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Ribosomal Proteins and Cancer

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Abstract: The translation process consists of translation factors and ribosomes. Ribosomal components include ribosomal proteins (RP) and ribosomal RNA. Many RPs are involved in assembling ribosomal particles and or stabilizing important regions of rRNA. Besides their conventional roles, RPs have been reported to exhibit secondary functions that have not yet been fully characterized in other cellular processes such as DNA repair, apoptosis, drug resistance, proliferation, and growth inhibition. Since cancer cells require a large amount of protein, they need ribosomes that work much more efficiently than normal cells. Several tumor suppressors and oncogenic proteins control the progression of cancer cells by regulating ribosome biogenesis and protein synthesis. Interestingly, free RPs also have diverse roles in tumorigenesis or tumor suppression. The physiological link between RPs and cancers has been extensively reviewed and elucidated on several pathways, including their interaction with the p53-MDM2 complex. The first evidence of an association between RPs and cancer came from observing the haploinsufficiency of eS4 in Turner Syndrome and eS19 mutation in Diamond-Blackfan Anemia. In the following years, the roles of different RPs in various cancer types such as colorectal cancer, breast cancer, lung adenocarcinoma, T-cell acute lymphoblastic leukemia, prostate cancer, breast cancer, gastric carcinomas, ovarian cancer, and liver cancer have been the subject of research. Apart from their effects on carcinogenesis, it was also emphasized that RPs could be evaluated as predictive biomarkers for diagnosis, prognosis, and treatment for some cancer types. In addition, some studies have been conducted on the use of these proteins in cancer treatment. Identifying novel extra-ribosomal functions of some RPs has identified these proteins as a new class of oncogenic or tumor suppressor factors. Suppression and stimulation of the expression of these novel oncogenic and tumor suppressor proteins, respectively, are considered could open up new therapeutic strategies in cancer therapy.

Keywords: Ribosomal proteins, Carcinogenesis, Cancer biomarkers, Cancer treatment

Introduction

The cell is the smallest metabolically functional unit of life. Cells can sense external signals and give tightly regulated responses to them at the transcriptional and translational levels. Translation is a coordinated multi-step process in eukaryotic cells. The translation mechanism consists of translation factors and ribosomes. Ribosomal components include ribosomal proteins (RP) and ribosomal RNA (rRNA). Biogenesis of eukaryotic ribosomes occurs within the nucleolus and requires the coordinated assembly of four different rRNAs and approximately 80 RPs (Fatica & Tollervey, 2002). RPs are important for ribosome formation and are synthesized by RNA polymerase II (Pol II). Ribozum formation and synthesis of RPs are coupled processes; After translation, RPs migrate to the nucleolus to assemble the 40S and 60S ribosomal subunits. The structure of the ribosome has revealed that many RPs can function as RNA chaperones during assembly of ribosomal particles and/or stabilization of important regions of rRNA (Fatica and Tollervey, 2002). Some RPs participate in the interaction between the 40 and 60S subunits (S13, S15, S19, L2, L5 and L14), while others associate with tRNA (S7, S9,

S12, S13, L1 and L5) or play a role in ribosome stabilization (L22, L24 and L29). Besides their role in stabilizing the ribosome, RPs have been reported to exhibit secondary functions that have not yet been fully characterized in other cellular processes such as DNA repair, apoptosis, drug resistance, proliferation, and growth inhibition (Shen et al., 2006; Du et al., 2005).

Ribosome-Related Functions of Ribosomal Proteins

The eukaryotic ribosome is the cellular translation machinery primarily responsible for protein synthesis from messenger RNAs (mRNA) and consists of four types of ribosomal RNA (rRNA) and 80 ribosomal proteins (RP). Production of this machine, called ribosome biogenesis, is an extraordinarily complex process involving all three RNA polymerases and >150 non-ribosomal factors required for the synthesis, processing, transport and assembly of pre-ribosomes (Fatica and Tollervey, 2002; Tschochner and Hurt, 2003). In principle, 47S/45S pre-rRNA synthesized by RNA Polymerase I (RNA Pol I), 5S rRNA produced by RNA Polymerase III (RNA Pol III), and RP-encoding mRNAs produced by RNA Polymerase II (RNA Pol II) non-ribosomal factors and small nucleolar RNAs (snoRNA) to obtain pre-90S ribosomes within the nucleolus, which undergo multiple modifications and subsequent separation into pre-60S and pre-40S particles. During their transport from the nucleolus to the cytoplasm, these anterior ribosomes are detached from most of their non-ribosomal factors and then matured into 60S and 40S subunits for protein translation (Fatica and Tollervey, 2002; Tschochner and Hurt, 2003).

RP'ler ribozom içersinde rRNA'nın katlanmasına yardımcı olmaktadır (Traub ve Nomura, 1969; Roth ve Nierhaus, 1980). RP'lerin yokluğunda, rRNA'nın hızla katlandığı ancak süreç esnasında yerel enerjetik olarak elverişli tuzaklarda kolayca hapsolduğu belirtilmiştir. Katlanma sırasında RP'lerin varlığı, rRNA'nın bu enerjik tuzaklara düşmesini engeller ve ayrıca, karmaşık RNA kıvrımlarını stabilizisayonunda rol oynar (Woodson, 2011).

Some RPs contribute to the process during translation. It has been suggested that in bacteria bS1 actively participates in initiating translation, possibly by interacting with mRNA and directing it to the ribosome (Suryanarayana & Subramanian, 1983). Also, in bacteria, several r-proteins affect the accuracy of the decoding and ultimately the fidelity of the ribosome's translation of the mRNA sequence into a protein (Agrawal et al., 1998). The role of eukaryotic RPs in translation in general is not yet fully understood. However, various methodological approaches have revealed that RPs in eukaryotes are involved in numerous interactions with translation machinery (Graifer & Karpova, 2015).

Extra Ribosomal Functions of Ribosomal Proteins

In general, the extra ribosomal functions of RPs are subsumed under the cell cycle, DNA repair, and apoptosis and various cellular processes associated with them (Molavi et al., 2019; Penzo et al., 2019).

Regulation of The Cell Cycle

Some RPs, cyclins or cyclin-dependent kinases (CDKs) modulate positive cell cycle regulators such as heterodimeric protein kinases that coordinate cell cycle progression through phosphorylation (Penzo et al., 2019). For example, RPL10m regulates the activity of Cyclin B1/CDK1, a key player in the cell cycle transition from late G2 to mitosis (Li et al., 2016). Beyond cyclins and CDKs, other important effectors such as Akt and E2F Transcription Factor 1 (E2F1) play an important role in cell cycle regulation. Knockdown of S8 strongly reduces phosphorylated Akt (pAkt) level with consequent G0/G1 cell cycle arrest (Yao et al., 2016), while RPL21 controls G1/S phase progression through regulation of E2F1 transcription factor and E2F1 target genes (Li et al., 2020).

DNA Repair

Over the past few decades, many studies have shown that different RPs are involved in DNA repair. For example, RPS3 is involved in the base excision repair (BER) pathway. A strong correlation has been demonstrated between intracellular levels of RPL3 and the activity of specific DNA repair processes such as homologous recombination (HR) and non-homologous end-joining (NHEJ) (Esposito et al., 2014). Furthermore,

MDM2 has been reported to specifically bind the telomere maintenance protein nibrin (NBS1), a component of a specific DNA repair complex, significantly compromising genomic stability. Interestingly, the NBS1 binding site on MDM2 overlaps with the binding site for some CRPs, including RPL14, RPL24 (L26) and RPS11. Thus, the maintenance of genomic stability is likely due to masking of the NBS1 binding site on MDM2 by these RPs (Kim et al., 2014; Zhang et al., 2006). In addition, RPS26 participates in the DNA repair process by directly modulating p53 transcriptional activity in response to DNA damage (Cui et al., 2014).

Regulation of Apoptosis

RPS3 exhibits a pro-apoptotic function. RpS3-mediated pro-apoptotic signaling is thought to be mediated through activation of the caspase-8/caspase-3 cascade and the c-Jun N-terminal kinase (JNK) pathway (Jang et al., 2012). In laryngeal carcinoma cells, enhanced expression of RPS14 induces p38, MAPK and JNK signaling, leading to activation of apoptosis. It has been suggested that uS14 exerts its apoptotic function through activation of both apoptotic pathways (death receptor-mediated and mitochondrial-mediated) (Saini et al., 2009).

Ribosomal Proteins in Cancer

Cancer cells that are constantly growing and proliferating require large amounts of protein, and this causes an increase in protein synthesis. This phenomenon means that cancer cells require much more efficient ribosomes than normal cells. Consistent with this view, a number of tumor suppressor and oncogenic proteins frequently control the progression of cancer cells by regulating ribosome biogenesis and overall protein synthesis (Silvera et al., 2010). Besides the importance of the ribosome for the growth and proliferation of cancer cells, non-ribosomal RPs may also play a role in tumorigenesis. Multiple RPs have been found to be upregulated at the mRNA or protein level in various human tumors (Artero-Castro et al., 2011; Chen et al., 2014). It has also been reported that overexpression of RPS3A leads to neoplastic transformation of the NIH-3T3 cell line and promotes tumor growth in mice (Naora et al., 1998). In addition, RPS13, which is highly expressed in gastric cancer cells, has been shown to inhibit drug-induced apoptosis and promote gastric cancer cell proliferation (Guo et al., 2011). Contrary to the oncogenic functions of some RPs, some non-ribosomal RPs have been shown to play a role in suppressing tumorigenesis by activating tumor suppressors or inactivating oncoproteins (de Las Heras-Rubio et al., 2014). Over the past 10 years, more than a dozen RPs have been reported to suppress tumor cell proliferation by regulating the MDM2/MDMX-p53 cascade. The RP-MDM2 interaction was first revealed by RPL11, RPL5 and RPL23 regulating the MDM2-p53 feedback loop (Zhou et al., 2015). When cells are under nucleolar stress triggered by various external factors or RP depletion, these three RPs are prevented from binding to the ribosome outline or released from the pre-ribosome to the nucleoplasm, where they bind to MDM2 and inhibit MDM2-mediated p53 ubiquitination and degradation, resulting in cell cycle and proliferation arrest. and they lead. Although most of the RPs interact directly with MDM2, RPS15, RPS20 and RPL37 have also been shown to bind to MDMX, the homolog of MDM2 (Daftuar et al., 2013). RPL26 is one of the most unusual RPs because it not only interacts with MDM2 but also associates with p53 mRNA and enhances its translation (Takagi et al., 2005).

Ribosomal Proteins as a Biomarker in Cancer Diagnosis

The study of changes in the ribosome biogenesis process in cancer cells is promising for the emergence of predictive biomarkers for early diagnosis, prognosis and treatment. Somatic mutations in RPL18 and RPL16 have been identified in T-cell acute lymphoblastic leukemia (T-ALL) (Mushtaq et al., 2018). RPL3 mutations are present in Diamond-Blackfan anemia, a ribosomopathy characterized by bone marrow aplasia and increased hematologic cancer (Engidaye et al., 2019). A study showed that decreased RPL3 expression in colon cancer tissues with p53 deletion is associated with malignant progression and tumor grade, and also with the development of resistance to different chemotherapeutic agents such as 5-FU and OHP (Esposito et al., 2014). By quantitative analysis of human prostate cancer tissues (CaP), three RPs overexpressed in CaP patients, namely RPS19 (S19), RPS21 (S21), and RPS24 (S24), were identified. The efficacy of RPS24 as a biomarker has been reported for human colon carcinoma (Arthurs et al., 2017). RPS17 (S11) has been identified as a potential prognostic biomarker in hepatocellular carcinoma (HCC). Specifically, a study conducted in a cohort of 182 patients showed that high RPS17 levels were associated with shorter survival and recurrence-free survival after surgical resection (Zhou et al., 2020). RPS17, RPS9 (S16) and RPS13 (S18) have also been identified as putative biomarkers for the response to Topoisomerase II (TOP2) in the treatment of glioblastoma, the most malignant brain tumor in adults (Awah et al., 2020). The characterization of mutations and aberrant

expression of RPs holds promise for the emergence of useful tools in cancer diagnosis, prognosis, and treatment predictions.

Ribosomal Proteins in Cancer Treatment

Studies have shown altered expression of several individual RPs in different types of human cancers, and the identification of novel extra-ribosomal functions of some RPs has identified these proteins as a new class of oncogenic or tumor suppressor factors (Penzo et al., 2019). In prostate cancer, the expression of RPS5 (S2) and RPL19 is significantly elevated, and some studies have identified these proteins as new therapeutic targets. To date, silencing of RPS5, which promotes expression of oncogenes such as Ras and c-Myc via a ribozyme-like oligonucleotide delivered locally or systemically, appears to eradicate metastatic tumors in mice (Wang et al., 2012). RPL39 (L39) and RPL32 (L32) are potential therapeutic targets for breast cancer therapy. To turn off the function of these CRPs, gene silencing has been shown to exert anticancer effects (Xu et al., 2020). Several studies have shown that RPL32 may be a promising therapeutic target for lung cancer. RPL32 silencing has been shown to affect ribosome biogenesis stress, resulting in migration of RPL18 and RPL5 from the nucleus to the nucleoplasm. Here, these proteins bind MDM2, leading to p53 accumulation resulting in inhibition of lung cancer proliferation. RPS6 is significantly upregulated in many cancers, including non-small cell lung cancer, esophageal squamous cell carcinoma, pancreatic neuroendocrine tumors, and sarcoma (Xie et al., 2020). In particular, RPS6 has been proposed as a therapeutic target for patients with ovarian cancer. Knockdown of RPS6 by LV-small hairpin RNA (shRNA) significantly inhibits the migration and invasion ability of ovarian cancer cells and induces G0/G1 phase arrest (Yang et al., 2020). As with overexpression, loss of individual RPs is associated with specific changes in cellular phenotype. Co-transduction of RPL14 enhances the therapeutic efficacy of adenoviral-mediated p53 in suppressing the proliferation of p53-mutated cancer cells. The ectopic RPL14 protein stabilizes p53 and leads to its accumulation in cells, accompanied by increased expression levels of the p53 downstream target genes MDM2 and p21 in vitro and in vivo (Zhang et al. 2013). Moreover, RPL41 (L41) induces the degradation of activating transcription factor 4 (ATF4), a master regulator of tumor cell survival, and contributes to sensitization of tumor cells to chemotherapy (Wang et al., 2012).

It is thought that tumor cells are more sensitive to nucleolar stress than normal somatic cells and thus targeting the ribosome biogenesis of tumor cells may be a reasonable strategy for the development of anti-cancer therapy. Anti-ribosome biogenesis drugs may be less toxic to normal and differentiated cells because they generally do not cause DNA damage and therefore may be slightly genotoxic to normal cells and induce nucleolar stress, unlike traditional chemotherapeutic anti-cancer drugs such as cisplatin and doxorubicin, which are genotoxic. Several anti-cancer chemotherapeutic agents have been identified that selectively target RNA Pol I, thereby inducing RS. The CX-3543 molecule was identified as the first G-quadruplex interacting agent to lead to specific inhibition of RNA Pol I-dependent transcription (Drygin et al., 2009). Another specific inhibitor of RNAPol I identified by the same group, CX-5461, prevents recruitment of SL1 to the RNA Pol I sensitive promoter and suppresses rDNA transcription initiation (Drygin et al., 2011).

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

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