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Review Article

When Ribosomal Protein Go Bad-Mutation of Ribosomal Protein RPS23 in Different Diseases

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Abstract

Ribosomal protein (RP) gene mutations, mostly are associated with inherited or acquired bone marrow failure; it is believed that RP to drive disease by slowing the rate of protein synthesis. Ribosomes, are responsible for protein synthesis; ribosome, consist of a small 40S subunit and a large 60S subunit. These subunits are composed of 4 RNA species and approximately 80 structurally distinct proteins. Size of RPL23 is 143 amino acids, and molecular mass of this protein is 1508 Da. The gene for encoding this protein is placed in chromosome 5q14.2 by HGNC, Entrez Gene and Ensemble. It is shown that PRS23 is responsible for development and many cancer diseases.

Introduction

Ribosomal protein RPS23 is part of small ribosomal subunit 40S. It is shown that RPS23 is responsible for many human disorders which cause different disease. This disorders are caused by participation of RPS23 in many biochemical reaction.

2-oxoglutarate (2OG)-dependent oxygenase catalyze a range of important biological oxidations. Singleton *et al* 2014 [1] describe that 2OG and Fe (II)-dependent oxygenase domain-containing protein 1 (OGFOD1) is a protein hydroxylase that participate in modification of the small ribosomal subunit protein RPS23 at a conserved prolyl residue in the ribosome-decoding center; suppression or deletion of OGFOD1 also is shown to associate with the activation of translational stress pathways.

The enzyme oxygenase it is shown to catalyze hydroxylation of small ribosomal protein RPS23, although this is much conserved in eukaryotes such as yeast, flies and human. This is demonstrated by Loenarz *et al.*, 2013 [2]. In basal eukaryotes it is shown, that RPS23 undergoes two hydroxylations; whereas in animals Loenarz *et al.*, 2013 [2] observe only one hydroxylation. Hydroxylation lacking in ribosome of yeast cell, and stop codon readthrough is manifest up to ~10-fold. Thus results from study by Loenarz *et al* 2013 [2] explain how oxygen-dependent modifications regulate translational accuracy, and suggest to modulating ribosomal accuracy for medical application.

Two important factors such as prolyl-3, 4-dihydroxylase (Ofd1) and nuclear import adaptor (Nro1) it is shown to regulate the hypoxic response in fission yeast, this is shown by Clasen *et al.* 2017 [3] when is identify an extra-ribosomal function for uS12/Rps23 to regulate this system.

Nro1 binds Rps23, and in this form Nro1 import Rps23 into the nucleus for assembly into small ribosomal subunit 40S. But low oxygen have affinity to inhibit Ofd1 hydroxylase activity, and in this form participate in stabilization complex, which is building by Ofd1-Rps23-Nro1. Ofd *in vitro* bind directly three other factors: Rps23, Nro1, and Sre1. Interestingly, the Rps23 expression it is shown to modulate Sre1 activity by changing the Rps23 substrate pool available to Ofd1.

In study by Paolini *et al.*, 2017 [4] *de novo* missense mutations in the RPS23 gene, are reported in two patients with microcephaly, hearing loss, and overlapping dysmorphic features. Experiments with primary cells show that hydroxylation of OGFAD1 participate in proline residue, and in this form results in blocking on polysome formation. It is predicted that other disrupt of pi-pi stacking interaction among two phenylalanine residues destabilized uS12/RPS23 and that was not tolerated in 40S subunit biogenesis [4].

In drosophila melanogaster is identify the gene (sudestada1-sud1) which is responsible for normal growth [5]. The gene sud1 encodes a prolyl-hydroxylase and in this form participate in modification of small ribosomal protein 23 (RPS23). The gene Sud1 participate also not only in protein modification but induce apoptosis and increase autophagy also.

RPS23 and Cancer

It shown by Wang *et al.*, 2014 [6] that miR-542-3p suppressed ribosome biogenesis by downregulating a subset of small ribosomal protein 23 (RPS23), and with upregulation of large ribosomal protein 11 (RPL11) they influence in stabilization of p53. The 3'UTR in the RPS23 transcript contained a miR-542-3p binding site; this suggest that RPS23 is a direct target of miR-542-3p.

In HCC (hepatocellular carcinoma) miR-490-5p is down-regulated and moreover, miR-490-5p might directly target small ribosomal protein (RPS23) together with SRC, SRP9, PDGFRB, and RPL28; and in this form play an important role in HCC [7].

Changing in gene expression occurred by different genes; among them is gene doxorubicin (DOX). In two cancer cell line such as HeLa and DOX-resistant KB-V1 is evaluated gene expression. This is shown by Drozd *et al.*, 2016 [8]. It is shown that DOX treatment changed gene expression in both cell line and in this form induce sufficient of RPS23.

In cancer cells such as colorectal adenocarcinomas it is found that small ribosomal protein (RPS23) and large ribosomal protein (RPL35) are overexpressed in both stages: early and advanced stage [9].

The results from the study by Zhang *et al* 2017 demonstrate that RPS23 together with TPT1 and small ribosomal protein (RPS13) was the most stably expressed reference gene [10].

Mutation of RPS23 is report to associate with hair pathology of a patient, including hypotonia, autism, extra teeth, elastic skin, and thin/brittle hair; when Alsop *et al* 2016 analyzed hair structure of a patient with a de novo disrupted ribosome [11].

Small ribosomal protein (RPS23) increase the weight of immune organs. This is result from study by Wang *et al.*, 2013 [12]. Small ribosomal protein (RPS23) has antitumor activity in host cells.

Various small ribosomal proteins such as, RPS3, RPS5, RPS6, RPS16 and RPS23, were shown to downregulate abnormal sperm, in the study by Zhang *et al.*, 2018 [13].

The effect of bowel inflammation on housekeeping gene (HKG) remains unknown. Expression stability of 15 (housekeeping gene) HKG such as gene ACTB, B2M, GAPDH, GUSB, HPRT1, IPO8, MRPL19, PGK1, PPIA, RPLP0, RPS23, SDHA, TBP, UBC, and YWHAZ in 166 bowel specimens (91 normal, 35 cancerous, and 40 inflamed) was analyzed by Krzystek-Korpacka *et al.* 2014 [14] when they present the top-ranked housekeeping gene and it is shown, that RPS23, PPIA, and RPLP0 were top-ranked; other housekeeping gene which are analyzed by Krzystek-Korpacka *et al.*, 2014 [14] such as IPO8, UBC and TBP were lowest-ranked across inflamed/cancerous/normal colonic tissues.

Maltseva *et al.*, 2013 [15] showed that that different genes, such as gene ACTB, RPS23, HUWE1, EEF1A1 and SF3A1 proved to be least variable and in this form they are more efficient for research and clinical analysis of breast cancer.

Studies in yeast and bacteria revealed that mutations in RPS28 or RPS12 (RPS23 homologs in S. cerevisiae and E. coli respectively) provoke to increase stop codon read-through, while other mutations in the same proteins provoke reduced stop codon read-through [16-18].

Stability of Gene RPS23

Jiang *et al.*, 2016 [19] shown that RPS23 play pivotal role in normalization of RT-qPCR data yak mammary tissue during the lactation cycle. During the normalization it is shown collaboration of RPS23 with MRPS15 and UXT.

In three programs such as BestKeeper, geNorm and NormFinder also are analyzed expression of this gene, RPS23 together with other genes, such as β-ACT, ArgK, EF1-α, GAPDH, RPL12, α-TUB, 18S and 28S in A. eugenii but under different conditions [20]. The results revealed that the stably of gene expression in A. eugenii varied depend of experimental condition during experiment: developmental stages of gene such as EF1-α, 18S and RPL12, small ribosomal protein 23 and large ribosomal protein in sex (RPS23 and RPL12), low and higher temperature in different genes (GAPDH and α-TUB, α-TUB and RPS23), starvation (RPL12 and α-TUB), and dsRNA exposure (α-TUB and RPL12).

The importance of study by Kaur *et al* 2018 [21] stems from the fact that riverine buffaloes are major dairy species of Indian sub-continent and the information generated here will be of great interest to the investigators engaged in functional genomic studies of this important livestock species.

geNorm, NormFinder and BestKeeper softwares, are three different algorithms which are used to evaluate the stability of 10 potential reference genes from different functional classes. The M-value given by geNorm it is shown to range from 0.9797 (RPS9 and UXT) to 1.7362 (RPS15). Ranke of gene from most stable to least stable are: UXT/RPS9> RPL4> RPS23> EEF1A1> ACTB> HMBS> GAPDH> B2M> RPS15. The analysis of software NormFinder ranked genes as below: UXT> RPS23> RPL4> RPS9> EEF1A1> HMBS> ACTB> β2M> GAPDH> RPS15. Based on standard deviation (SD) value and range of fold change expression, the software analysis of BestKeeper is: RPS9> RPS23/UXT> RPL4> GAPDH> EEF1A1> ACTB> HMBS> β2M> RPS15. In this study it is shown that RPS23, RPS9, RPL4 and UXT genes to be the most stable [21].

Cardiac allograft rejection (AR) can cause graft dysfunction and even mortality, ribosomal proteins show that are good indicator for diagnosis of this diseases. Ribosomal protein from large subunits such as RPL7, RPL11, and ribosomal protein from small subunits such as RPS23, RPS25, were good biomarkers in peripheral blood for monitoring cardiac AR. The up-regulation of ribosomal protein from large subunit RPL7 and RPL11, and from small subunits RPS25, RPS23 might promote the translation of AR-related cytokines. This is shown Shen and Gong 2015 [22].

The study from Kapila *et al.*, 2013 [23] is done to determine the panel genes in heat-stressed buffalo mammary epithelial cells (MECs), small ribosomal protein 23 (RPS23) together with EEF1A1 and RPL4 are shown to be more stable genes for normalization of gene expression in heat -stressed buffalo MEC.

In the study by Kapila *et al.*, 2013 [23], is used reverse transcription-polymerase chain reaction (RT-PCR) to amplify the cDNA of RPS23 gene from skeleton muscle of giant panda, based on relative information regarding the RPS23 gene of the designed primers of some mammals, such as Homo sapiens, Bos Taurus, Felis catus, Mus musculus and Rattus norvegicus. The protein sequence also is analyzed, and compared with those of human and other animals reported.

It is shown the gene down-regulation in translation including ribosomal proteins from large and small subunits such as our candidate small ribosomal protein (RPL13A, RPL22, RPS23, RPL13 and RPL10A), that could be used like a good biomarkers for future experiments [24].

Conclusion

The so-called Ribosomal Oxygenases (ROXs) (a subfamily of 2OG dependent dioxygenases), has been found to modulate protein synthesis through the hydroxylation of ribosomal proteins and tRNAs [25-27]. Feng *et al.* 2014 [28] recently report that only optimal translation termination depends on the hydroxylation of the termination factor eRF1 by the 2OG-dependent dioxygenase Jmjd4. These works highlight the importance of 2OG dependent dioxygenases in protein synthesis regulation. RPS23 is a good immunological biomarker and that is shown in different diseases. In many cancer disease is shown that RPS23 is overexpressed, and we can concluded, RPS23 is good indicator for adenocarcinomas, hapotecellular cancers.

Conflict of Interest

No conflict of interest was declared by the authors.

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