Cell biology at the host–microbe interface

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Talks at the “Cell Biology at the Host–Microbe Interface” Minisymposium highlighted mechanisms used by viral, bacterial, and eukaryotic pathogens to hijack host-cell functions and establish a replicative niche.

Manipulation of membrane dynamics

Nihal Altan-Bonnet (National Institutes of Health) described positive-sense RNA entoviruses that manipulate the host to generate phosphatidylinositol 4-phosphate (PI4P) and cholesterol-rich membrane platforms for efficient viral replication. The enzyme PI4KIIIβ is hijacked by the entoviral protein 3A to generate new pools of PI4P at these membrane platforms and to recruit RNA-dependent polymerases that are important for viral replication. Indeed, inhibition of PI4K activity led to decreased viral replication, which might provide an antiviral strategy for positive-strand RNA viruses.

Altan-Bonnet also described how entoviruses stimulate endocytic uptake of cholesterol, which is re-routed to Rab11-positive recycling endosomes that eventually fuse with viral replication organelles. Increased cholesterol levels may facilitate viral replication by decreasing the fluidity of replication organelle membranes.

This reprogramming of membrane trafficking is not unique to viruses. Charles Larson (Heinzen Laboratory, Rocky Mountain National Labs) described the manipulation of endocytosis by a secreted protein from the bacterial pathogen Coxiella burnetti, the causative agent of Q fever. In infected cells, Coxiella resides in a vacuole that shares many of the features of classical lysosomes. For the pathogen to survive in this organelle, it delivers specific “effector” proteins, including Coxiella vacuolar protein A (CvpA), which Larson described as being essential for bacterial replication in mammalian cells. CvpA localizes to the pathogenic vacuole and interacts with adaptor complex 2 (AP2). Depletion of cellular AP2 or clathrin with small interfering RNA impaired Coxiella replication, suggesting regulation of AP2–clathrin membrane transport events contributes to pathogen growth.

Xing Liu (Yao Laboratory, Morehouse) provided an example of a bacterial toxin that reprograms proton secretion in the stomach. Normally, gastric acid secretion involves translocation of proton pumps by ACAP4 and associated proteins to the apical membrane, so protons can be released into lumen of gastric glands. VacA from the bacterium Helicobacter pylori, a leading cause of gastric ulcers and cancers, inhibits the dephosphorylation of ACAP4, resulting in the translocation of ACAP4 and the proton pump to the basolateral membrane, and low acid secretion to the gastric lumen.

Altering the normal function of host organelles

Anju Sreelatha (Orth Laboratory, University of Texas Southwestern) presented an example of a pathogen protein that modifies the function of organelles to drastically impact the health of the cell. Sreelatha presented data indicating that the protein VopQ from Vibrio parahemolyticus, a marine bacterium that causes food poisoning, makes a gated channel in lysosomal membranes. The mechanism of VopQ action appears to be a disruption in the turnover of autophagosomes, which causes lowered autophagic flux. Sreelatha and coworkers demonstrated that VopQ forms a channel in liposomes that permits passive diffusion of small molecules. They presented a model wherein VopQ blocks lysosomal function by dissipating the proton gradient, leading to the accumulation of autophagosomes and death of cells.

Rewiring of cellular processes by obligate intracellular pathogens

Malina Bakowski (Troemel Laboratory, University of California, San Diego) described infection of the nematode Caenorhabditis elegans by its natural pathogen Nematocida parisii, which belongs to the Microsporida phylum of fungal-related pathogens. N. parisii infection induces expression of genes involved in the C. elegans ubiquitin proteasome system (UPS). This pathway appears to be an important arm of the worm’s innate immune system, as interfering with the UPS system limits the ability of the worm to control microsporidia replication and viral replication. A subset of intracellular microsporidia is decorated with conjugated ubiquitin, which requires a host E3 ubiquitin ligase. Interestingly, lowered UPS capacity induces expression of ubiquitin ligases, indicating that the host monitors UPS function to regulate defense responses to intracellular infection.

Yi-Shan Chen (Valdivia Laboratory, Duke University) described a new effector delivered by Chlamydia trachomatis, an obligate intracellular bacterium that is a leading cause of sexually transmitted infections. This protein, named TepP, is rapidly phosphorylated at tyrosine residues during bacterial entry. The host scaffolding protein CrK is subsequently recruited to the early Chlamydia vacuole in a process that is entirely dependent on TepP, as Chen described that a mutant strain defective for this factor—a first for this formerly “genetically intractable” pathogen—no longer recruited CrK. These mutants are defective for global changes in tyrosine phosphorylation patterns in infected cells, altered induction of immunity-related genes, and the disruption of cell–cell junctions in polarized endocervical epithelial cells.

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Molecular Biology of the Cell Volume 25 Page 729

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Volume 25 March 15, 2014 729