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Ribosomal Protein RpL35/uL29 Function and Role in Different Diseases

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Abstract. RpL35/uL29 is member of large subunits. It is shown that RpL35/uL29 participate in different processes in diseases and development. It is shown that RpL35/uL29 is important for ribosome mature. Many authors show that RpL35/uL29 is good indicator for diagnosis. Here we will describe role and function of ribosomal protein RpL35/uL29 in different cancer diseases such as colorectal adenocarcinoma and atherosclerosis.

Keywords: RpL35/uL29, Cancer diseases, RpL35/uL29 Processing

Introduction

RpL35/uL29 play a pivotal role during the assembly of the ribosome. RpL35/uL29 is located close to RpL19/eL19 and RpL25/uL23 in the exit tunnel. Some authors suggest that RpL35/uL29 causes slow growth defects by generating low 60S subunit level. Arx1 participates in ribosome biogenesis. Arx1 binds to pre-60S subunits exactly in the vicinity of the RpL35/uL29 and RpL25/uL23 at the exit tunnel. For release of Arx1 in the cytoplasm from subunit 60S (RpL35/uL29) the protein Rei1 must interact with Arx1 (Greber, B.J. et al., 2016) (Figure 1).
L35/uL29 assembles onto the ribosome in the nucle(ol)us and stably interact with 27S pre-rRNAs, therefore suggesting that it is added early in the assembly pathway. It has been suggested that zebrafish RPL35/uL29, as many other r-protein genes, acts as a haploinsufficient tumor suppressor by an as yet unknown mechanism (Babiano R., and de la Cruz J., 2010).
Yeast L35 is an essential small r-protein of 120 amino acids with a predict mass of 13.9 kDa and a predicts basic pI of 11.36 (Saccharomyces Genome Database, www.yeastgenome.org). As two thirds of the eighty years r-proteins, RpL35/uL29 is encoded by two paralogous genes, RPL35A (SOS1, YDL191W) and RPL35B (SOS2, YDL136W), which both localize to the left arm of chromosome IV.
The coding regions of these two genes are nearly identical, differing in only 3nt out of 362, but resulting in no change in the amino acid sequences of the predicted L35A and L35B proteins (Babiano R., and de la Cruz J., 2010). Human RpL35/uL29 is small protein of 123 amino acids and is encoded by gene which is placed at chromosome 9 q arm (Uechi T., et al., 2001) (Figure 2)
R-protein L35/uL29 together with RpL20/eL20 is expressed from a dicistronic operon in archaea and eukaryotes which follows the general regulatory scheme of r-protein synthesis: when in

excess, RpL20/eL20 binds to its own mRNA and directly inhibits the translation of the first cistron of the operon, rpmI, encoding L35/uL29. This inhibition is then transmitted by translational coupling to the second cistron, rpIT, encoding L20/eL20 itself. Haentjens-Sitri J., et al., (2008) show that this is not the case for rpmI-rpITmRNA, the regulation of the synthesis of L35/uL29 and L20/eL20 obeys a competition mechanism between the repressor and the ribosome for binding that mRNA (Haentjens-Sitri et al., 2008).
The expression profile of RpL35/uL29 together with three other ribosomal protein genes (RPL18/eL18, RPL31/eL31, and RPS3/uS3) were validated by RNA blots using additional, independent crosses from the same families. Expression of RPL35/uL29 was monitored throughout early larval development, revealing that these expression patterns were established early in the development (in 2-day-old larvae) (Meyer E., and Manahan D.T., 2010).

Role and function of RpL35/uL29 in Ribosomal Processing

RpL35/uL29 assembles in the nucle(ol)us and stably interacts with 27S pre-rRNAs, therefore suggesting that it is added early in the assembly pathway. RpL35/uL29 participates in processing of 27SA rRNAs. Based on the crystal structure of the yeast 60S ribosomal subunit (Ben-Shem A., et al., 2010), rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpL34/eL37, lie close to each other, adjacent to 5.8S rRNA, whose 5'-end is generated by 27SA3 pre-rRNA processing. Four ribosomal proteins- rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpL37/eL37 specifically cannot assocaye with pre ribosomes when A3 factors are depleted. These four r-proteins bind adjacent to each other on 5.8S rRNA in mature 60S ribosomes in S. cerevisiae (Ben-Shem A., et al., 2010) this results indicates that the presence of A3 factors, which are required for proper formation of the 5-end of 5.8S rRNA, stabilizes this neighborhood of r-proteins within assembling ribosomes. We also show here that in the absence of A3 factors and rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpL37/eL37, Rat1 cannot stop at the B1S site and proceeds beyond this site to turn over 27S pre-rRNA.
A third important function of A3 factors is to ensure stable association of r-proteins rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpL37/eL37 with pre ribosomes. Interestingly, the binding sites in mature ribosomes of rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpl37/eL37 are near each other in domains I and III of 5.8S/25S rRNAs (Ben-Shem A., et al., 2010). Three of the four r-proteins most affected in the A3 mutants are not required for 27SA3 pre-rRNA processing, but are required for 27SB pre-rRNA processing. In the absence of rpL17/uL22, rpL35/uL29 or rpL37/eL37, 27SB pre-rRNA, but not 27SA3 pre-rRNA.
Once A3 factors dissociate from pre ribosomes, it is imperative that this base pairing between 5.8S and 25S rRNAs be maintained. Stable association of rpL17/uL22, rpL26/uL24, rpL35/uL29, and rpL37/eL37 may play a role in maintaining base pairing between these two rRNAs after release of A3 factors, and in mature functioning ribosomes (Sahasranaman A., et al., 2011). In the hypothalamus, numerous ribosomal genes changed their expression under CSDS (14 Rps and 22 Rpl genes). Rps14/uS11, Rps8/eS8, Rps6/eS6, Rps9/uS4, Rps5/uS7, Rps19/eS19, Rps16/uS19, Rps/uS3, Rpsa/uS2, Rps26/eS26, Rps10/eS10, Rpl37a/eL43, Rpl41/eL41, Rpl19/eL19, Rpl23a/uL23, Rpl37/eL37, Rpl8/uL2, Rpl10a/uL1, Rpl36/eL36, Rpl7a/eL8, Rpl2/uL11. Rpl35/uL29, Rpl34/eL34, Rpl0/uL10, Rpl6/eL6, Rpl28/eL28, Rpl18/eL18, Rplp2/P2, Rpl13/eL13, Rpl18a/eL20, Rpl29/eL29 and Rplp1/P1 were upregulated, and Rpl22/uL22, Rps6/eS6, were downregulated. Smagin D.A., et al., suggest that enhanced expression of the Rpl18/eL18 and Rpl35/uL29 genes was overlapped in the hippocampus and hypothalamus (Smagin D.. eta., 2016).

Role and function of RpL35/uL29 in Cancer Diseases

Many RP genes might also be cancer genes in human, where their role in tumorigenesis could easily have escaped detection up to now.

In humans, several ribosomal proteins regulate p53 activity by abrogating Mdm2-induced p53 degradation or by increasing translation of p53 mRNAs. RpL35/uL29 also is associated with the highest tumor incidence. The finding that mutations in so many different RP genes, including S7/eS7, S8/eS8, S15a/uS8, S18/uS13, S29/uS14, L7a/eL8, L13/eL13, L23a/uL23, L35/uL29, L36/eL36, and L36a/eL42, predispose to cancer suggests that a function shared by RPs underlines their role in this phenotype. However, not all RP genes were cancer genes: S12/eS12, S15/uS19, L3/uL3, L24/eL24 and LP1/P1 heterozygotes appeared normal (Amsterdam A., et al., 204b).
A study from Huang L., et al., reports a 11-gene signature for predicting PLNM (predicting lymph node metastasis) in cervical carcinoma which are identified 7 genes (RPL35/uL29, TMSB10, YWHAZ, BTD, LDHA, GUSB and SOD2) were up-regulated in patients without PLNM and down-regulated in patient with PLNM (Huang L., et al., 2011).
Luzp4 is an RNA binding protein that associates with TREX subunits. With mass spectrometry following IP is identified an interaction of Luzp4 with RpL35/uL29 I test cancer (Viphakone N., et al., 2015). The RPL35/uL29, RPS23 and TIMP1 genes were found to be overexpressed in both early and advanced stage colorectal adenocarcinomas ($p<0.05$) (Lau T.P., et al 2014).
RpL35/uL29 is a good indicator and for other diseases such as development of atherosclerosis (Wang H.X., and Zhao Y.X., 2016). Signal recognition particle (SRP), together with its receptor (SR), mediates the targeting of ribosome-nascent chain complexes to the endoplasmic reticulum. Using protein crosslinking, it was detected that there are distinct modes of binding of SRP to the ribosome. During signal peptide recognition, SRP54 is positioned at the exit site close to ribosomal proteins L23a/uL23 and RpL35/uL29. When SRP54 contacts SR, SRP54 is rearranged such that it is no longer close to L23a/uL23. This repositioning may allow the translocation channel (Pool M.R., et al., 2002).
F-box proteins are best known for their role as substrate receptors of SCF ubiquitin ligases. FbxL16 is member of F-box protein which bind and regulate the function of protein phosphatase 2A (PP2A), a heterotrimeric serine phosphatase that has diverse functions including modulation of TGF beta signaling and cell cycle control. With mass spectrometry is observed that RpL35/uL29 co-immunoprecipitates have low affinity to bind FBXL16 (Honarpour et al., 2014). RpL35/uL29 is regulatory factor involving in the Met-mediated regulation of CSN2 (casein) translation elongation and secretion also (Jiang N., et al., 2015).

Discussion

Here in this manuscript we show that ribosomal protein RpL35/uL29 interact with different ribosomal protein such as Rps14/uS11, Rps8/eS8, Rps6/eS6, Rps9/uS4, Rps5/uS7, Rps19/eS19, Rps16/uS9, Rps/uS3, Rpsa/uS2, Rps2/uS5, Rps26/eS26,Rps10/eS10, Rpl37a/eL43, Rpl41/eL41, Rpl19/eL19, Rpl23a/uL23, Rpl37/eL37, Rpl8/uL2, Rpl10a/uL1, Rpl36/eL36, Rpl7a/eL8, Rpl12/uL11, Rpl35/uL29, Rpl34/eL34, Rplp0/uL10, Rpi6/eL6, Rpl28/eL28, Rpl18/eL18, Rplp2/P2, Rpl13/eL13, Rpl18a/eL20, Rpl29/eL29 and Rplp1/P1 were is upregulated, but in interaction with ribosomal proteins such as Rpl22/uL22, Rps6/eS6, is downregulated, but in interaction with ribosomal proteins such as S7/eS7, S8/eS8, S15a/uS8, S18/uS13, S29/uS14, L7a/eL8, L13/eL13, L23a/uL23, L35/uL29, L36/eL36, and L36a/eL42 shown higher cancer incidence. We can conclude that RpL35/uL29 is good indicator for diagnosis.

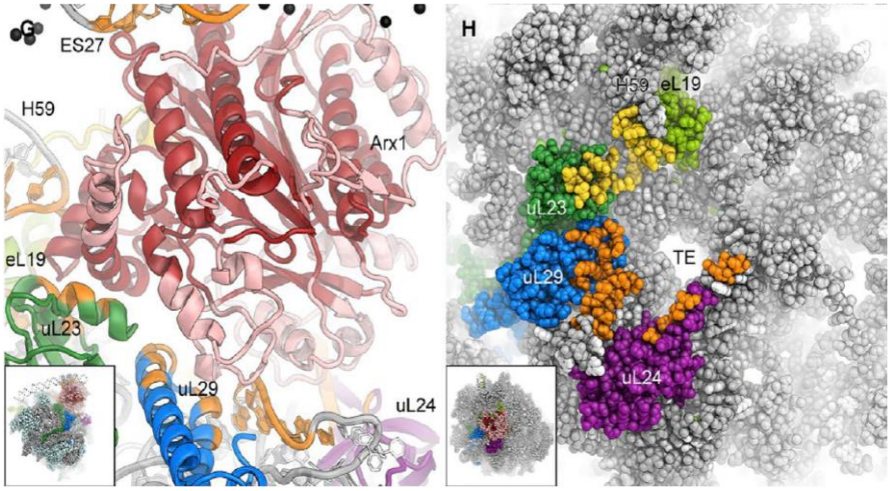

Fig. 1. (G) Arx1 interacts with RpL23a/uL23, RpL26/uL24, RpL35/uL29, and RpL19/eL19 as well as the rRNA in vicinity of the tunnel exit. 60S residues involved in contacts are shown in orange. (H) Contact sites of Arx1 on the 60S subunit with ribosomal proteins. Greber, B.J. et al., Insertion of the Biogenesis Factor Rei1 probes the Ribosomal Tunnel during 60S Maturation. Cell 2016; 164, 1-12

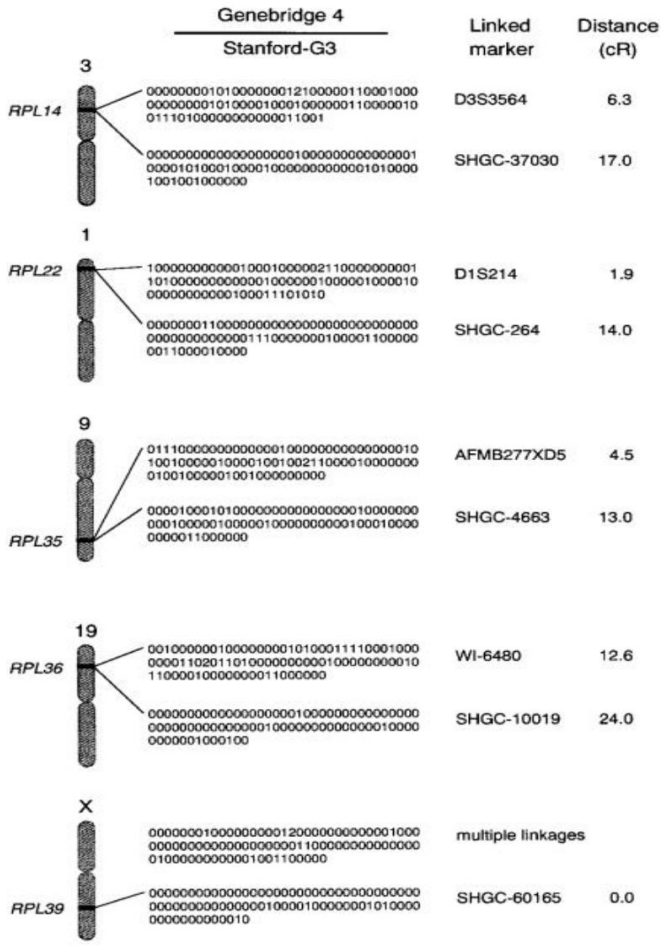

Fig. 2. Localization of the human RPL14/eL14, RPL22/eL22, RPL35/uL29, RPL36/eL36, and RPL39/eL39 genes by radiation hybrid mapping. Uechi, T. et al., A Complete Map of the Human Ribosomal Protein Genes: Assignment of 80 Genes to the Cytogenetic Mapand Implications for Human Disorders. Genomics72, 223–230 (2001).

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