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Conformational dynamics revealed by ensemble cryo-EM

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Virus propagation depends on efficient synthesis of viral proteins by the host translational machinery. Internal ribosome entry sites (IRESs) of viral mRNAs mediate cap-independent initiation. Intergenic-region (IGR) IRESs of *Dicistroviridae* family, which includes the Taura syndrome virus (TSV) and Cricket paralysis virus (CrPV), use the most streamlined mechanism of initiation, independent of initiation factors and initiator tRNA. A tRNA-mRNA like pseudoknot of IGR IRESs binds the ribosomal A (aminoacyl-tRNA) site of the 80S ribosome. The pseudoknot translocates to the P site to allow binding of the first tRNA and initiate translation. Using electron cryo-microscopy of a single specimen, we resolved five ribosome structures formed with the Taura syndrome virus IRES and translocase EEF2 GTP bound with sordarin. The structures suggest a trajectory of IRES translocation, required for translation initiation, and provide an unprecedented view of eEF2 dynamics. The IRES rearranges from extended to bent to extended conformations. This inchworm-like movement is coupled with ribosomal inter-subunit rotation and 40S head swivel. eEF2, attached to the 60S subunit, slides along the rotating 40S subunit to enter the A site. Its diphthamide-bearing tip at domain IV separates the tRNA-mRNA-like pseudoknot I (PKI) of the IRES from the decoding center. This unlocks 40S domains, facilitating head swivel and biasing IRES translocation *via* hitherto-elusive intermediates with PKI captured between the A and P sites.

Biography

Andrei Korostelev is passionate about mechanisms of translation regulation. He received PhD in Michael S Chapman laboratory at Florida State University in 2003 and performed Postdoctoral studies with Harry F Noller in 2004-2010. The Korostelev laboratory at the RNA Therapeutics Institute uses recent advances in biochemical and structural methods to elucidate detailed mechanisms that govern translation and regulation of translation under stress conditions or during disease. Recent work revealed high-resolution "frames" of the motions that the translational machinery undergoes during bacterial stress responses (including the stringent response) and viral infection, as summarized on the laboratory web site: http://labs.umassmed.edu/korostelevlab/research.htm

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