1998 - 2002	Ph.D. - European Molecular Biology Laboratory (EMBL) Heidelberg, Germany and Charles University in Prague, Czech Republic
2002 - 2008	PostDoc - Wellcome Trust Centre for Cell Biology, University of Edinburgh, Great Britain
2008 - 2015	Junior Group Leader - Excellence Cluster “CellNetworks”, BZH
since 2016	Junior Group Leader - BZH

Martin Koš

Ribosomal RNA processing and modification

Goal

Our aim is to extend our understanding of molecular mechanisms underlying ribosome biogenesis and its regulation in response to environmental stresses and during senescence. We focus on the roles of RNA modifications and functions of specialized ribosomes.

Background

Ribosome biogenesis is a major energy consuming process in all organisms that is tightly regulated with cell growth. This highly conserved process begins with transcription of a large ribosomal RNA (rRNA) precursor that is subsequently covalently modified and processed into mature 18S, 5.8S and 25S rRNAs. The process of ribosome maturation is very complex and highly dynamic. At least 180 non-ribosomal proteins and 70 small nucleolar RNAs (snoRNAs) have been implicated in ribosome biogenesis in yeast. A dysregulation of ribosome biogenesis is observed in cancer and multiple human diseases. Recently, existence of differently modified so called specialized ribosomes within cells was revealed, however, their function remains unknown.

Research Highlights

Role of rRNA modifications

In addition to the complex structure, rRNAs are also extensively modified by methylation and pseudouridylation at approximately 100 sites. The role of these modifications in either biogenesis or function of mature ribosomes remains largely unclear. We analyzed the role of a cluster of rRNA methylations located near the inter-subunit bridge B3 in 25S rRNA. We identified Rcm1 as an enzyme required for highly conserved cytosine-5 methylation of C2278 in the 25S rRNA (Gigova *et al.* 2014). We showed that methylation at two sites, C2278 and G2288 is required for stability of the mature 60S ribosomal subunit. Ribosomes lacking these two methylations exhibited changes in the structure of 25S rRNA and the loss of several ribosomal proteins (Figure 1.)

Oligomerization of TGS1 is required for an efficient trimethylation of snRNAs and snoRNAs

Trimethylguanosine Synthase catalyses the transfer of two methyl groups to the m7G cap of snRNAs, snoRNAs and telomerase RNA TLC1 to form a 2,2,7-trimethylguanosine cap. While *in vitro* studies indicate that Tgs1 functions as a monomer and the dimethylation of m7G caps is

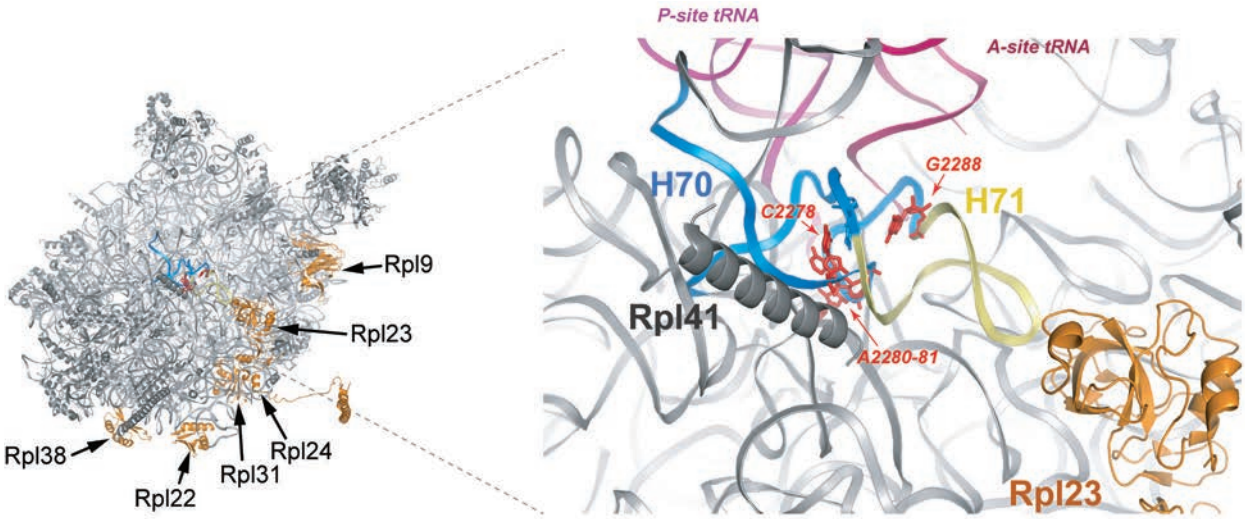

Fig. 1.Figure 1. Proteins affected in ribosomes lacking methylations of nucleotides C2278 and G2288.
Left: *crystal structure of the 60S ribosomal subunit. Proteins that are lost from ribosomes lacking rRNA methylation are highlighted in orange.* ***Right:*** *Detailed view of the domain IV of 25S rRNA. The methylated nucleotides are in red, the helix H71, which participates in the intersubunit bridge B3, is highlighted in yellow. From Gigova et al. 2014.*

not a processive reaction, partially methylated sn(o)RNAs are typically not detected in living cells. We found that both yeast and human Tgs1p possess a conserved self-association domain located at the **N-terminus. A disruption of Tgs1 self-association led to a strong reduction of sn(o)RNA trimethylation (Boon *et al*., 2015). We speculate, that TGS1 forms dimers *in vivo* that are capable to efficiently dimethylate the caps of the targeted RNAs without the need to dissociate from the substrate.

Regulation of alternative rRNA processing pathways by TORC1 in stress response

We observed that the processing of pre-rRNA abruptly changes when yeast cells are exposed to an environmental stress or upon depletion of nutrients (Kos I *et al*., submitted). We found that this switch in pre-rRNA processing is regulated by the Tor complex 1 (TORC1) and the casein kinase 2 (CK2). Importantly, Sch9 (the yeast homologue of S6 kinase), considered to be the major downstream effector of TORC1 regulating ribosome biogenesis, is dispensable indicating that an unidentified branch of TORC1 signalling controls ribosome biogenesis at the post-transcriptional level.

Selected Publications

Koš-Braun, I.C., Jung, I. and Koš,M. (2017). TORC1 and CK2 kinase control a switch between alternative ribosome biogenesis pathways in a growth dependent manner. PLOS Biology (in press).

Kornprobst,M., Turk,M., Kellner,N., Cheng,J., Flemming,D., Koš-Braun,I.C., Koš,M., Thoms,M., Berninghausen,O., Beckmann,R., Hurt,E. (2016). Architecture of the 90S Pre-ribosome: A Structural View on the Birth of the Eukaryotic Ribosome. Cell 166, 380–393.

Theile,D. and Koš,M. (2016). Structural and functional evaluation of interaction between mammalian ribosomal RNA with platinum-containing antineoplastic drugs. Toxicology Letters 242, 47-52.

Boon,K.-L., Pearson,M.D. and Koš,M. (2015). Self-association of Trimethylguanosine Synthase Tgs1 is required for efficient snRNA/snoRNA trimethylation and pre-rRNA processing. Sci Rep 5, 11282.

Gnanasundram,S.V. and Koš,M. (2015). Fast protein depletion system utilizing tetracycline repressible promoter and N-end rule in yeast. Mol Biol Cell 26, 762-8.

Schosserer,M., Minois,N., Angerer,T.B., Amring,M., Dellago,H, Harreither,E., Calle-Perez,A., Pircher,A., Gerstl,M.P., Pfeifenberger,S., Brandl,C., Sonntagbauer,M., Kriegner,A., Linder,A., Weinhäusel,A., Mohr,T., Steiger,M., Mattanovich,D., Rinnerthaler,M., Karl,T., Sharma,S., Entian,K.-D., Koš,M., Breitenbach,M., Wilson,I.B.H., Polacek,N., Grillari-Voglauer,R., Breitenbach-Koller,L. and Grillari,J. (2015). Methylation of ribosomal RNA by Nsun5 is a conserved mechanism modulating organismal life span. Nat Commun 6, 6158.

Bock,T., Chen,W.-H., Ori,A., Malik,N., Silva-Martin,N., Huerta-Cepas,J., Powell,S., Kastritis,P., Smyshlyaev,G., Vonkova,I., Kirkpatrick,J., Doerks,T., Nesme,L., Bassler,J., Koš,M., Hurt,E., Carlomagno,T., Gavin,A.-C., Barabás,O., Mueller,C., van Noort,V., Beck,M. and Bork,P. (2014). An integrated approach for genome annotation of the eukaryotic thermophile Chaetomium thermophilum. Nucl Acids Res 42, 13525-33.

Gigova A, Duggimpudi S, Pollex T, Schaefer M, Koš M. (2014). A cluster of methylations in the domain IV of 25S rRNA is required for ribosome stability. RNA 20, 1632-44.

Martin Koš
Phone: +49 (0)6221-54 4151
E-mail: martin.kos@bzh.uni-heidelberg.de