セミナーのお知らせ

How to trigger the ribotoxic stress response: ZAK activation at the collided ribosome

Lecturer: Prof. Dr. Dr. h.c. Roland Beckmann

Gene Center and Department of Biochemistry,
University of Munich, LMU

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Abstract

Ribosome collisions are a central signal of translational stress and trigger a conserved ribotoxic stress response involving the MAP3K ZAK, which activates downstream MAPKs such as p38 and JNK to shape cellular outcomes. Although ZAK is recognized as a key sensor of perturbations in translation, the molecular basis of its recruitment to ribosomes and the mechanism by which collisions promote its activation have remained unclear. Biochemical assays and cryo-electron microscopy were combined to delineate distinct modes of ZAK–ribosome association, one enabling its constitutive binding to translating ribosomes, and another specifically triggered by collisions. The data show that ribosome collision interfaces promote dimerization of ZAK's SAM domains, facilitated by contacts with the ribosomal protein RACK1, thereby driving kinase activation. Further, the ribosome-associated factor SERBP1 was identified as a negative regulator that restricts inappropriate activation by competing with key ZAK–ribosome interactions. Analysis of engineered and pathogenic SAM-domain variants underscores the importance of this domain in controlling ZAK activity, with certain mutations capable of activating the kinase independently of ribosomes. Together, these findings provide a broader mechanistic framework for how ZAK senses and responds to translational stress signals at collided ribosomes.