical carcinoma (ACC), AML, BLCA, BRCA, cervical squamous cell carcinoma (CESC), cholangiocarcinoma (CHOL), COAD, diffuse large B cell lymphoma (DLBC), esophageal carcinoma (ESCA), GBM, brain lower grade glioma (LGG), head and neck squamous cell carcinoma (HNSC), kidney chromophobe carcinoma

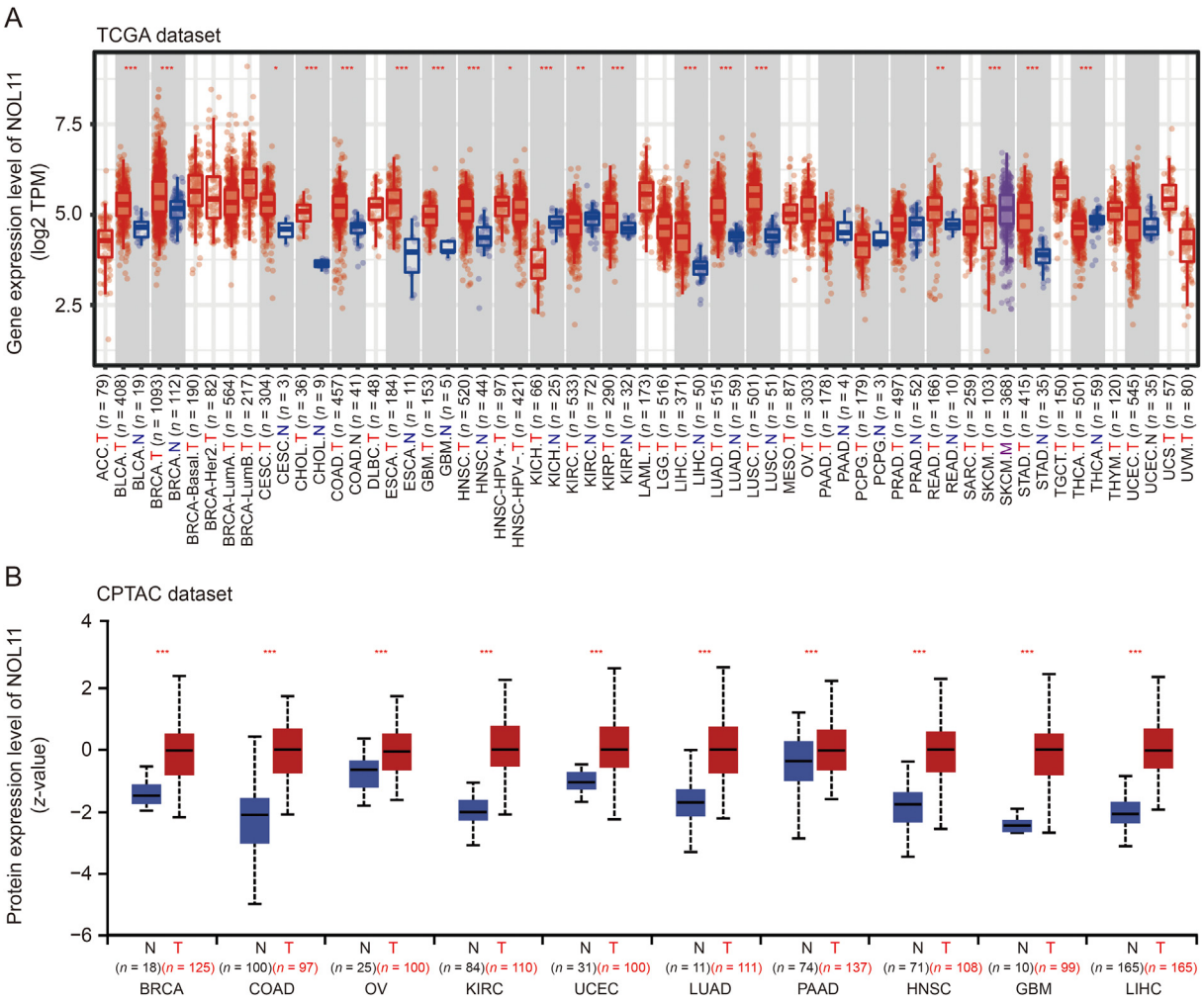

Fig. 2. Gene and protein expression status of *NOL11* in pan-cancer. (A) Comparison of gene expression levels between tumor samples and paired normal tissues in The Cancer Genome Atlas (TCGA) cohort was assessed using TIMER2.0 (http://timer.cistrome.org/, accessed on 19 June 2022). (B) Comparison of protein expression levels between tumor samples and paired normal tissues was assessed from the Clinical Proteomic Tumor Analysis Consortium (CPTAC) dataset using UALCAN (http://ualcan.path.uab.edu/analysis-prot.html, accessed on 30 June 2023). $^{*}P < 0.05$; $^{**}P < 0.01$; and $^{***}P < 0.001$. TPM: transcripts per million; ACC: adrenocortical carcinoma; BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; CESC: cervical squamous cell carcinoma; CHOL: cholangiocarcinoma; COAD: colon adenocarcinoma; DLBC: diffuse large B cell lymphoma; ESCA: esophageal carcinoma; GBM: glioblastoma; HNSC: head and neck squamous cell carcinoma; HPV: human papilloma virus; KICH: kidney chromophobe carcinoma; KIRC: kidney renal clear cell carcinoma; KIRP: kidney renal papillary cell carcinoma; LAML: acute myeloid leukemia; LGG: brain lower grade glioma; LIHC: liver hepatocellular carcinoma; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; MESO: mesothelioma; OV: ovarian serous cystadenocarcinoma; PAAD: pancreatic adenocarcinoma; PCPG: pheochromocytoma and paraganglioma; PRAD: prostate adenocarcinoma; READ: rectum adenocarcinoma; SARC: sarcoma; SKCM: skin cutaneous melanoma; STAD: stomach adenocarcinoma; TGCT: testicular germ cell tumor; THCA: thyroid carcinoma; THYM: thymoma; UCEC: uterine corpus endometrial carcinoma; UCS: uterine carcinosarcoma; UVM: uveal melanoma; T: tumor tissue; N: normal tissue; M: tumor metastases.

(KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), LIHC, LUAD, lung squamous cell carcinoma (LUSC), mesothelioma (MESO), ovarian serous cystadenocarcinoma (OV), PAAD, pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), READ, sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), and uveal melanoma (UVM). Methodologically, we obtained the results from public bioinformatic websites that integrated the data based on the TCGA database, a public data platform that provides a comprehensive record of genetic data collected from a tumor patient's sample, including its DNA sequence, transcriptional information, epigenetic modification, and related information. As follows, we obtained gene expression alternations during tumorigenesis and disease progression as well as the relationship with disease prognosis of these ribosomopathy genes among human cancers. These outcomes more directly reflect the relationship between these ribosomopathy genes and cancer, and more accurately suggest the potential value of these genes in cancer diagnosis and treatment. Future experimental and prospective studies of these genes in different cancer types are necessary and will provide in-depth insights into regulatory mechanisms and further support the development of therapeutic strategies targeting ribosomopathy genes.

5.1. Expression pattern of ribosomopathy genes in pan-cancer

We obtained the differences in total protein/gene expression levels of these ribosomopathy genes between adjacent normal tissues and tumor tissues in pan-cancer via TIMER2.0 (http://timer.cistrome.org/) and UALCAN (http://ualcan.path.uab.edu/analysis-prot.html). As shown in Figs. S2 and S3, these ribosomopathy genes (*NOL11*, *BMS1*, *DNAJC21*, *EMG1*, *LTV1*, *RBM28*, *RPL10*, *RPS20*, *RPS23*, *RPSA*, and *ZNHIT3*) showed dysregulated gene expression and protein expression in the tumor tissue as compared to the

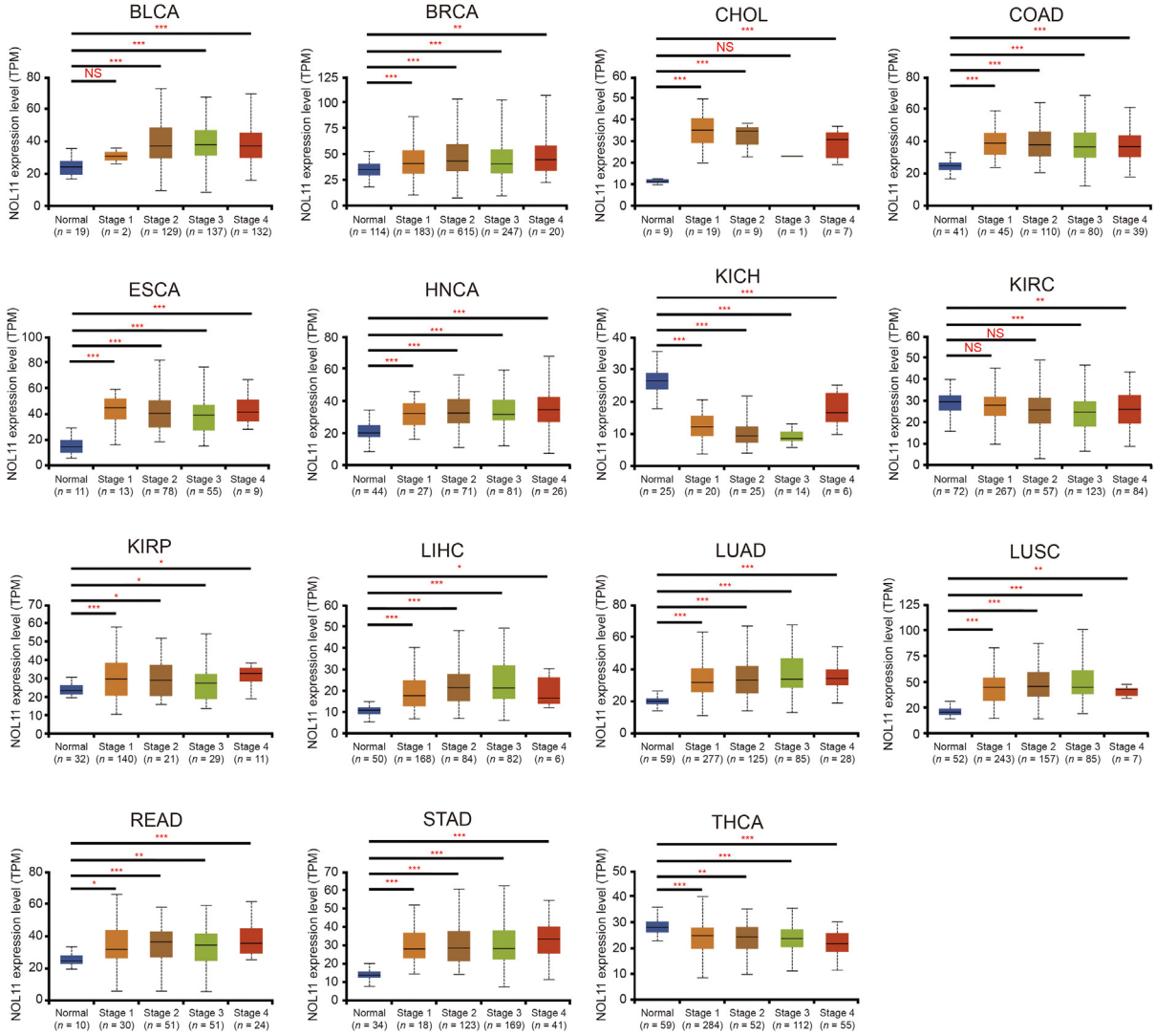

Fig. 3. Correlations between *NOL11* gene expression and the main pathological stages in normal and stages I, II, III, and IV bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe carcinoma (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), and thyroid carcinoma (THCA) tissues in The Cancer Genome Atla datasets were analyzed through UALCAN (http://ualcan.path.uab.edu/analysis-prot.html, accessed on 30 June 2023). $^{*}P < 0.05$; $^{**}P < 0.01$; and $^{***}P < 0.001$. NS: no significance. TPM: transcripts per million.

normal tissues in multiple cancers. Fig. 2 shows that both the gene and protein expression of *NOL11* were significantly enhanced in COAD, LUAD, HNSC, GBM, and LIHC, which suggests *NOL11* may exert a key role during the tumorigenesis and possesses the potential to be a clinical diagnostic marker of these cancer types. Similarly, all of the expression level alterations of these genes represent the same potential value. Interestingly, both the gene expression and protein expression of all these ribosomopathy genes (except *RPS23*) showed the unified upregulation in LUAD. It may imply the strongly correlation between abnormal Ribi and LUAD.

5.2. Relationship of ribosomopathy genes with disease progression in pan-cancer

To further explore the association between these ribosomopathy genes and human cancers, the relationship between each gene and the clinicopathological stage of tumors was investigated via UALCAN. As shown in Fig. 3, in cancer types such as HNSC, LUAD, KICH, KIRP, READ, and STAD, *NOL11* showed a significant association with clinicopathological stage. For instance, the expression of *BMS1* was observed to increase with disease progression in HNSC, LUAD, and READ, and the expression of *DANJC21* was found to decrease with disease progression in KIRC. Details of other genes are described in Fig. S4. These results further suggest that these genes may play a critical role in the disease development of multiple cancers, while the function of different genes in the same cancer or the same gene in different cancers is heterogeneous.

5.3. Relationship of ribosomopathy genes with disease prognosis in pan-cancer

We obtained the Kaplan-Meier mapper using GEPIA2 (http://gepia2.cancer-pku.cn/) to analyze the prognostic significance of these ribosomopathy genes in pan-cancer. As shown in Fig. 4, highly-expressed *NOL11* was associated with poor OS in patients with ACC, LGG, LIHC, LUAD, and SARC. Conversely, in PAAD and THYM, lowly-expressed *NOL11* was correlated with poor OS prognosis in patients suffering PAAD and THYM. Details of other genes are described in Fig. S5. These intuitive outcomes indicated the potential of these ribosomopathy genes as the prognostic markers in multiple cancer.

6. Ribi can be a promised target for cancer therapy

Numerous studies have stated the promised potential of Ribi as the target for cancer therapy. We further focused on these ribosomopathy genes which can function as more precise targets in cancer treatment, given the tumor heterogeneity and the possible side effects on normal tissues caused by targeting Ribi. As mentioned above, not all ribosomopathy genes exhibit upregulated expression in cancer. Some genes, such as *RPL5* encoding ribosomal protein L5, are known as tumor suppressors because they bind to MDM2 and prevent the degradation of p53. In contrast, other RPs can promote tumor development. For example, the expression of *RPL35A* is significantly upregulated in GC cells and is associated with increased cell invasiveness. *RP* genes frequently undergo mutations and display altered expression patterns in various cancers. For instance, *RPS7* and *RPS24* expression are elevated in LUAD, while *RPL5* and *RPL11* expression is decreased in BRCA. In addition, many RPs are associated with the cell cycle, and in LUAD, RPL19 knockdown inhibits the synthesis of cyclin D1 and cyclin D3, and also leads to an increase in the G1-phase fraction and a decrease in the S-phase fraction [170]. Therefore, these dysregulated ribosomopathy genes are closely related to cancer and can potentially act as both consequences and causative factors of cancer. Therefore, targeting ribosomes for cancer therapy is a feasible and crucial approach.

Targeting Ribi in cancer therapy is based on the rationale that tumor cells produce more ribosomes than normal cells, making them more susceptible to inhibition by Ribi. Numerous novel anticancer drugs are being developed to target Ribi, primarily by inhibiting Ribi to induce nucleolar stress and activate p53. Transcription of rRNA Pol I is widely recognized as the rate-limiting step

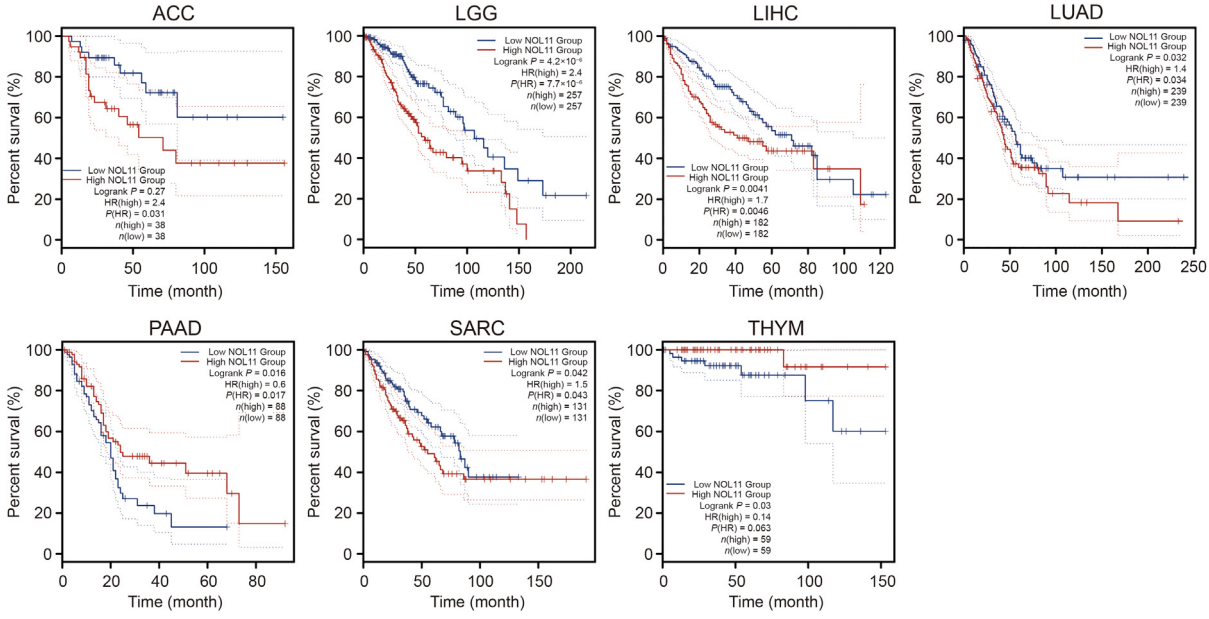

Fig. 4. Overall survival prognosis of groups with high and low *NOL11* expression levels in multiple cancers, including adrenocortical carcinoma (ACC), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), pancreatic adenocarcinoma (PAAD), sarcoma (SARC), and thymoma (THYM) according to the Kaplan-Meier plotter using GEPIA2 (http://gepia2.cancer-pku.cn/, accessed on 30 June 2023). HR: hazard ratio.

in Ribi. CX-5461, a specific inhibitor of rRNA synthesis that acts on RNA Pol I, has demonstrated significant antitumor activity against advanced hematologic cancers [171]. It exhibits a more sensitive inhibitory effect on cancer cells, as indicated by its lower half maximal inhibitory concentration (IC_{50}) value in cancer cells (3 nM) compared to non-transformed cells (5 μM) [172]. CX-5461 has shown survival benefits in highly aggressive AML and MM mouse models that are refractory to standard treatment [173]. However, CX-5461 also affects Ribi in healthy tissues, particularly skeletal muscle, leading to impaired muscle growth [174].

5-Fu, a commonly used chemotherapeutic drug, exerts its effects on rRNA biogenesis by blocking the maturation of 47S pre-rRNA, which results in disruptions in RNA and DNA and eventually leads to cell death [175]. In the clinical setting, however, 5-Fu resistance remains a major limitation and has been associated with adverse effects such as symptomatic cardiotoxicity [176]. Ribi includes steps, including rRNA transcription and processing, RP synthesis, and incorporation of assembly factors. These steps represent potential targets for therapeutic intervention. Overcoming the challenge of 5-Fu resistance and improving treatment efficacy can be achieved through the combination of drugs or the discovery of safer and more effective targets. Consequently, the mechanisms underlying Ribi have emerged as a prominent area of research in various types of malignancies.

Traditionally, it was believed that cells produced only a single type of ribosome. However, recent studies have shown that cells can produce heterogeneous populations of ribosomes. This has led to an alternative perspective proposed by numerous researchers, suggesting the existence of “specific ribosomes” or “cancer ribosomes” in organisms. The composition of the ribosome exhibits variation depending on the cellular, environmental conditions, developmental stage, and the modification and expression patterns of RPs and rRNAs under both physiological and pathological conditions. These variations in ribosome composition can result in altered protein output, leading to overexpression of oncogenes (e.g., *JAK-STAT* protein or *VEGF*) and underexpression of tumor suppressors (e.g., *CDKN1B* or *TP53*) [177]. Consequently, targeting the assembly process of ribosomes, as well as the processing and chemical modification of specific ribosomal components, holds promise as a therapeutic approach. The potential of utilizing targeted drugs to enhance the identification and elimination of cancer cells is of immense significance in this regard.

7. Conclusion and future perspectives

Ribosomopathy, which is characterized by a diminished proliferative phenotype such as early-onset bone marrow failure and anemia, tends to be associated with higher risk of hyperproliferative diseases, such as cancer. As early as the 1960s, William Dameshek described this contradictory observation and called this paradox as “Dameshek riddle”. This transition from a hypoproliferative to a hyperproliferative state raises intriguing questions in the field of hematology. The mechanistic explanations for this paradox mainly involve in the altered translation caused by gene mutations and the extra-ribosomal function of these genes promotes oncogenic transformation in ribosomopathy patients. Perturbations in ribosomal function lead to oxidative stress, increased mutagenesis, and the emergence of rescue mutations that facilitate extensive cellular proliferation. In addition to structural and regulatory roles in ribosome assembly, these ribosomopathy genes also serve extra-ribosomal functions, including modulating cell growth, proliferation, differentiation, immunity, and DNA repair, which directly influence cancer progression. The hyperactivated Ribi generated the “oncoribosomes” that resulted in the altered translatome of some oncogenes such as *BCL2, JAK-STAT* proteins, and tumor suppressors such as *TP53* or *CDKN1B.* Therefore, ribosomopathy patients exhibited increased susceptibility to cancer.

The conventional notion of ribosomes as static molecular machinery involved in protein synthesis is now outdated. Even subtle perturbations in ribosome assembly can have profound pathological consequences, highlighting the potential of targeting RP mutations or other assembly factors in cancer treatment. Multiple lines of evidences have shown that a significant proportion of tumor forms, including AML, MM, COAD, GBM, BRCA, and melanoma revealed recurrent somatic mutations in RPs. Hyperactivated cell proliferation in cancer has long been associated with increased translational capacity and dysregulated Ribi. The disruption of important checkpoints in protein synthesis may contribute to the onset and progression of cancer, as precise Ribi control is vital for accurate cell growth and proliferation. Gaining a deeper understanding of the mechanism underlying ribosome assembly and translation, as well as unraveling the intricate relationship between these processes and tumorigenesis, significant implications for clinical cancer treatment. The in-depth exploration of ribosomopathy genes and cancer will provide a new perspective and possibility for Ribi-based cancer treatment strategies. Such knowledge will pave the way for the development of more precise and sensitive anti-cancer drugs targeting Ribi, offering promising avenues for therapeutic interventions.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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