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GENE EXPRESSION

Pioneering research

The pioneer round of protein translation represents the first passage of ribosomes on newly spliced mRNAs that are associated with the cap-binding protein (CBP) heterodimer CBP80/20. During this round, nonsense-mediated mRNA decay (NMD) occurs following nonsense codon recognition. This mRNA surveillance pathway requires the exon-junction complex (EJC), which also influences the translation efficiency of spliced mRNAs. Two studies now provide unexpected insights into how pre-mRNA splicing, mRNA surveillance and translation are connected.

By investigating a possible link between mammalian target of rapamycin (mTOR) signalling, which positively regulates protein synthesis, and splicing-modulated protein translation, Ma *et al.* found that rapamycin inhibits the increase in translation efficiency gained by splicing. They

also showed that rapamycin inhibits the phosphorylation of substrates in the CBP-bound mRNA–protein complexes (or mRNPs), suggesting a role for mTOR signalling in pioneer translation initiation. In addition, the activated form of the mTOR effector S6 protein kinase-1 (S6K1) was present in these complexes. The authors identified an S6K1-specific interactor named SKAR, which associates with CBP80-bound mRNPs in a splicing-dependent manner and binds to the EJC. So, mTOR and S6K1 contribute to the assembly of an efficient pioneer-round initiation complex.

Does SKAR recruit S6K1 to newly spliced mRNA? And does the recruitment of S6K1 affect the splicing-dependent translation efficiency? Knocking down the expression of SKAR or the EJC component eIF4AIII led to a decrease of S6K1 that is associated with CBP80-bound mRNP, and a reduction in the phosphorylation of mRNP-associated proteins. In addition, the knockdown of S6K1, SKAR and eIF4AIII led to a similar decrease in the translation efficiency of spliced mRNAs. So, an intact EJC and SKAR are essential for the recruitment of S6K1, which modulates the splicing-dependent increase in translational efficiency. How the EJC contributes to translation of newly synthesized mRNAs and how the pioneer round contributes to overall translational efficiency are issues that remain to be addressed.

The EJC also participates in NMD, which is triggered when translation terminates sufficiently upstream of an EJC, and the consequential binding of UPF1 to the EJC results in UPF1 phosphorylation. Isken *et al.* showed that phosphorylated UPF1

co-immunoprecipitates with decay factors, which suggests that these interactions occur after nonsense codon recognition. The authors demonstrated that phosphorylated UPF1 also interacts with eukaryotic initiation factor (eIF)3 and inhibits eIF3-dependent translation by preventing the eIF3-mediated conversion of 40S–Met–tRNA_i^{Met}–mRNA to translationally competent 80S–Met–tRNA_i^{Met}–mRNA initiation complexes. However, it is not clear how the binding of phosphorylated UPF1 to eIF3 inhibits its function.

Consistent with the notion that phosphorylated UPF1 mediates translational repression during NMD through eIF3, nonsense-containing mRNA that initiates translation using an eIF3-dependent mechanism was immune to NMD. On the basis of their observations, the authors suggest that “translational repression is a key transition that precedes mRNA delivery to the degradation machinery.”

So, the pioneer round of translation provides an intriguing example of how various gene-regulatory processes, such as pre-mRNA splicing, mRNA degradation and translational efficiency, are functionally linked through highly intricate regulatory complexes and events.

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FURTHER READING Amrani, N. *et al.* Early nonsense: mRNA decay solves a translational problem. *Nature Rev. Mol. Cell Biol.* **7**, 415–425 (2006)