Exploring the link between translation termination and nonsense-mediated mRNA decay

Nonsense-mediated mRNA decay (NMD) is best known for its role in cellular mRNA quality control by recognizing and degrading aberrant mRNAs with prematurely truncated reading frames. However, many physiological mRNAs have meanwhile been found to be targeted by NMD, strongly suggesting that NMD represents yet another mechanism contributing to post-transcriptional gene regulation. NMD is essential in vertebrates and appears to be mechanistically linked with translation termination. To gain more insight into the connection between NMD and translation termination, we conducted ribosome profiling in cells depleted of the core NMD factor UPF1 or the ribosome recycling factor ABCE1. While UPF1 knockdown did not cause any significant changes in the ribosome profiles neither on NMD sensitive nor on NMD insensitive transcripts, ABCE1 knockdown unexpectedly resulted in an upregulation of many but not all endogenous NMD-sensitive mRNAs. Notably, the suppression of NMD on these mRNAs occurs at a step prior to their SMG6-mediated endonucleolytic cleavage. Ribosome profiling revealed that ABCE1 depletion results in ribosome stalling at stop codons and increased ribosome occupancy in 3’ UTRs, indicative of enhanced stop codon readthrough or re-initiation. Using reporter genes, we further demonstrate that the absence of ABCE1 indeed increases the rate of readthrough, which would explain the observed NMD inhibition, since enhanced readthrough has been previously shown to render NMD-sensitive transcripts resistant to NMD by displacing NMD triggering factors like UPF1 and exon junction complexes (EJCs) from the 3’ UTR. Collectively, our data show that improper ribosome disassembly interferes with proper NMD activation.

Biography

Oliver Mühlemann is professor of biochemistry at the University of Bern and the director of the NCCR RNA & Disease. After studies in biology at the University of Bern, Mühlemann conducted his PhD research at the Karolinska Institute in Stockholm and at Uppsala University. Following postdoctoral work with Melissa Moore at Brandeis University in Boston, U.S.A., he returned to the University of Bern as a junior group leader in 2000. He was awarded an ERC starting grant in 2007 and appointed as full professor in 2010. Since 2018, he is also a member of the SNF research council.

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