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REVIEW

Ribosomal rodeo: wrangling translational machinery in gynecologic tumors

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Abstract
Gynecologic cancers are a significant cause of morbidity and mortality among women worldwide. Despite advancements in diagnosis and treatment, the molecular mechanisms underlying the development and progression of these cancers remain poorly understood. Recent studies have implicated translational machinery (ribosomal proteins (RPs) and translation factors (TFs)) as potential drivers of oncogenic processes in various cancer types, including gynecologic cancers. RPs are essential components of the ribosome, which is responsible for protein synthesis. In this review paper, we aim to explore the role of translational machinery in gynecologic cancers. Specifically, we will investigate the potential mechanisms by which these components contribute to the oncogenic processes in these cancers and evaluate the feasibility of targeting RPs as a potential therapeutic strategy. By doing so, we hope to provide a broader view of the molecular pathogenesis of gynecologic cancers and highlight their potential as novel therapeutic targets for the management of these challenging diseases.

Keywords Ovarian cancer · Cervical cancer · Endometrial cancer · Ribosome · RPL · RPS

1 Introduction

The translational machinery encompasses a complex system of cellular components responsible for protein synthesis, including ribosomes, messenger RNA (mRNA), transfer RNA, (tRNA), translational factors, and regulatory proteins [1]. The eukaryotic ribosome consists of two asymmetric subunits, large (60S) composed of 47 proteins and 3 types of rRNA (5S, 5.8S, and 28S) and small (40S) composed of 33 proteins and 18S rRNA [2, 3], and is responsible for translating the genetic code into functional proteins. The protein biosynthesis is a cyclic process that occurs in four phases — initiation, elongation, termination, and recycling. In the initiation phase, the initiation factors put mRNA together with the initiator Met-tRNA on a small subunit, and at the end of this phase, joining of a large subunit makes translationally active ribosomes [4]. In the elongation phase, eEF1A brings new, adequate aa-tRNA to the A-site of the ribosome, leading to the formation of peptides. Then, eEF2 as a translocase pushes the ribosome onto mRNA exposing a new codon in the decoding center. Appearing of the stop codon in the decoding center causes the termination of protein synthesis and the nascent polypeptide is released. In the recycling phase, the ribosome undergoes splitting by eRF1, eRF3, and eABCE1, and the free subunits may enter the new translational cycle [4] (Fig. 1). Therefore, the fundamental role of the entire translational machinery is to synthesize proteins; however, over decades of research, this function has been further elucidated and expanded. Recent studies have highlighted that diversity in ribosome composition, referred to as ribosome heterogeneity and/or specialization, can influence translational efficiency and fidelity, impacting protein synthesis rate and accuracy [5]. It is now clear that any alternation in ribosomes' composition can result in pathological development and malignancy [6]. The relationship between translational machinery and cancer is a topic of significant interest in current research. Dysregulation of the translational machinery, including ribosomes and TFs, has been implicated in various aspects of cancer development, progression, and metastasis [7, 8]. This applies perfectly to gynecologic cancers in which the dysregulation of translational elements adds another layer to the already complex molecular structure. The importance of the

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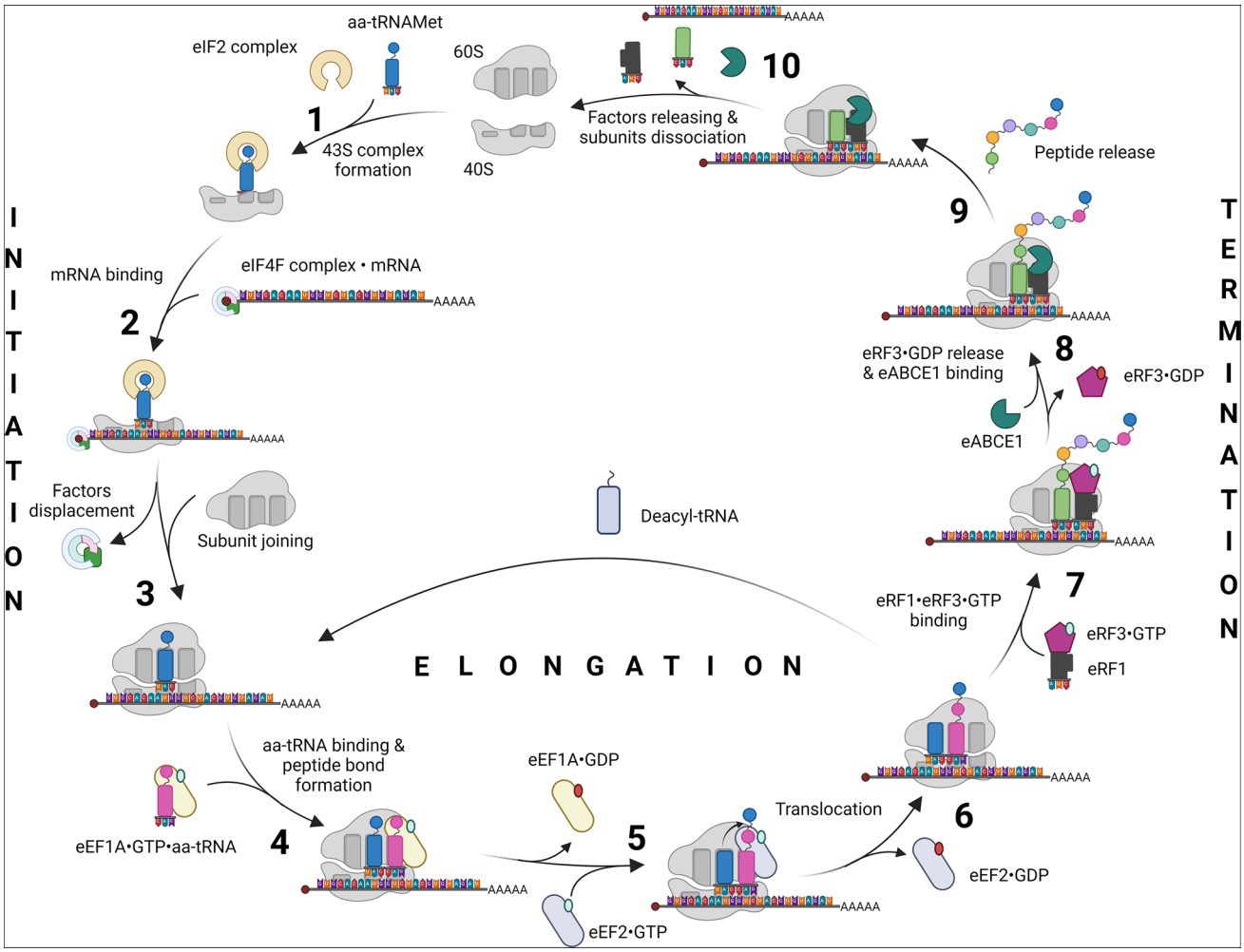

Fig. 1 Schematic view of eukaryotic translational cycle. In the initiation, the eIF2 complex and aa-tRNAi bind to create the 43S pre-initiation complex (1), and then the mRNA together with the eIF4F complex binds to the 43S (2). The start codon is recognized by subsequent mRNA scanning, which causes the displacement of the eIF4F and eIF2 complexes and the subsequent combining of the subunits (3). The exchange factor eIF2B recycles back eIF2*GDP into eIF2*GTP. New amino acids are added to the ribosome's A-site during the elongation step by the eEF1A*GTP*aa-tRNA complex (4). When this complex is accommodated, GTP hydrolysis is triggered, eEF1A*GDP is released, peptide synthesis between two amino acids takes place, and comes eEF2*GTP complex (5). GTP hydrolysis provides the energy needed to move the ribosome on the mRNA and release empty tRNA, or deacyl-tRNA, from the E-site (6). Until the stop codon is reached, the elongation phase is repeated. Release factor 1 (RF1), which enters the termination phase together with the RF3*GTP complex and provides the energy for RF1 accommodation in the A-site, recognizes the stop codon (7). The entering eABCE1 ATPase causes RF3*GDP release (8), and consequent peptide release from the ribosome (9). The 80S is ultimately divided into discrete subunits during the recycling stage (10), which may then go through a new translation process. GTP is shown as a green ball and GDP as a red ball throughout. The figure was created with BioRender.com

translational machinery in the specific context of gynecologic tumors was first explored in the early 1990s when studies reported the synergistic effect of drugs inhibiting protein synthesis and cytokines against ovarian cancer [9, 10]. Although the interest in the field has grown over time, only in the past 10 years has research in translational control in cancer made such significant advances, allowing not only to gain a better understanding of the biological mechanisms but also to bring these insights closer to clinical application. However, a comprehensive review of the role of the translational machinery in the context of gynecological cancers is still lacking. With this review, we aim to fill this gap, by examining the relationship between translational machinery — RPs and TFs, and gynecologic cancers such as endometrial, ovarian, cervical, and vulvar. The alterations in expression and modification of translational machinery factors have been linked to gynecologic cancers. Our analysis covers TFs involved at different stages of protein synthesis, as well as the complex realm of RPs, to provide readers with a broad view of their roles in the onset and development of gynecologic cancers.

2 Endometrial cancer

Endometrial cancer (EC) (Fig. 2) is the most common gynecologic cancer in developed countries, showing an upward trend of 417,367 new cases globally reported in 2020 [11]. EC is classified into various histological subtypes, such as endometroid, serous, clear cell, mixed, undifferentiated, carcinosarcoma, mesonephric-like, and gastrointestinal mucinous, being endometroid is the most prevalent [12]. Genetic factors play a critical role in EC development, i.e., women suffering from Lynch or Cowden Syndrome have up to 50% or 30% probability, respectively, of developing EC. The percentage of EC development in these syndromes depends on the type of mutated gene [13]**.** Lifestyle factors, including smoking and obesity, have also been linked to a higher risk of EC, further highlighting the importance of comprehensive risk assessment and management [14, 15]. Even if there is no prevention program, EC is generally diagnosed at an early stage because of alarming symptoms, like uterine bleeding in postmenopausal age [16]. Nevertheless, the detection of specific markers would be very useful for early diagnosis of EC in asymptomatic patients.

3 Cervical cancer

Cervical cancer (CC) (Fig. 2), on the other hand, stands out as a significant health concern globally, ranking as the fourth most common cancer among women worldwide. In 2020, there were an estimated 600,000 new cases and 340,000 deaths attributed to cervical cancer [17]. Squamous epithelial is the most common histological subtype, and generally, cervical cancer is associated with high morbidity and mortality rates, particularly in developing countries. The disease is characterized by early metastasis of the primary tumor, leading to poor prognosis and therapeutic outcomes [18]. CC is primarily caused by human papillomavirus (HPV) infection, with HPV being identified as the leading cause of cervical cancer for over 25 years [19]. The two most common high-risk HPV types, HPV-16 and HPV-18, are linked to 60–70% of cervical cancer cases globally [20].

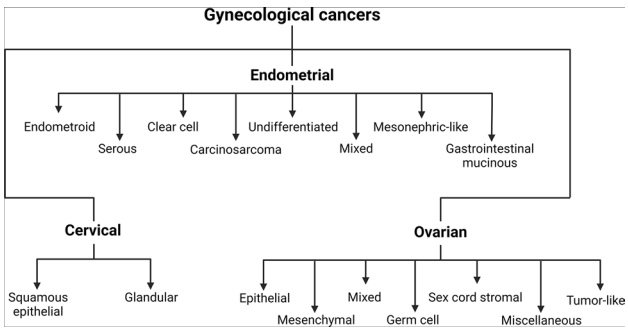

Fig. 2 Types ofgynecologic cancers. Histological subtypes of endometrial (upper graph), cervical and ovarian (lower graph). Classification of gynecologic cancers based on world health organization classification of tumors: female genital tract tumors, 5th edition [27] and FIGO cancer report 2021 [28]. The figure was created with BioRender.com

4 Ovarian cancer

Ovarian cancer (OC) (Fig. 2) is a complex disease encompassing a heterogeneous group of malignancies with varying etiologies and molecular characteristics [21]. Epithelial ovarian cancer (EOC), the most common subtype, is morphologically divided into serous, endometrioid, clear cell, and mucinous subtypes, with serous being the most malignant [22]. The disease is known for its aggressive nature and high mortality rates, making it one of the deadliest among gynecologic malignancies [23]. The Globocan in 2020 reported more than 300,000 new cases and 200,000 deaths [24]. What is of concern is the wide prevalence of ovarian cancer in highly developed countries which can be associated with lifestyle changes [24]. Higher saturated fat intake, reduced physical activity, and, as a consequence, obesity are factors that increase the probability of mucinous OC development. Moreover, the presence of *BRCA1* and *BRCA2* mutated genes and Lynch Syndrome are genetic risk factors responsible for OC development [25]. Despite advancements in medicine, ovarian cancer is challenging to treat and is often diagnosed at advanced stages, contributing to its poor prognosis [26].

5 Diagnosis and treatment of gynecologic cancers

Diagnosis and treatment of gynecologic cancers involve a multidisciplinary approach aimed at improving patient outcomes and quality of life. Current treatment methods for gynecologic cancers typically include a combination of surgery, chemotherapy, radiotherapy, and chemoradiotherapy ([29] and https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gynaecological-cancers or https://www.nccn.org/guidelines/category_1). These modalities are tailored to the specific type and stage of the cancer to achieve the best possible results. As made clear in the treatment guidelines of the European Society of Medical Oncology – ESMO and of the National Comprehensive Cancer Network – NCCN, surgery is the gold standard in the management of gynecologic tumors, often used for diagnosis, staging, and primary treatment [29, 30]. Radiotherapy and chemotherapy are essential components

of gynecologic cancer treatment, either as adjuvant therapy following surgery or as primary treatment for advanced or metastatic disease [29, 31].

In recent years, emerging therapies such as immunotherapy and hormonal therapy have shown promise in the treatment of gynecologic cancers. Immunotherapy, including checkpoint inhibitors, aims to harness the body's immune system to target and destroy cancer cells [32, 33]. Hormonal therapy, on the other hand, involves the use of medications to modulate hormone levels and inhibit cancer growth, particularly in hormone-sensitive tumors [34]. However, in advanced or recurring diseases, treatment choices are limited, and the prognosis is unfavorable. For patients who have advanced beyond initial platinum/taxane-based chemotherapy, treatment options have been scarce, resulting in dismal outcomes. Therefore, there is an urgent need for innovative therapeutic strategies.

Early diagnosis and screening are crucial in the management of gynecologic cancers. In addition, analysis of specific biomarkers may complement the histological evaluations, for instance, CA125 and HE4 might indicate OC's degree of malignancy [35]. In recent years, the liquid biopsy approach for detecting circulating tumor DNA (ctDNA) has shown promise in the early diagnosis and staging of OC, due to its higher sensitivity compared to serum CA125 [36]. Although the diagnostic and prognostic potential of liquid biopsy has so far only been partially unveiled in translational research, certain companion diagnostic tests for ovarian cancer have been approved by the FDA. These tests are designed to detect mutations in the BRCA1 and BRCA2 genes in ctDNA, which are valuable for identifying patients eligible for targeted therapies such as olaparib and rucaparib.

6 Involvement of the translational machinery in the development of gynecologic cancers

As mentioned above, the translation machinery is an extremely complex system, with hundreds of players, and it is often de-regulated in cancer, thus contributing to modulating gene expression and generating a cancer-supporting environment [37]. De-regulation can involve factors related either to protein synthesis (initiation, elongation, and termination/recycling factors) or to ribosome biogenesis (RPs and ribosome biogenesis factors). In this paragraph, we will give an overview of the recent literature reporting studies on altered TFs and RPs in gynecologic cancers (Fig. 3) and Tables 1 and 2 serve as a thorough reference, summarizing the most relevant information, respectively.

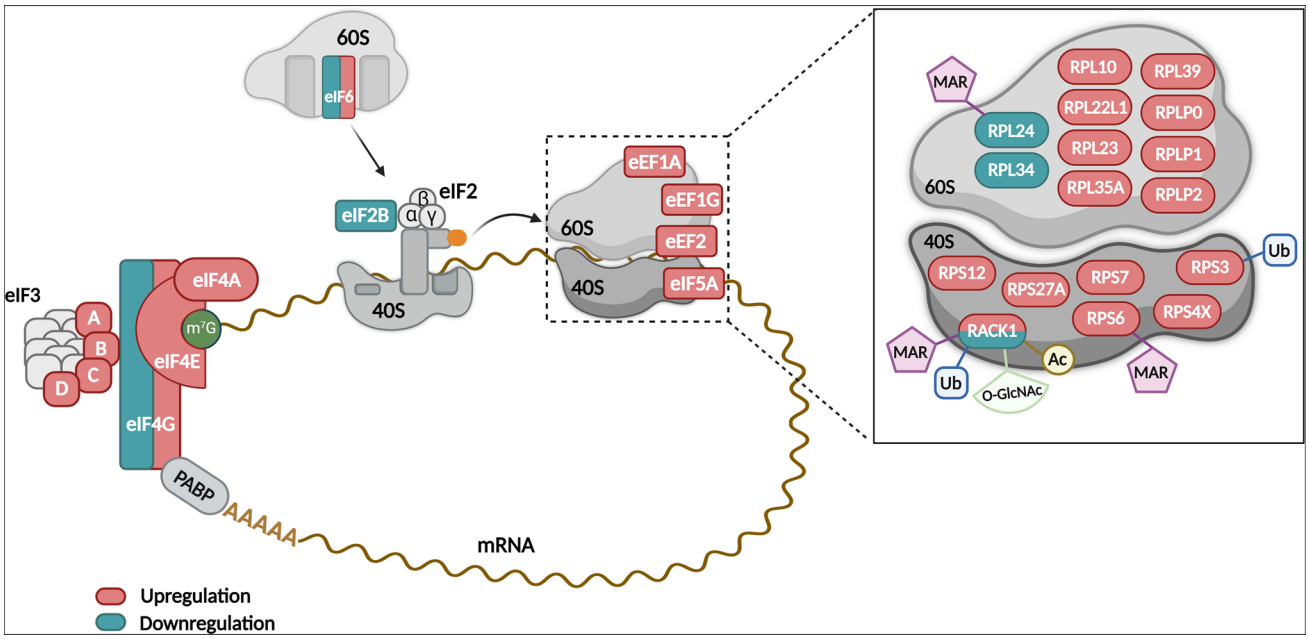

Fig. 3 Altered expression and post-translational modifications of translational machinery elements in gynecologiccancers. A schematic view of translation initiation and elongation steps with an enlarged "gynecologic" 80S ribosome. The RPs from "gynecologic" ribosome can be also post-translationally modified by MARylation (MAR), ubiquitination (Ub), acetylation (Ac), and O-linked β-*N*-acetylglucosamination (O-GlcNAc). Alterations and modifications of the translation machinery are crucial for gynecologic cancer progression. The up- and downregulated TFs and RPs are marked with red and blue colors, respectively. The factors eIF4G, eIF6, and RACK1 protein can be either up- or downregulated depending on isoform, histological type of cancer, and post-translational modification, respectively. The figure was created with BioRender.com

Table 1 List of altered expressed TFs in gynecologic cancers

Translational factor	Cancer	Up-/downregulation	Outcome	Ref
eIF4G1	CC/OC	Up-	Cancer progression, metastasis	[41]
	EC	Up- (mRNA)	————————	[41]
eIF4G2	EC	Down-	Aggressiveness promotion	[42]
eIF4G	EC	Up-	Patient's worse survival	[43]
eIF4E	OC	Up-	Cell cycle promotion	[44]
	CC	Up-	Cell migration and growth	[46, 47]
	EC	Up-	Metastasis	[49, 50]
eIF4A	CC	Up-	Cancer progression and metastasis	[52]
eIF4A1	CC	Up-	Brachytherapy worse response	[52]
eIF4A3	OC	Up-	Cancer progression	[53]
eIF2B5	OC	Down-	Tumor suppressor	[55]
eIF3B	OC	Up-	Increased proliferation and survival	[60]
eIF3C				[59]
eIF3A	OC	Up-	Downregulation of cell cycle	[63]
eIF3D	OC	Up-	Cell proliferation	[64]
	CC	Up-	Increased invasion and Warburg effect	[65, 66]
eIF5A2	OC	Up-	EMT promotion	[69]
	CC	Up-	Cell's viability and mobility promotion	[74]
eIF6	OC	Down-	Metastasis promotion	[76]
		Up-	Cell's motility and invasiveness promotion	[77, 78]
eEF1A2	OC	Up-	Increased cell growth and spheroids formation	[82]
eEF1D	OC	————	PI3K/Akt pathway modulation	[88]
eEF1G	OC	Up-	Better OS	[85]
eEF2	OC	Up-	Cancer promotion	[86]

6.1 Translation factors

6.1.1 eIF4G

Protein biosynthesis is considered one of the most energy-consuming processes within living cells [38]. One of the hallmarks of cancer cells is altered protein expression which is needed for development and progression [37]. The overexpression of the translational machinery seems to be a crucial factor for cancer proliferation. The intricacies of how translational machinery is altered in cancer cells are multifaceted, with various factors playing a pivotal role (Fig. 3). One such critical element is the eukaryotic initiation complex 4F (eIF4F) which is composed of eIF4A, an ATP-dependent RNA helicase, eIF4E the cap-binding subunit, and the scaffolding eIF4G. The latter has three isoforms, and among them, eIF4G1 is the major isoform responsible for cap-dependent translation [39, 40]. The eIF4G family, specifically eIF4G1 and eIF4G2, are known to play a significant role in cancer progression [41, 42]. eIF4G1 is overexpressed in various cancers, including OC and CC, contributing to cancer advancement, proliferation, and metastasis [41]. Investigation of EC showed the slightly upregulated mRNA expression for eIF4G1 [41]. Conversely, eIF4G2 has been associated with promoting aggressiveness in grade EC, where its low expression correlates with unfavorable survival outcomes. The absence of eIF4G2 has been shown to worsen the response to chemotherapy and radiation, emphasizing its role in treatment efficacy and differentiation between non-aggressive and aggressive ECs [42]. In contrast, the study of Smolle et al. reported that in the EC, the elevated level of eIF4G was independently associated with worse survival of patients, irrespective of tumor stage and patients' age, and could serve as an alternative prognostic marker [43].

6.1.2 eIF4E

The eIF4E is another factor being overexpressed in gynecologic cancers. In OC, the expression of eIF4E is higher compared to noncancerous epithelial ovarian tissues [44]. The overexpression of the eIF4E factor may contribute to the progression of ovarian tumors by promoting proliferation and cell cycle by enhancing the translation of cyclin D1. There is a significant positive correlation between eIF4E and cyclin D1 in OC, and their upregulation was found in advanced OC (stages III/IV). Additionally, the overexpression of eIF4E was observed in patients with

Table 2 List of altered and/or modified RPs in gynecologic cancers

Ribosomal protein	Cancer	Up-/downregulation	Interaction/PTM	Outcome	Ref
RACK1	OC	Up-	————	Cancer progression	[96, 98]
		Up- (by PTM)	MARylation by PARP14 deMARylation by TARG1	Translation adjustment in stress	[100]
		Up- (by PTM)	Acetylation	Increased RACK1 stability	[99]
		Down- (by PTM)	Ubiquitination by SMURF2	Decreased RACK1 stability	[99]
	CC	Up- (by PTM)	O-GlcNAcetylation by HPV E6 protein	Cancer and metastasis progression	[97]
		Down-	Regulation of miR-302b/c/d-3p expression	Apoptosis inhibition	[101]
RPS3/uS3	OC	Up-	NF-κB, SIAH1 Ubiquitination by SIAH1	Cancer progression	[105]
RPS4X/eS4X	OC	Up-	————	Cancer progression	[106]
RPS6/eS6	OC	———	MARylation by PARP16	Translation adjustment	[110]
		Up-	————	Cancer proliferation and invasion	[107]
RPS7/eS7	OC	———-	Regulation of MAPK, PI3K/Akt pathways	Cancer inhibition	[111]
RPS12/eS12	CC	Up-	c-Myc	Invasiveness increase	[112]
RPS27A	CC	Up-	————	Bad survival prognosis	[113]
RPL10/uL16	OC	Up-	————	Apoptosis inhibition, cancer invasion	[114]
RPL22L1/ eL22L1	OC	Up-	————	EMT promotion	[115]
RPL23/uL14	OC	Up- (mRNA)	————	Worse prognosis	[117]
RPL24/eL24	CC	Down-	Regulation of p53-MDM2 pathway	Cancer development	[118]
	OC	———	MARylation by PARP16	Translation adjustment	[110]
RPL34/eL34	CC	Down-	Regulation of p53-MDM2 pathway	Cancer development	[119]
RPL35A/eL33	OC	Up-	YY1-CTCF interaction	Cell invasion, proliferation	[120]
RPL39/eL39	OC	Up-	AGK interaction	Mitochondria sustainability	[122]
RPLP0/uL10, RPLP1/P1, RPLP2/P2	OC/EC	Up-	————	Cancer progression, invasiveness	[123]
RPLP1/P1	CC	———	CNN3 interaction	Cancer progression, migration	[124]

cervical lymph node metastasis [44], implying that this factor may be involved in the control of those biological features correlated to cell movement and/or adhesion. The inhibition of eIF4E can suppress cell proliferation and enhance the cytotoxicity of cisplatin in ovarian cells [45]. Generally, the overexpression of the eIF4E factor in OC patients is negatively correlated with their survival status [44]. In the case of CC, the eIF4E plays a crucial role in the cancer-specific MNK-eIF4E-β-catenin axis. A significant upregulation of eIF4E expression and phosphorylation has been found in cancer compared to normal cells [46]. The eIF4E overexpression as well as phosphorylation at Ser209 residue by MNK kinase is crucial for the activation of the β-catenin pathway (Fig. 4A) which promotes growth, migration of CC, and consequently leads to a poor clinical outcome. Inhibition of the MNK-eIF4E-β-catenin axis by targeting the MNK kinase activity might serve as a potential therapeutic strategy for CC treatment [46]. Furthermore, the eIF4E expression in CC can be promoted by HPV E6 and E7 proteins in HPV-positive cancer cells [47, 48]. Either direct E6 binding to the eIF4E promoter or the degradation of the p53 protein may cause eIF4E expression in an E6-dependent manner [47]. In an E7-dependent manner, it is hypothesized that E7 binding to the pRb/E2F complex inhibits c-Myc activity, which is essential for eIF4E transcription [48]. However, these mechanisms of eIF4E overexpression remain unknown [47, 48] (Fig. 4B). In EC, there is evidence of the upregulation of eIF4E and metalloproteinase 9 (MMP-9), whose expression is positively correlated with the degree of lymphatic metastasis as well as the histological grade of cancer [49]. It should be noted that eIF4E expression might be potentially regulated by two miRNAs, miR-320a and miR-340-5p [50] (Fig. 4C). Their expression is downregulated in EC compared to the normal endometrial tissue. The experimental overexpression of miR-320a and miR-340-5p, as well as eIF4E inhibition, caused the suppression of movement and invasion of EC cells. Downregulation of eIF4E and its phosphorylation reduced the expression of MMP-9 and MMP-3, impairing cellular migration [50].

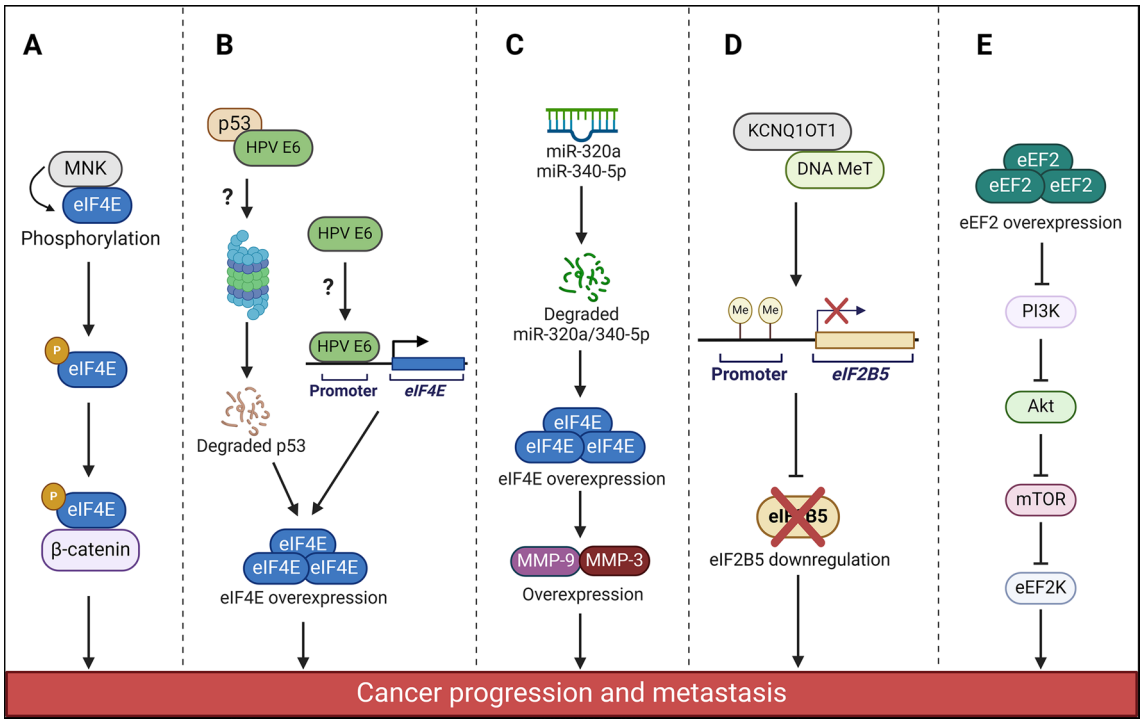

Fig. 4 Contribution of TFs to the progression of gynecologic cancers**.** CC progression may occur through (**A**) β-catenin pathway which is activated by MNK-dependent eIF4E phosphorylation, or by (**B**) HPV E6-dependent eIF4E overexpression. HPV E6's direct interaction with p53 might lead to proteasomal degradation of p53 or HPV E6 may stimulate the *eIF4E* gene transcription by stimulating its promoter. (**C**) The downregulation of miR-320a and miR-340-5p promotes overexpression of eIF4E, MMP-3, and MMP-9, leading to EC progression. Development of OC can be achieved by (**D**) KCNQ1OT1-dependent methylation of eIF2B5 promoter, leading to decreased eIF2B5 expression, or by (**E**) inhibiting eEF2K activity via PI3K/Akt/mTOR pathway due to eEF2 overexpression. The figure was created with BioRender.com

6.1.3 eIF4A

Another eIF, namely eIF4A, has been reported to be overexpressed in gynecologic cancers [51–53]. The elevated levels of eIF4A1 were positively correlated with CC size, stage, and lymph node metastasis. Patients with higher expression of eIF4A1 have a poor response to brachytherapy, making eIF4A1 an independent prognostic marker in CC [52]. According to Zhang et al., the overexpressed eIF4A3 might relate to the development of epithelial OC as its expression is negatively regulated by lncRNA cancer susceptibility 2 (CASC2). The application of sanguinarine caused the upregulation of CASC2 and thereby downregulation of eIF4A3, inhibiting epithelial OC progression [53].

6.1.4 eIF2B

eIF2B, a guanine exchange factor (GEF), plays an essential role in protein synthesis [54] and is aberrantly expressed mainly in OC. The significance of eIF2B5 expression in OC patients has been a recent focus of research. A pivotal study has established that low eIF2B5 expression is not only prevalent in OC tissues compared to normal tissues but is also intricately linked with shorter overall survival (OS) times in patients [55–57]. This association is particularly notable given the finding that eIF2B5 expression decreases progressively from stage I to stage IV of the disease, suggesting a possible functional shift of eIF2B5 in the progression of OC [55]. The expression of eIF2B5 in OC is regulated at the transcriptional level [56, 57]. The lncRNA KCNQ1OT1 recruits the DNA methyltransferases to eIF2B5 promoter, inhibiting its expression [56] (Fig. 4D). Furthermore, the identification of eIF2B5 as a novel target of miR-28 in OC adds a layer of complexity to our understanding of its role in disease mechanisms, with the circAHNAK/miR-28/eIF2B5 axis providing a new avenue for investigating tumorigenesis and progression [57].

6.1.5 eIF3

eIF3 is the largest initiation factor, containing 13 nonidentical subunits (from A to M), and its main role is to manage the formation of the preinitiation complex [58]. The dysregulation of eIF3 expression was described in gynecologic tumors. Building upon the limited understanding of eIF3 role in both OC and CC, recent studies have begun to

elucidate its impact on these cancers' progression. eIF3C and eIF3B significantly influence the proliferation and survival of OC cells. *In vitro* experiments revealed that silencing both eIF3B and eIF3C leads to notable changes in gene expression and biological processes, ultimately hampering cell proliferation and inducing apoptosis [59, 60]. Moreover, the eIF3C overexpression in OC caused elevated protein synthesis and in turn OC proliferation. It has been shown that eIF3C protein levels were positively correlated with YTHDF1 protein, which recognized m^6A modification present in eIF3C mRNA, and then stimulated its expression. This particular YTHDF1-eIF3C axis might be a potential target for OC treatment [61]. Zhao et al. highlighted the positive correlation of eIF3B overexpression with tumor size, cancer advancement, and lymphatic metastasis. Accordingly, patients with high eIF3B expression have decreased OS [62]. In contrast, patients with highly expressed eIF3A have a higher OS rate and respond better to cisplatin-based chemotherapy having downregulated expression of XPC, $p27^{kip1}$, and cell cycle proteins [63]. Additionally, experiments targeting eIF3D support the notion that eIF3 plays a pivotal role in cancer progression. eIF3D knockdown not only reduces mRNA and protein levels but also leads to a reduction in cell proliferation, further substantiated by the induction of G2/M cell cycle arrest [64]. This suggests that these eIF3 subunits are integral to the maintenance of cancer cell viability. In CC progression, eIF3D has turned particular attention. It has been observed that the manipulation of eIF3D expression levels considerably impacts the behavior of CC cells. Overexpression of eIF3D has been linked to heightened aggressiveness, with a marked increase in both the migratory and invasive capabilities [65, 66]. In detail, the direct interaction between eIF3D and glucose-related protein 78 (GRP78) activates focal adhesion kinase (FAK), which contributes to cancer progression [65]. The suppression of eIF3D not only curtails the ability of CC cells to move but also appears to impede their invasive potential, suggesting that eIF3D plays a critical role in the eIF3D-GRP78-FAK axis [65]. Moreover, the overexpression of eIF3D is positively correlated with the Warburg effect, a characteristic feature of cancer cells [66]. The eIF3D can be used as an indicator and potential target for CC treatment.

6.1.6 eIF5A

In gynecologic cancers, mainly in OC and CC, the eIF5A factor upregulation has been described. Initiation factor 5A plays a role during the initiation and elongation steps of protein biosynthesis [67]. Moreover, eIF5A has two isoforms: eIF5A1, expressed in most of the cells, and eIF5A2, showing cell specificity (e.g., ovarian and colon cancer cells) [68]. The heightened expression of both eIF5A1 and eIF5A2 has been linked to poor survival outcomes [69–71]. The expression and functional implications of eIF5A2 in OC cells have been the subject of extensive research, revealing a complex role in tumor progression and metastasis. Immunofluorescent staining techniques have confirmed eIF5A2 expression within ovarian carcinoma tissue sections, providing direct visualization of its presence in the tumor microenvironment [69, 72]. Studies demonstrate that high-risk ovarian carcinoma samples exhibit significantly higher levels of eIF5A2 when compared to those from the low-risk group [69, 73]. Further emphasizing its role in tumorigenesis, eIF5A2 has been shown to promote epithelial-mesenchymal transition (EMT) and activate the TGFβ pathway, both of which are pivotal processes in cancer metastasis [69]. In CC, eIF5A2 expression is upregulated, linking it to the aggressive nature of the disease [71]. In addition, eIF5A2 influences the viability and mobility of CC cells via the RhoA/ROCK pathway, underscoring the molecular mechanism by which eIF5A2 may affect tumor progression and metastasis [74]. This effect is further evidenced by functional studies where the knockdown of eIF5A2 not only inhibits tumorigenic abilities *in vivo*, but also leads to decreased cell growth, induces cell cycle arrest, and reduces cell migration capabilities in HeLa cells, a common CC cell line. These features show that eIF5A2 might be a good prognosis predictor as well as a new therapeutic target for CC treatment [74].

6.1.7 eIF6

eIF6, a ribosome anti-association factor, has been added to the group of initiation factors implicated in OC. eIF6 prevents the association of 40S and 60S subunits, modulating the availability of translating ribosomes [75]. The reduced expression of eIF6 in patients with ovarian serous adenocarcinoma is significantly correlated with their low disease-free survival. Furthermore, the low eIF6 expression is associated with a higher rate of lymph node metastasis [76]. In contrast, Benelli et al. showed that the upregulation of eIF6, controlled by the Notch-1 signaling pathway, is related to the invasiveness and motility of OC cells [77]. This suggests that eIF6 acts as a downstream effector of Notch-1, influencing cell motility under physiological and pathological conditions. Moreover, eIF6 overexpression has been linked to the upregulation of cdc42, a protein involved in actin organization during cell migration, further emphasizing its role in promoting cell motility [78]. These observations highlight the multifaced role of eIF6 in the migration of OC cells, shedding light on its significance in cancer progression.

6.1.8 eEF1A

The eukaryotic elongation factor 1A (eEF1A) is a ubiquitous protein that participates in protein biosynthesis bringing the aminoacyl-tRNA to the ribosomal A site [79].

Mammalian eEF1A has two paralogs: eEF1A1, widely expressed in cells, and eEF1A2 present in neurons and muscle cells [80]. So far, only eEF1A2 has been identified as a potential oncogene, associated with OC progression, being overexpressed at both mRNA and protein levels [81–83]. The unequivocal indication of increased eEF1A2 expression poses many problems due to divergent literature data. On the one hand, Anand et al. correlated eEF1A2 upregulation with its gene amplification [83], while Tomlison et al. showed that the amplification of eEF1A2 is not correlated with either genetic or epigenetic modification of its gene [81]. Moreover, the lentivirally induced overexpression of eEF1A2 determines apoptosis resistance, serum-independence, and increased saturation densities in *in vitro* 3D cultures of normal ovarian surface epithelial cells (OSE), indicating the transition to malignancy [84]. Another study has shown that eEF1A2 overexpression in serous ovarian carcinoma cell line SKOV3 increases its *in vitro* growth rate as well as enhances its ability to form spheroids in drop culture [82]. Furthermore, in contrast to the study by Sun et al., the upregulation of eEF1A2 in the SKOV3 cell line does not impact apoptotic resistance, anoikis, and sensitivity to chemotherapeutics. However, in patients with serous OC, high levels of eEF1A2 have been correlated with their increased 20-year survival probability [82]. Overall, these findings highlight the complexity of eEF1A2, and further studies should be carried out to elucidate its involvement in OC progression.

6.1.9 eEF1D/eEF1G/eEF2

Other TFs overexpressed in gynecologic tumors, especially in OC, are elongation factors eEF1G and eEF2 [85, 86]. These factors are involved in the elongation step that is crucial in the translational process [87]. Their impact on tumor outcome is not homogeneous. Bioinformatic studies predicted better OS and progression-free survival (PFS) of patients with overexpressed eEF1G [85]. In contrast, the research approach showed a correlation of eEF2 overexpression with reduced OS of patients. Furthermore, the eEF2 level was increasing with grade, and stage of OC and was positively correlated with Ki67 expression. The upregulation of eEF2 can promote OC proliferation, probably due to the inactivation of eEF2 kinase via the PI3K/Akt/mTOR pathway [86] (Fig. 4E). Also, eEF1D can be a part of the PI3K/Akt pathway, and its downregulation increases OC cell sensitivity to platinum-based chemotherapy. Lack of eEF1D inactivates the PI3K/Akt pathway and diminishes the Bax/Bcl-2 ratio, triggering the apoptosis process [88]. Interruption of eEF1D/PI3K/Akt might be a new potential target in treating OC.

6.2 Ribosomal proteins

RPs play a crucial role in the translation of mRNAs into proteins, by forming the ribosome, a nanomachine comprising four rRNAs and approximately 80 RPs. In addition, most RPs hold extra-ribosomal functions, including their involvement in DNA repair, replication, proliferation, apoptosis, and oncogenesis [89]. Mutations in RP-encoding genes are highly associated with inherited and acquired genetic diseases, such as ribosomopathies and cancer, respectively [90]. In both contexts, these mutations are thought to impact either (1) directly ribosomal functions, thus leading to the preferential translation of certain mRNAs, creating a pro-oncogenic proteome [91], or (2) ribosome-unrelated functions, which may alter signaling pathways related to oncogenesis (e.g., pro-survival, stress-resistance, anti-apoptotic, migration) [37].

6.2.1 RACK1

A unique RP, RACK1, a receptor for activated C kinase 1, has been identified as a significant player in various biological features, including the growth and invasion of cancer cells [92] by direct interaction with β1/β2 integrins [93] and Src kinase [94], and increasing FAK phosphorylation [95]. Recent studies have shown that RACK1 is frequently upregulated in CC and OC [96–99], and its expression gradually increases with the cancer stage [96]. Both clinical and cell-based experiments support the contribution of RACK1 to CC and OC progression, indicating its crucial role [96, 99]. In particular, the overexpressed RACK1 stimulated the cell cycle inter alia by enhancing the level of cyclin D1 and reducing p21 [96]. Additionally, a study by Liao et al. showed the RACK-1-dependent upregulation of NF-κB and CDK4 and downregulation of p53 and p38, thus contributing to generating a cancer-prone setting [98]. RACK1 can also inhibit apoptosis by increasing the potential of the mitochondrial membrane [98]. Interestingly, gynecologic cancer development can be a result of post-translational modifications of RACK1 which increase its stability [97, 99] or give RACK1 an extra-ribosomal function [100]. A recent study demonstrated that RACK1 reversible MARylation controls stress granule assembly and protein biosynthesis. Specifically, during stress, PARP14-mediated MARylation at Asp144, Glu145, and Asp203 residues of RACK1, mediates its binding with G3BP1, eIF3η, and 40S RPs in the stress granules, allowing OC cells to overcome the emerging stress. After prolonged stress, RACK1 undergoes TARG1-dependent deMARylation and is incorporated into ribosomes (Fig. 5A). Moreover, inhibition of RACK1 MARylation triggers apoptosis in stress conditions due to the lack of presence of stress granules [100].

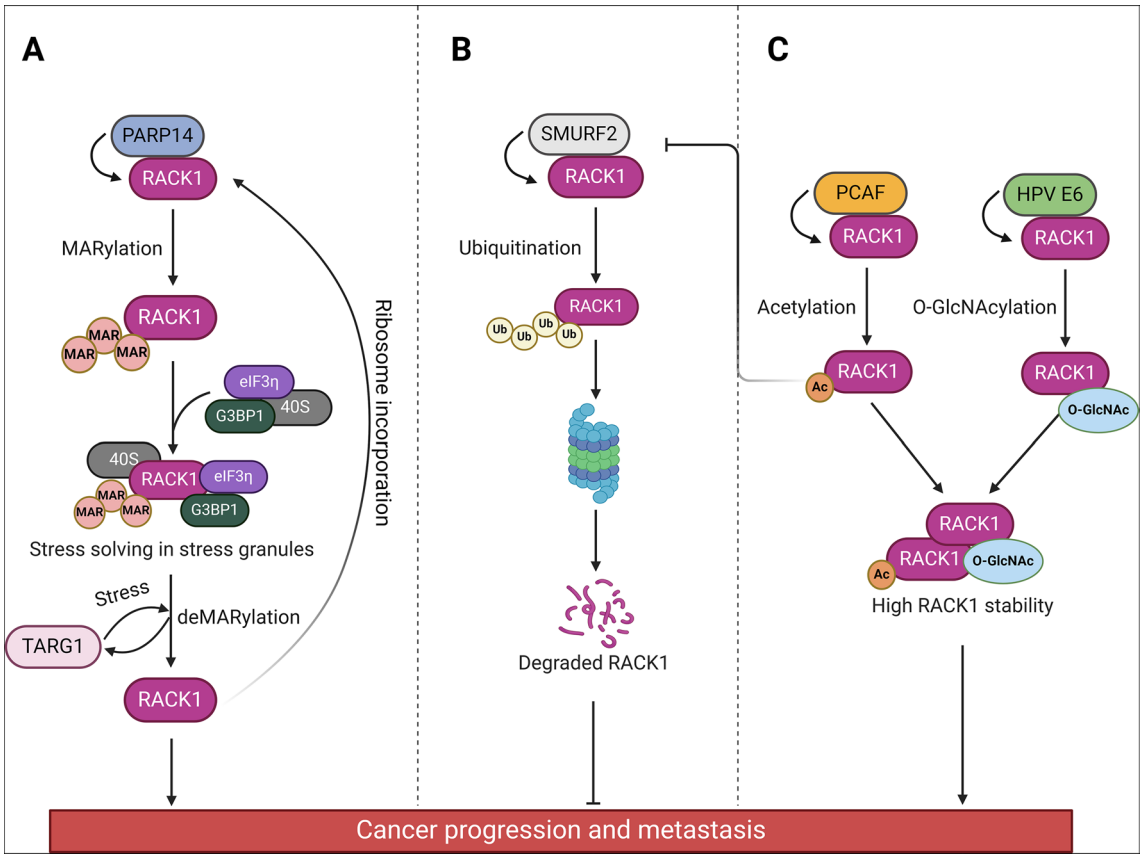

Fig. 5 Multifaceted involvement of the RACK1 protein in the development and invasion of OC and CC. The post-translational modifications influence RACK1 behavior and stability, which are crucial for cancer progression. **A** RACK1 MARylation by PARP14 controls stress granule assembly which is crucial to overcome emerging stress. In homeostasis conditions, deMARylated RACK1 by TARG1 is incorporated into ribosome to restore protein synthesis. **B** Ubiquitination by SMURF2 drives RACK1 degradation in a proteasome, inhibiting cancer advancement. **C** RACK1 acetylation by PCAF prevents SMURF2 binding and together with HPV E6-dependent O-GlcNAcylation improves RACK1 stability, leading to cancer promotion. The figure was created with BioRender.com

On the other hand, analysis of OC described RACK1 acetylation and ubiquitination, and these modifications have an opposite effect on its stability. It has been found that Smad ubiquitin regulatory factor 2 (SMURF2)-dependent RACK1 ubiquitination at Lys225 and Lys257 residues leads to its degradation (Fig. 5B). While RACK1 acetylation at Lys130 residue by P300/CBP-associated factor (PCAF) acetyltransferase prevents SMURF2-RACK1 interaction, causing its upregulation due to lower level of ubiquitination [99] (Fig. 5C). In CC, the HPV E6 oncogene drives RACK1 O-GlcNAcylation at Ser122 residue, increasing its stability and at the same time its abundancy within cells [97] (Fig. 5C). The upregulated RACK1 boosted cell invasion, lymphangiogenesis, and lymph node metastasis in cervical adenocarcinoma (Fig. 4). Mechanistic investigations have unveiled the involvement of RACK1-dependent expression and secretion of galectin-1 protein upon miR-1275 reduction and enhanced integrin-β1 pathway downstream of galectin-1 [97]. In a different histological context, Wang and Chen showed that RACK1 is downregulated in cervical squamous cell carcinoma (CSCC) compared to noncancerous tissues, and it is involved in cancer progression [101]. In this CC histotype, upregulation of RACK1 leads to enhanced expression of miR-302b/c/d-3p, which inhibits Cyclin O, in turn resulting in apoptosis activation [101]. In summary, the multifaceted role of RACK1 in CC highlights the complexity of these pathogenetic pathways, suggesting that the interplay with other yet-to-be-defined factors could be key in determining the effect of RACK1 alterations in CC. A better understanding of these mechanisms will provide valuable insights into potential therapeutic targets as well as prognostic markers for faster diagnosis of CC.

6.2.2 RPS3 (uS3)

Ribosomal protein S3, a component of the 40S subunit is involved in translation initiation [102]. Beyond its ribosomal function, RPS3 possesses extra-ribosomal functions, including interactions with the NF-κB transcription factor family [103, 104]. Overexpression of RPS3 plays a crucial role in

epithelial OC progression, through the direct interaction with the p65 subunit of NF-κB. Moreover, the RPS3 level can be regulated by E3 ubiquitin ligase SIAH1, ubiquitinating RPS3 at Lys214, leading to its degradation in the proteasome. Low RPS3 levels inhibit the NF-κB pathway and overcome the chemoresistance of this cancer. Thus, therapy targeting the SIAH1-RPS3-NF-κB axis could be a good objective in the fight against chemoresistance in EOC [105].

6.2.3 RPS4X (eS4X)

In the case of the RPS4X protein, patients with its upregulation had better OS and disease-free progression [106]. It has been demonstrated that endogenous expression of RPS4X is lower in cisplatin-resistant cell lines, showing its potential usefulness as a protein marker in the platinum-based chemotherapy. In addition, RPS4X depletion increased the cisplatin resistance in the OC cell lines, probably due to ribosomal stress that caused the retarded growth. However, this mechanism has not been described yet [106].

6.2.4 RPS6 (eS6)

RPS6 contribution to cancer proliferation can be attributed to its altered expression. The upregulated expression of RPS6 is associated with poorer OS in epithelial OC patients [107]. The higher level of RPS6 is positively correlated with the clinical stage and pathological grade of OC. There is evidence showing that, when RPS6 is knocked down, cell proliferation, migration, and invasion are also effectively inhibited. At the molecular level, RPS6 absence diminishes both cyclin E and D1 protein levels as well as CDK2, CDK4, CDK6, and Rb phosphorylation, which are critical in controlling the cell cycle [107]. Similarly, these observations are in line with another study reporting that RPS6 participates in cell cycle progression, cell proliferation as well as migration and invasion which play an essential role during tumor development [108]. Taking together, RPS6 might be another prognostic marker and/or therapeutic target in OC diagnosis and treatment [109].

Furthermore, a recent study indicated that RP MARylation (mono(ADP-ribosyl)ation), a post-translational modification can participate in OC progression. This modification has been ascribed to the Glu35 residue of RPS6 and is catalyzed by PARP-16 [110]. This PTM has been shown to fine-tune the levels of translation and prevent toxic protein aggregation. Indeed, loss of MARylation at these RPs leads to decreased enrichment of eIF6 on the ribosomes, leading to augmented polysome formation, protein synthesis, and in turn protein aggregation. Thus, in OC, increased MARylation determines a reduction in cell proliferation rate while conferring to OC cells a selective advantage in terms of resistance to proteotoxic stress [110]. Consequently, an increase in MARylation has been correlated to a poorer outcome.

6.2.5 RPS7 (eS7)

Investigation of RPS7's role in OC revealed that this protein regulates apoptosis, angiogenesis, and the cell cycle [111]. RPS7 silencing increases cell proliferation, migration, and invasion; however, it attenuates apoptosis and cisplatin chemosensitivity [111]. Notably, RPS7 positively regulates PI3K/AKT, MAPK signaling pathways, and the expression of pro-apoptotic factors (Bax, Bak), but negatively the expression of anti-apoptotic factors like Bcl-2 [111]. These findings suggest that RPS7 could be used as a potential marker for diagnosis and treatment of OC.

6.2.6 RPS12 (eS12)

RPS12 has been reported to be markedly overexpressed in CC, and in turn, increases the invasiveness of CC through activation of c-MYC, a part of the Akt/mTOR pathway. The application of dietary flavonoids such as quercetin and luteolin can reduce cell mobility via the inhibition of the Akt/mTOR/c-Myc/RPS12 pathway [112]. These findings indicate this pathway as a potential target against the development of CC.

6.2.7 RPS27A (eS31)

The bioinformatic analysis revealed that RPS27A was diversely expressed in different clinical stages of CC and its upregulation was associated with advanced CC [113]. The HPV16-positive CC patients with upregulated RPS27A had a worse survival prognosis, indicating RPS27A as a new possible prognostic biomarker [113].

6.2.8 RPL10 (uL16)

RPL10 is another important RP involved in OC progression. It has been shown that in epithelial OC, RPL10 is upregulated in both mRNA and protein levels, and its expression is higher in malignant rather than benign tumors [114]. Nevertheless, overexpression of RPL10 is not correlated with age, histological stage, and clinical stage in patients with epithelial OC. Molecular studies have shown that overexpression of RPL10 in OC cells causes their faster migration and reduces the number of apoptotic cells [114]. Furthermore, the amount of RPL10 is negatively regulated by miR-143-3p, indicating a potential regulatory role in OC development [114]. This suggests the potential of RPL10 to drive the transformation of cancer cells into a more invasive phenotype, and it could be used as a novel prognostic marker and/or therapeutic target for OC.

6.2.9 RPL22L1 (eL22L1)

The contribution of RPL22L1 in OC progression is attributed to its upregulation in this type of cancer. The TCGA analysis showed that RPL22L1 is overexpressed in both mRNA and protein levels, and this is a consequence of *RPL22L1* gene amplification [115]. RPL22L1 upregulation has been positively correlated with cancer stage, invasion, and lymph node metastasis due to reduced expression of epithelial marker proteins (E-cadherin, α-/β-catenin) and increased mesenchymal markers (fibronectin, vimentin, α-SMA) expression [115], characteristic features of EMT [116]. To sum up, RPL22L1 makes OC a more invasive phenotype, and its features make it a good prognostic marker and/or possible therapeutic target for OC.

6.2.10 RPL23 (uL14)

The diversity in expression patterns among the various RPs indicates their unique aspect in OC development and progression. For instance, recurrent high-grade serous ovarian cancer (HGSOC) patients have higher RPL23 expression than patients without recurrence. Analysis of the TCGA database described the significant correlation between worse prognosis in HGSOC patients and higher RPL23 expression [117]. This may indicate that upregulation of RPL23 might cause a recurrence of HGSOC and, as a consequence, result in a poor prognosis. Thus, RPL23 might serve as a prognostic marker for HGSOC patients.

6.2.11 RPL24 (eL24)

In the intricate web of cellular processes that contribute to gynecologic cancer development, another RP has emerged as a significant player. Notably, in CC cells, RPL24 is downregulated and indicates an unfavorable recurrence-free survival, OS, and PFS [118]. It should be noted that cisplatin-based chemotherapy inhibits the cell cycle in the G2/M phase and, as a consequence, significantly increases both RPL24 and p53 expressions. This observation suggests that RPL24 might be a part of the MDM2-p53 pathway, modulating the CC development [118]. Therefore, RPL24 can be a meaningful target for prognosis and the future treatment of CC patients.

In addition, RPL24 undergoes PARP-16-dependent MARylation at the Glu4 residue in OC cells [110].

6.2.12 RPL34 (eL34)

A recent study has presented RPL34 as an RP involved in CC development and progression. In CC cells RPL34 expression is negatively correlated with the severity of cervical lesions and is downregulated compared to the normal tissue [119]. In particular, the expression of RPL34 is controlled by an antisense lncRNA named RPL34-AS1, whose level is regulated by the eIF4A3 factor [119]. The downregulation of the RPL34 protein resulted in the P53 downregulation and MDM2 upregulation that inhibited CC proliferation, invasion, and metastasis [119]. This suggests that RPL34 may influence CC development, through the MDM2-P53 pathway, and might be used as a target for prognosis and future treatment.

6.2.13 RPL35A (eL33)

In the case of RPL35A upregulation correlated with shorter overall and disease-free survival of patients with OC [120]. The overexpression of RPL35A enhances cell proliferation and migration (EMT) but inhibits apoptosis. It has been shown that RPL35A expression is positively correlated with CTCC-binding factor (CTCF) [120], which previously has been implicated in the progression of various cancers such as breast cancer [121]. RPL35A facilitates the direct binding of the YY1 transcription factor to the CTCF promoter in OC cells. Furthermore, RPL35A stimulates the PPAR signaling pathway, by enhancing p38 phosphorylation, PPARα, and PPARγ expression [120]. In summary, RPL35A promotes OC progression through the YY1-CCTF axis and could serve as a promising candidate for future targeted therapeutic strategies.

6.2.14 RPL39 (eL39)

A role in OC development has been associated also with upregulated RPL39 [122]. Direct interaction of RPL39 with acylglycerol kinase (AGK) in mitochondria was indispensable to sustain the mitochondrial function and structure. This leads to chemoresistance through augmenting the cancer stem cell ability of self-renewal [122]. Thus, targeting the RPL39-AGK axis may be a potential candidate for inhibition of OC progression.

6.2.15 Ribosomal P-proteins — RPLP0 (uL10), RPLP1 (P1), and RPLP2 (P2)

Ribosomal P-stalk proteins (RPLP0, RPLP1, and RPLP2) have been reported to show an elevated expression in EC and OC [123], whereas RPLP1 has been implied in CC [124]. Generally, uL10, P1, and P2 form a pentameric structure, being a protein part of the GTP-associated center (GAC) responsible for the stimulation of GTP hydrolysis by translational GTPases [125]. The overexpression of ribosomal P-proteins has been observed at the mRNA and protein level and has been positively correlated with the advancement of EC and OCs [123]. In serous OC, the correlation between overexpressed P-proteins, high p53 levels, and the presence

of lymph node metastases has been shown. Interestingly, in endometrial tumors, ribosomal P-proteins accumulate in cells with infiltrating properties, emphasizing their role in invasiveness [123]. On the other hand, in CC, expression of P1 is correlated with calponin 3 (CNN3), and downregulation of CNN3 leads to decreased P1 protein level. In CNN3 knockdown Hela cells, the overexpression of P1 restores cell proliferation, invasion, and migration, indicating a crucial role of P1 in the regulation of malignancy in CC cells [124]. Taken together, there is available evidence that the overexpression of P-proteins might be associated with a worse prognosis and might serve as a potential marker for malignancy in gynecologic tumors.

7 Therapeutic perspectives and discussion

The exploration of translational machinery elements as potential biological markers and therapeutic targets in gynecologic tumors presents a compelling avenue for advancing precision medicine in oncology. The identification and understanding of key components within the translational machinery, including translation factors, ribosomes, and mRNA/tRNA modification targets, offer a nuanced perspective on the molecular pathways driving tumor progression. By dissecting the intricate regulatory mechanisms governing protein synthesis, researchers can unravel the underlying dysregulation that fuels tumor proliferation in gynecologic malignancies. Rapidly proliferating cancer cells depend on elevated protein synthesis rates, which are sustained by enhanced ribosome biogenesis (and RP synthesis), and upregulation of translation factors (reviewed in [126]). In addition, cancer cells can adjust to various stress conditions, whether induced by internal or external factors, by modulating gene expression at the translational level [127]. While this connection is intuitive, the link between a downregulation (or functional modulation) of RPs/TFs and cancer is less obvious. However, it should be kept in mind that, for different RPs, pleiotropic (or extra-ribosomal) functions (either pro-oncogenic or tumor-suppressive) have been described [128], which are carried out through the functional interaction with other signaling pathways and/or transcriptional regulators. In addition, many genes encoding RPs and TFs are host genes of non-coding RNAs (including microRNAs and small nucleolar RNAs), whose functions are also linked to cancer [129]. Therefore, future research in the field should strive to explore the diverse molecular effects of the expression de-regulation of RPs and TFs, by keeping an open view at different levels (e.g., transcriptional, post-transcriptional, translational, and post-translational) to highlight nodes of convergence that may represent formidable therapeutic targets against cancer.

What reported so far underscores the multifaceted involvement of translational machinery in gynecologic cancer, implying the possibility of targeting specific elements to disrupt oncogenic signaling cascades and inhibit tumor growth. The development of tailored therapies that exploit these molecular vulnerabilities holds immense promise for improving clinical outcomes in patients with gynecologic tumors. The exploration of this therapeutic avenue is supported by prior experience, which has highlighted the efficacy of inhibiting protein synthesis downstream of the PI3K/AKT/mTOR pathway [130]. The mammalian Target Of Rapamycin (mTOR) was discovered in the early 1990s and subsequently characterized as being a key integrator of extra- and intra-cellular signals to maintain cellular homeostasis and metabolism, including protein synthesis [130]. Rapamycin and its derivatives (sirolimus, temsirolimus, everolimus), along with other inhibitors of mTOR complexes, AKT, or PI3K, have been tested, either alone or in combination with other drugs, in various clinical trials for the treatment of ovarian and endometrial cancers (reviewed in [131]). Similarly, the Ras/Raf/MEK/ERK signaling cascade, leading, through the activation of the MNK kinases, to the phosphorylation of eIF4E and initiation of translation, is a promising target in cancer treatment [46]. Inhibitors of MNK1/2 kinases (like BAY1143269, eFT508, and ETC-206) have been recently investigated in clinical trials to treat solid cancers and leukemia [46]. None of these compounds, however, has been passed on to the clinics for these cancer types. This highlights that it is imperative to delve deeper into the functional roles of these translational components, elucidate their interactions within the tumor microenvironment, and explore novel therapeutic strategies that exploit these biological markers. Targeting ribosomes or different stages of translation in gynecologic cancers could represent a promising new treatment strategy. In this regard, various compounds are being tested in multiple oncologic contexts, including gynecologic cancers. For a thorough information about the topic, the reader is referred to specific literature [132–134]. Here, we provide a concise overview, focusing on the molecules that, in our view, show the greatest potential for future clinical applications. These compounds fall into three categories: inhibitors of ribosome biogenesis, of ribosomes themselves, or of translation factors.

7.1 Inhibition of ribosome biogenesis

Targeting the production of ribosomal proteins (RPs) presents significant challenges due to the difficulty of achieving this without affecting overall protein synthesis. Moreover, no compounds have yet been developed to inhibit the entire RP family or its members. However, creating an imbalance in RP and rRNA production remains a viable approach for exploiting the endogenous ribosomal stress response to

activate p53 and halt cancer cell growth [135]. The first-in-class selective inhibitor of RNA Polymerase I is CX-5461 [136]. Blocking rRNA synthesis while maintaining regular RP production triggers the ribosomal stress response, leading to cell death [137]. Over the past decade, CX-5461 has shown effectiveness against various malignancies, including HGSOC [138, 139]. The efficacy of the molecule in preclinical tumor models has propelled it towards clinical studies, and the molecule has been/is being tested in different phase I and/or II clinical trials on hematologic and solid malignancies, including OC (NCT02719977, NCT04890613, NCT06606990, NCT05425862, www.clinicaltrials.gov).

7.2 Inhibition of the 80S ribosome

Several compounds can inhibit the eukaryotic ribosome by specifically targeting functional sites within the 60S or 40S subunits, thereby blocking protein synthesis. Most of these molecules bind to rRNA moieties (reviewed in [140], but due to the intricate interplay between RPs and rRNAs within ribosomes, changes in RPs can also affect rRNA structure [141]. Many compounds and their derivatives have been explored in recent years, but only a few have been tested in the context of gynecologic cancers. Agelastatins, halogenated alkaloids isolated from the marine sponge *Agelas dendromorpha*, form a class of natural molecules that inhibit the peptidyl transferase center (PTC), a crucial ribosome functional center. Agelastatin A has been extensively studied in cancer models both *in vitro* and *in vivo*, demonstrating inhibitory activity against different cancer types, including cervical and ovarian cancer [142]. Among alkaloids, haemanthamine, derived from *Amaryllidaceae* bulbs, binds to the PTC and inhibits the elongation step of protein synthesis. Its anticancer effectiveness has been demonstrated *in vitro* on various cancer cell models, including cervical and ovarian carcinoma, where it inhibited protein synthesis and induced nucleolar stress and apoptosis by stabilizing p53 [143, 144]. Members of the mycotoxin family, i.e., verrucarin A, verrucarin J, and deoxynivalenol, bind to the A-site of the 60S, inhibiting the elongation step. These natural compounds can effectively inhibit cancer growth both *in vitro* and *in vivo* across various oncological contexts. For example, verrucarin J has demonstrated efficacy against OC models [145], although it has not been tested in humans due to concerns about potential toxicity.

PTC124, or Ataluren (marketed as Translarna™), is a small molecule that promotes stop codon readthrough by encouraging the misincorporation of near-cognate aminoacyl-tRNAs at premature termination codons. Although Ataluren has been extensively studied in clinical settings for treating genetic diseases arising from nonsense mutations, it is worth noting that a phase I-II trial is ongoing to evaluate the safety and efficacy of combining Ataluren with Pembrolizumab in patients with metastatic mismatch repair-deficient endometrial carcinoma (NCT04014530, www.clinicaltrials.gov). However, the results of this study are not yet available.

7.3 Inhibition of translation factors

Many efforts are being put into research to exploit translation initiation, elongation, and termination factors as targets for translation inhibition in cancer. Among all, inhibition of eEF1A emerges as a promising strategy to inhibit cancer cell growth. Plitidepsin, a natural extract, is a potent inhibitor of cancer growth through eEF1A inhibition [132]. It has proven effective in multiple *in vitro* and *in vivo* cancer models, including OC [146], and it has undergone multiple clinical trials, mainly for the treatment of hematologic malignancies, but also for solid tumors (NCT00780975, NCT01149681, NCT00884286, NCT01102426, NCT03070964, NCT01876043, NCT00229203, NCT00788099, NCT02100657, NCT00780143, www.clinicaltrials.gov); it is now marketed in Australia with the name of Aplidin® to treat multiple myeloma. Metarrestin, another eEF1A inhibitor, has shown its effectiveness against OC pre-clinical models [147] and is currently under clinical investigation to treat advanced solid tumors (NCT04222413).

As highlighted in this review, the contribution of ribosomal proteins and translation factors in gynecologic cancers underscores their critical importance in tumor biology. By harnessing the potential of translational machinery elements as diagnostic tools and therapeutic targets, we can pave the way for more personalized and effective treatments for gynecologic cancers, ultimately transforming the landscape of oncology care. Continued research in this field will be crucial to uncover novel mechanisms and optimize clinical applications, ensuring that these advancements translate into tangible improvements in patient outcomes and long-term cancer management.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interests The authors declare that they have no conflict of interest.

Competing interests The authors declare no competing interests.

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