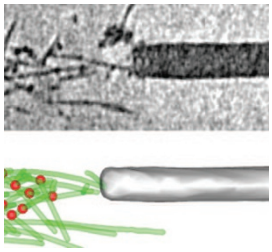
Pushing virus



A number of bacterial and viral pathogens are able to divert the actin-based motility machinery of infected cells to generate a propulsion system that facilitates microbial dissemination. In those instances, pathogen-induced nucleation of actin filaments gives rise to 'comet tails' that appear to trail the invader as it moves toward the cellular periphery. Although the cellular components involved in comet tail generation are known, exactly how actin filaments organize themselves to generate directional movement remains unclear. Small and colleagues now expose the mechanics of actin-based pathogen propulsion with a combination of cryo-electron tomography and mathematical modeling. Baculoviruses normally infect insect cells, but they can also generate actin comet tails in human cells, where the filaments can more easily be analyzed. Using this system, the authors were able to obtain detailed cryo-tomographic views of virus-induced comet tails. The structures revealed fishbone-like arrangements of short actin filaments generated by frequent branching, with the fast polymerizing plus end of the filaments directed forward. The authors also carried out simulations based on stochastic mathematical models. When certain assumptions were used, the simulations could reproduce both the experimentally observed actin comet structures and the typical path taken by the virus while being propelled through the cytoplasm. A model in which the actin filaments proximal to the virus were continuously attached to, and branching was biased toward, the viral surface best reproduced the experimental observations. This mechanism of propulsion, in which a few proximal filaments push the virus through their fast polymerizing ends, is likely to apply to other pathogens such as the bacterium *Listeria monocytogenes*. (*PLoS Biol.* doi:10.1371/journal.pbio.1001765, 14 January 2014) *SL*

Structure to a mystery

Flaviviruses, including dengue and West Nile viruses, have an RNA genome that encodes a single polyprotein that is processed into three structural and seven non-structural proteins inside the host cell. Six of the non-structural proteins form an ER membrane–associated replicative complex. The remaining non-structural protein, NS1, is highly conserved and essential for viral replication. NS1 is known to be lipid associated, localizing with the viral replicative complex as a dimer during early stages of infection and interacting with the host complement system when secreted in a hexameric form, but its exact function is unknown. To address this, Smith and colleagues have determined the crystal structures of glycosylated NS1 from West Nile virus and dengue virus type 2. The structures of the NS1 proteins are quite similar. NS1 forms a dimer centered around an extended β-sheet. Each monomer is composed of a β-roll domain involved in dimerization, a wing domain that can be divided into connector and α/β subdomains, and a core β-ladder domain that contributes nine rungs to the extended central β-sheet. The connector subdomain and β-roll form a hydrophobic surface that extends from the dimer and is a good candidate for membrane interactions. Mutations within the connector subdomain permitted liposome remodeling but affected viral replication, suggesting that interactions with the viral replicative complex were compromised. NS1 crystallized as trimer of dimers, and the resulting hexamer fits well with two-dimensional EM class averages of NS1. In the hexamer, the β-rolls line an interior central cavity, and antibody epitopes map to the exterior surface in the wing and β-ladder domains. Although the structures reveal distinct regions for membrane association and immune system interactions, insight into how these features contribute to pathogenicity await further study. (*Science* doi:10.1126/science.1247749, 6 February 2014) *MM*

Poly(A)-tail switch

Understanding the function of poly(A) tails has been challenging because of difficulties in measuring their lengths in a genome-wide manner. Bartel and colleagues now report a new high-throughput sequencing method, called PAL-seq ('poly(A)-tail profiling by sequencing'), that accurately measures individual poly(A) tails, irrespective of their length. By measuring the poly(A)-tail lengths of millions of individual RNAs isolated from vertebrate, fly, plant and yeast cells, the authors found that poly(A)-tail lengths were conserved among orthologous mRNAs, and that mRNA encoding ribosomal proteins and other 'housekeeping' proteins tended to have shorter tails. In early embryos of both zebrafish and *Xenopus laevis*, poly(A)-tail length was strongly correlated with translational efficiency, confirming and extending previous reports. However, this strong coupling largely disappeared during gastrulation, suggesting that translational control undergoes a mechanistic change that uncouples translational efficiency from poly(A)-tail length during development. The weak or negative correlation between tail length and translational efficiency in yeast and mammalian cells was confirmed by the observed lack of intragenic coupling between poly(A)-tail length and translational efficiency. The authors also analyzed miRNA-mediated poly(A)-tail shortening of target mRNAs during early zebrafish development. Interestingly, the developmental switch in translational control coincided with a switch in the predominant outcome of miRNA-mediated deadenylation, which changes from translational repression to mRNA destabilization during embryonic development. Overall, these findings reveal a transient relationship between poly(A)-tail length and translation in early embryos and provide a compelling explanation for why the ultimate effect of miRNAs on gene expression changes during development. (*Nature*, doi:10.1038/nature13007, published online 29 January 2014) *AH*

Written by Arianne Heinrichs, Stéphane Larochelle & Michelle Montoya

© 2014 Nature America, Inc. All rights reserved.