SUMO pathway is required for ribosome biogenesis

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Ribosomes, acting as the cellular factories for protein production, are essential for all living organisms. Ribosomes are composed of both proteins and RNAs and are established through the coordination of several steps, including transcription, maturation of ribosomal RNA (rRNA), and assembly of ribosomal proteins. In particular, diverse factors required for ribosome biogenesis, such as transcription factors, small nucleolar RNA (snoRNA)-associated proteins, and assembly factors, are tightly regulated by various post-translational modifications. Among these modifications, small ubiquitin-related modifier (SUMO) targets lots of proteins required for gene expression of ribosomal proteins, rRNA, and snoRNAs, rRNA processing, and ribosome assembly. The tight control of SUMOylation affects functions and locations of substrates. This review summarizes current studies and recent progress of SUMOylation-mediated regulation of ribosome biogenesis. [BMB Reports 2022; 55(11): 535-540]
Ulp2 in *S. cerevisiae* have been studied for their functions and localizations in humans, but the recently discovered three SENPs have not been extensively investigated. SUMO conjugation can alter the interaction between its substrate and binding partner proteins, which possess one or more SUMO-interaction motifs (SIMs) for recognizing SUMO-conjugated proteins, maintaining protein stability, or bringing conformational changes in target proteins (21).

**SUMO regulates ribosome biogenesis**

Ribosomal proteins are general targets of SUMO. Recent advances in molecular techniques and quantitative proteomics have revealed several interesting SUMO target proteins. Pioneering studies have been conducted in *S. cerevisiae* (22-26). Although SUMO substrates have been found in all cellular compartments, amounts of SUMO-conjugated proteins are much higher in the nucleus than in other regions. This finding is consistent with the extremely concentrated SUMO and SUMO pathway enzymes in the nucleus. Interestingly, all yeast studies have revealed proportionally high numbers of ribosomal proteins and assembly factors as SUMO targets, suggesting that SUMO is closely linked to ribosome biogenesis and remodeling. Furthermore, the SUMOylated ribosome itself and its regulators are also observed in proteomic analyses for the detection of targets of all three active SUMO isoforms (SUMO-1 to -3) in human cells or stem cells (27-34). Although factors involved in ribosome biogenesis are major targets of the SUMO pathway, how such SUMO modifications affect ribosome development and the mechanism underlyng the regulation of SUMO conjugation levels of ribosomes are yet unknown.

SUMO promotes expression of ribosomal genes and rRNA. Primary target proteins of SUMO are transcription factors and chromatin-associated proteins in eukaryotes (35, 36). It was initially thought that SUMO mainly would suppress gene transcription because it either blocked the function of transcription activators or facilitated the function of transcription repressors (37). However, recent investigations have uncovered its more diverse roles in co-transcriptional processes, including transcription activation and chromatin remodeling (33). In particular, SUMO is highly enriched in genes encoding ribosomal pro-
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Fig. 2. SUMOylation regulates ribosome biogenesis. SUMOylation and deSUMOylation are highly dynamic cellular processes, and their versatile control is essential for ribosome biogenesis. First, several transcription factors, including yeast Rap1, are major substrates of the SUMO pathway. Their SUMOylation regulates the expression of genes encoding ribosomal proteins (RPs) and rRNAs (components of ribosomes) and snoRNAs (required for rRNA maturation). While the association of Net1, Tof2, and Fob1, which are required for rDNA silencing (43). Histone SUMOylation has diverse roles in transcriptional regulation and is highly enriched at ribosomal protein and rDNA loci (44, 45). However, its function in ribosome biogenesis has not been reported yet.

SUMO affects rDNA processing
rRNA processing is essential for ribosome biogenesis. It is mediated by small nucleolar ribonucleoprotein complexes (snoRNPs) composed of snoRNAs and nucleolar proteins (46). snoRNAs are classified into two groups, box C/D snoRNAs responsible for 2'-O-ribose methylation and box H/ACA snoRNAs for mediating pseudouridylation. SUMOylation of the core box C/D snoRNP protein Nop58 is imperative for its association with snoRNAs, nucleolar positioning of snoRNAs, and proper snoRNP assembly, and blockade of SUMO conjugation to Nop58 facili-
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SUMO guides ribosome assembly
During ribosome biogenesis, 90S pre-ribosomal particles are established in the nucleolus and then split into 60S and 40S pre-ribosomes. These pre-ribosomal subunits are transported into the cytoplasm for final maturation (52). Human SENP3 is co-purified with PELP1, TEX10, WDR18, and LAS1L. SENP3-mediated control of SUMO conjugation level of PELP1 and LAS1L is essential for the maturation of rRNA and nuclear export of 60S pre-ribosomal particles (53-55). SUMO can negatively affect conjugation of NEDD8, another ubiquitin-like protein, to human Rpl25, and facilitate the translocation of Rpl11 from nucleoli (56). Rps3, a DNA repair endonuclease, is also a substrate of the SUMO pathway that increases the stability of Rps3 protein (57). SUMOylation of Rpl22e is important for nucleoplasmic distribution of Rpl22 in Drosophila meiotic spermatocytes (58). SUMO protease SMiT7-mediated control of SUMO levels on Rpl30 might affect various cellular processes, including cell division in Chlamydomonas reinhardtii (59). In S. cerevisiae, an additional copy of the UBAS gene complements abnormal nucleolar accumulation of the ribosomal 60S subunit Rpl25 in a rix16-1 mutant strain, in which the export of the pre-60S ribosomal subunit is impaired and mutations in ubc9, up1, and smt3 causes export defects of pre-60S particles (60). In particular, Up11 genetically interacts with nuclear export factor Mtr2 in the pre-60S export pathway. However, their exact correlation has not been reported yet. Taken together, these findings indicate that the SUMO pathway ensures the fidelity of pre-ribosomal import into the cytoplasm and routes ribosome maturation via successful assembly of ribosome subsets (Fig. 2).

CONCLUSION
SUMOylation is known to play critical roles in ribosome biogenesis, and regulation of this modification is associated with gene expression, nuclear import, and assembly of ribosomal subunits. However, the ultimate and detailed functions of the SUMO pathway in ribosome establishment have remained unclear until recently. Here, we briefly summarize recent observations of how the SUMO pathway is involved in ribosome biogenesis. Several ribosomal proteins themselves and various factors required for ribosome assembly are substrates of SUMOylation. These SUMO modifications are tightly regulated by SUMO-specific proteases, leading to regulation of gene expression, localization, and function as well as proteolytic control of target proteins during ribosome maturation. Functionally healthy ribosomes are vital for cell survival, and several mutations in ribosomes or ribosome assembly factors have been found to be lethal (61, 62). Especially, specific defects in ribosome biogenesis or function could cause various clinical abnormalities, including skin and bone marrow failure syndromes such as X-linked dyskeratosis congenita and Schwachman-Diamond syndrome (63, 64). Thus, studying SUMO functions in ribosome biogenesis and activities might provide clues to develop new therapies and drug targets for human disorders of ribosome dysfunction.

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CONFLICTS OF INTEREST
The authors have no conflicting interests.

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