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Reactive oxygen species (ROS) on Ribosome: from damage to regulation

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ABSTRACT

The chemical reactive molecule ROS (Reactive Oxygen Species) is a product of normal cellular metabolism. ROS plays a pivotal role in a wide range of biological processes, including aging, cancer and neurodegenerative diseases. Recent studies have shown that ROS can also affect the ribosomes – molecular machines responsible for protein synthesis. ROS leads to errors in protein synthesis and the production of misfolded proteins, causing damage to ribosomes. However, it has also been suggested that ROS is implicated in the regulation of the ribosome activity under certain conditions. The aim of this paper is to review current knowledge regarding the effects of ROS on ribosomes, with a focus on the mechanisms by which ROS can cause damage to ribosomes and the potential role of ROS in regulating ribosome activity.

INTRODUCTION

The ribosome is a ribonucleoprotein organelle responsible for protein synthesis. This process is vital for all kingdoms of life [1-3]. While, ribosome biogenesis is complicated and very coordinated, it is known that each cell is exposed to approximately 1×10^5 oxidative hits per day leading to ribosomal damage. This demonstrates that oxidative stress is implicated in different processes in the many pathophysiological pathways of cancer [4].

The influence of reactive oxygen species (ROS) in ribosomal protein modification in rare genetic diseases is a subject of current research. It has been observed that changes in the expression level, mutation, or assembly factors of ribosomal protein can cause dynamic adaption within the cellular metabolism. It is also known that RP (ribosomal protein) mutant diseases are associated with increased cellular ROS levels. To date, however, the mechanism of the defective ribosome which induces elevated ROS levels is not well understood. In some diseases, such as leukemia, it has shown an association with ribosome protein mutation, such as RPL10-R98S (a ribosomal protein derived from the large subunit 10/uL16-R98S), which is a result of the enhancing of peroxisome activity [5,6].

Some authors have reported that the wild type of RPL10 (ribosomal protein from large subunits 10) is involved in regulating the expression of protein related to ROS production, and to control ROS from mitochondria produced in cancer cells in the pancreas [7]. Research work has notably indicated that ribosomal protein from the large subunit RPL10-R98S may regulate ROS function.

Many other ribosomal proteins are associated with oxidative stress. ROS have the possibility to induce different agents that can induce RPS3/uS3 (ribosomal protein from the small subunit 3/uS3) translocation in the mitochondria. In this form, the cells are protected, because, as some authors have shown, ROS can damage mitochondrial DNA [8]. In some experiments, it has been observed as well that a low level of ROS can stimulate cell proliferation. This may be brought about by *PI3K* (phosphatidylinositol 3-kinases) and *MAPK* (mitogen activity protein kinase) signal pathway activation. Alternately, a higher level of ROS has been shown to cause toxicity and to inhibit cell proliferation [9-12]. In contrast, the lower level of ROS in antioxidants has been shown to restore the proliferation defects in RPL10-R98S

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cells [5,6]. This effect indicates that RPL10-R98S are associated with ROS production during cell proliferation.

An increase in the ROS level is also connected with an increase in DNA (deoxyribonucleic acid) damage and genomic instability in cancer cells [13]. For example, leukemia diseases have appeared to associate with different ribosomal protein mutations and diverse levels of DNA damage, and the protein mutation encountered in cases of leukemia consists of oxidative stress [6,13]. Diamond Blackfan Anemia (DBA) is one example of the mutation of large and small subunit ribosome protein (ribosomal protein from the large subunit 5/uL18 – RPL5/uL18 and ribosomal protein from small subunits 19/eS19 – RPS19/eS19). Patients with this disease have a higher level of ROS and DNA damage (double break) and 8-oxoguanine oxidative DNA damage [14]. Moreover, myeloid cells TF-1, which are a knockdown in patients with Shwachman-Bodian-Diamond syndrome (SBDS) and Shwachman-Diamond syndrome (SDS), seem to have elevated oxidative stress [15,16]. SDS generates a mutation in the SBDS gene, but also in *DNAJC21*, *EFL1*, *SRP54* – all of which are involved in ribosome biogenesis. Therefore, SDS is ribosomopathetic [17].

In mice with the deletion of the SBDS gene, inflammation is induced by ROS accumulation and genotoxic stress in neighboring hematopoietic cells [18]. Patients with DC (dyskeratosis congenital) T-lymphocytes also display an elevated ROS level, but suppression of dyskeratosis congenita 1 (DKC1) can induce oxidation and expression of the enzyme in HeLa cells (anti-oxidation enzyme) [19,20]. Furthermore, patients with cartilage hair hypoplasia (CHH) display approximately 2-4 times higher expression of the ROS scavenger catalase [21].

The expression of a gene, such as superoxide dismutase 2, appears to be involved in detoxification by ROS, and this enzyme is decreased in organism models for DBA diseases, such as mutations in *Rpl11/uL5* of zebrafish and a cell line with a mutation in *RPS19/eS19* [22,23]. Mutation analysis shows that mutational patterns in the ribosomal protein RPL10-R98S (*uL16-R98S*) in T cell acute lymphoblastic leukemia (T-ALL) are dominated by C: G>A: T transversion mutation. This is caused by oxidative damage to DNA. Mutation of ribosomal protein in T-ALL and chronic lymphocytic leukemia (CLL) patients displays higher mutation enriched for mutations that may diminish oxidative stress, compared to patients with wild-type ribosomes. This higher mutation can reduce oxidative stress, among others, in NOTCH1-activating mutations in T-ALL, and *P53* (protein 53) in patients with inactivated CLL [24,25]. Expression of *NOTCH1* eliminated these phenotypes in RPL10 R98 cells, in part via downregulation of PKC-θ, with no effect on RPL10-WT cells [24].

Mutations of P53 in SDS patients have been described in the transformation to acute myeloid leukemia (AML) [26]. Ribosomal protein damage is the main source of cellular mutagenic potential in this way, and this damage can initiate a higher level of cellular stress. Those cells, however, have the chance to survive the initial stress conditions.

Ribosomal RNA (rRNA) is shown to be a target for oxidative nucleobase damage. Increasing oxidative stress in another way has the possibility of interfering in ribosome protein assembly, the translation elongation cycle, and in the reduction of protein translation [27,28]. Specific phenotypes in patients with ribosomal protein mutations show that ribosomal protein has a unique function in tissue, adding-in the concept of a specialized ribosome. Most ribosomopathies are impaired in hematopoiesis, and several other diseases [29,30], but, interestingly, only patients with ribosomopathy defects evident in hematopoiesis, progress towards cancer. Among others, this includes diseases with anemia and bone marrow failure such as DBA, DC, SDS and CHH. All these diseases are caused by mutation of ribosomal proteins, assembly factors and failures in different factors during translation. It appears, therefore, that ROS is directly connected to the genetic instability of hematopoietic stem cells. In this form, the mutagenic pool of cell growth is increased [31]. Moreover, a higher level of ROS brings about broad metabolic reprogramming of the hallmark of cancer cells – cell transformation, protein synthesis and production of ATP (adenosine triphosphate) [32]. In this review, we will try to explain the connection of ROS and ribosomopathies.

Metabolic changes and Ribosomopathies

Metabolic changes are-associated with ribosome defects. These metabolic changes also contribute to the oncogenic potential of RPs. For example, the T-ALL that is associated with RPL10-R98S mutation has been linked to oxidative stress [24,33]. Not much is known currently about metabolic changes in ribosomopathies diseases, however, but recent data show that glycolytic change is connected with ribosome defects. In CHH patients, upregulation of glycolytic processes is shown, for example, in fructose-1, 6-bisphosphatase 1 (*FBP1*), glucokinase (*GK*), and hexokinase 2 (*HK2*). All these enzymes play a pivotal role during glycolysis [21]. In cancer cells, lactate blocks immune functions, and monitors cell activity [34].

Rare genetic diseases such as CHH and SDS are shown have connection with a higher level of glycolytic process; this is the opposite to DBA, when in a model organism, such as zebrafish, deficiency of ribosomal proteins RPL11/uL5 (Ribosomal protein from large subunits 11/uL5) is indicated; and in a mouse model when deficiency of ribosomal proteins RPS19/eS19 is found. RPS19/eS19 is responsible for enzyme regulation of glycolytic processes, and in the up-regulation of the gene expression that is involved in this process [23].

The most important glycolytic enzymes, such as pyruvate kinase isozyme 2 (PKM2), fructose-bisphosphate aldose A (ALDOA), lactate dehydrogenase A (LDHA), are shown to be connected with the ribosome, which demonstrates that ribosomal processes may directly impact glycolytic enzyme availability and activity [32].

Glycolytic pathways in ribosomal disorders have been described. In leukemia, a proteomic change is observed (ie. RPL10-R98S (uL16-R98S) mutation). This mainly affects several metabolic pathways. In mutant RPL10-R98S (uL16-R98S), combined analysis of transcriptome and translatome show that serine synthesis-phosphoserine phosphatase (PSPH) is transcribed and translated. Herein, serine is converted to glycine. During this reaction, one carbon is

released, which, in turn, sustains nucleotide synthesis, and these metabolic pathways contribute to cancer biology and display therapeutic potential [5]. Similar results are observed in the fibroblasts of DBA patients when the levels of serine/glycine synthesis enzyme phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and the mitochondrial serine hydroxymethyltransferase 2 (SHMT2) are elevated [35]. In this review, we discuss current knowledge on the effect of ROS in the ribosomal protein damage response, and its clinical relevance.

ROS and TCA cycle

Mitochondrial dysfunction appears to link with a higher level of oxidative stress, which in this form interferes in mitochondrial respiration and the tricarboxylic acid cycle (TCA) that results in the end product, ATP [5,15]. This can generate hypo-proliferation of the cells in the early stage of ribosomopathies [15,16,36]. It has been observed that restricting the TCA substrate can engender an increase in metabolic enzyme activity, and fulfill another role as an mRNA-protein binder [32].

rRNA has been shown to be the target of damage by oxidative nucleobases. In this form, the oxidative stress level is increased and interference can occur in ribosome assembly, in diverse sub-steps of the translation cycle, and in protein folding [27,28]. Enhancing the ROS product has been found to elevate stress in the endoplasmic reticulum and mitochondria, and induce higher peroxisome activity [5,15]. Oxidative stress can interfere with oxidative phosphorylation, and bring about dysfunction of the mitochondrial chain and ATP production [5,15]. This can cause hypo-proliferation of some ribosomal proteins and mutation of ribosomal proteins in cancer diseases and ribosomopathies [5,15,16]. In contrast, damage of DNA during oxidation can increase mutagenesis, empowering these cells to acquire rescuing mutations.

ROS and cancer diseases

It is noted that dysregulation of glucose metabolism plays a pivotal role during cancer development. Ribosomal protein mutant diseases suffer from a high level of oxidative stress in cells, hence ROS level increases (Table 1). This mechanism has not been completely understood to this day. In patients with leukemia associated with RPL10-R98S (*uL16-R98S*), the defect appears to enhance the level of ROS and this ROS can arise from the higher activity of the peroxisome. In peroxisomes, oxidation of fatty acids occurs, and the last product of this process is a large amount of hydrogen peroxide (H_2O_2). Several enzymes that act in the peroxisome, such as peroxisomal N (1)-acetyl-spermine/spermidine oxidase (*PAOX*), have been shown to upregulate transcriptionally in ribosomal proteins from large subunits of RPL10-R98S (uL16-R98S) [5].

Table 1. Cancer types and associated RP mutations or deletions

Cancer type	RP mutation/deletion	Reference
Diamond Blackphone Anemia (DBA)	RPL5/uL18; RPS19/eS19; RPL11/uL5; RPS19/eS19	[21,22]
T cell acute leukemia	RPL10-R98S (uL16-R98S)	[5,45,46,52]
Cartilage Hair Hypoplasia (CHH)	RPS19/eS19	[54]
Shwachman-Diamond Syndrome (SDS)	RPL11/uL5; RPS19/eS19	[14]

The wild type of ribosomal protein from large subunits of RPL10/uL16 participates in the regulation of protein expression, and controls mitochondrial ROS in pancreatic cancer cells [7]. It is not clear yet how this protein, RPL10-R98S, regulates ROS function, so it requires further research in this direction. Of note, other ribosomal proteins have been observed to participate in oxidative stress. ROS agents, for example, can cause RPS3/uS3 to translocate to mitochondria when cells are protected from ROS and the mitochondrial DNA is not damaged [8]. However, research indicates that a low level of ROS can cause cell proliferation (Figure 1). This can occur by stimulation of the signaling pathways *PI3K* and *MAPK* [9,11,12]. When the ROS level is higher, cell proliferation is inhibited because ROS in this case is toxic.

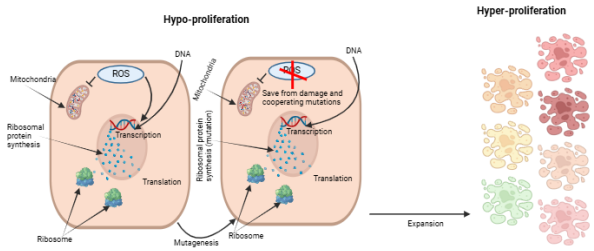

Figure 1. A model of the transition form from hypo-to hyperproliferation in mutated ribosome-cancer diseases. Defects in ribosome is shown to promote ribosomal protein expression profile. Defects in the assembly and function of ribosomal proteins also is shown to increase stress and production of ROS (reactive oxygen species) which inhibit cell proliferation and promote DNA damage

Researchers have demonstrated that ribosomal protein mutation can be a cause of reduction in ROS in the cell by an anti-oxidant, and in this form it can rescue the proliferation defects in RPL10-R98S [5]. Further study has revealed that RPL10-R98S is associated with ROS production, which is impaired with cell proliferation. A higher level of ROS in the cell is connected with DNA damage and genomic instability [5]. In rare genetic diseases such as DBA, the association has been shown between oxidative stress and damage of DNA. In ribosomal proteins, mutation or deficiency of ribosomal proteins RPL5/uL18 and RPS19/eS19, double break DNA and 8-oxoguanine oxidative DNA damage have been shown[14]. Another rare disease that is associated with a higher level of ROS is SDS. Patients with SDS and mouse models have shown elevated oxidative stress [15,18].

Cysteine (Cys) and methionine (Met) have the ability to oxidate and reduce in the protein chain; modulations in this form are very important in regulating the protein function. In the amino acid Cysteine, sulfur can reduce the thiol (-SH) side chain of Cys, and Cys can be oxidized to a disulfide bond (Cys-S-S-Cys), sulfenic (-SOH), sulfinic (SO2H), and sulfonic acids (-SO3H), showing that Cys is a good redox stress sensor [37].

Most ribosomal proteins are likely to oxidize during cell growth in yeast [38]. Also, the human cells line HT-29 (human colon cancer cell line) has shown the same results [39]. Ribosomal proteins are a prominent cluster in the redoxome analysis, using an oxidative isotope in different

model organisms such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, and *Drosophila melanogaster* [37,40-43]. Ribosomal proteins appear to mediate in protein synthesis in the response to oxidative stress, so ribosomal proteins also appear to act as a redox sensor [37]. However, it is not yet known which ribosomal proteins affect translation inhibition. ROS appears to mediate the modification of amino acid residues, such as cysteine, methionine, tyrosine, tryptophan and histidine, and in this form cause a complex set of secondary reactions that damage the proteins and biological molecules with which they interact [44-46].

Another important type of ribosomal protein modification is carbonylation. Carbonylation is mostly known to affect amino acid residues, such as arginine, lysine, proline, threonine and other amino acid side chains [47]. Carbonylation appears to be irreversible in some cases during DNA damage and in destabilized protein. This is observed during the repair of the oxidization of the Cys and Met residue [48]. During the oxidation of tryptophan residue, approximately seven potential carbonylated products seem to form [49-51].

A recent study examining the carbonyl-modification of ribosomal proteins has detected different components of the translation machinery such as aminoacyl tRNA (transfer RNA) synthetases, and ribosomal protein from large subunit 32/eL32 (RPL32/eL32), and ribosomal protein from large subunit 35/uL29 (RPL35/uL29) in HeLa cells [52]. Another derivate which is produced by oxidation of different cellular components, such as aldehydes (malondialdehyde – *MDA*), and 4 hydroxy-2-nonenal (*HNE*) has been observed to operate in the carbonylation of proteins. The aldehydes originating from ROS have been noted to induce peroxidation of fatty acids. In this way, fatty acids are used as oxidative stress markers [53].

CONCLUSION

Several studies support the idea that ribosome-defective cells undergo metabolic reprogramming to benefit from glycolysis and one-carbon metabolism. Further investigation is required into this. It is very important to remember that oxidative stress comes in "shades of grey", with different intensities, types, locations and durations of ROS in cells. It is important to know the spectrum of oxidation which occurs in cells, and the modification of r-RNA and ribosomal proteins when the amount of ROS starts to increase or is much higher.

The production of ROS, or deactivation of cellular antioxidants or a specific inducer to cause cell death, could be an approach for cancer therapeutics in the future. However, it is very important to implement ROS therapeutic strategies carefully, because the level of ROS differs from cell to cell, and ROS is known to mediate carcinogenesis through the modulation of several cell signaling pathways. Therefore, targeting of ROS is another promising approach to preventing cancer.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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