CELLULAR MICROBIOLOGY

Make yourself at home

If *Legionella pneumophila* — an aquatic bacterium that infects protozoan hosts in freshwater ecosystems — is inhaled by humans, it causes a severe form of pneumonia known as Legionnaires' disease. Once in the lungs, *L. pneumophila* is internalized into phagosomes by alveolar macrophages. However, rather than being degraded by the macrophage lysosome, this bacterium makes itself at home. It hijacks host vesicle trafficking to make an endoplasmic reticulum (ER)-derived vacuole that supports its replication. So, how does it do it?

New insights are now reported by Kagan and Roy in *Nature Cell Biology*. They began by showing that phagosomes containing *L. pneumophila* mature into ER-derived vacuoles in a biphasic manner. They first interact with early secretory vesicles (vesicles travelling from the ER to the ER–Golgi intermediate compartment (ERGIC)), and then acquire markers that are concentrated in the ER. But, how do they get to the ER?

Cholera and Shiga toxins are known to reach the ER using a pathway that takes them through the Golgi, but Kagan and Roy showed that phagosomes containing *L. pneumophila* do not interact with intermediate compartments (the Golgi or ERGIC). Instead, they found that these phagosomes interact directly with transitional ER (tER) sites — dynamic sites where early secretory vesicles exit the ER — and that *L. pneumophila* makes an ER-derived vacuole by subverting vesicular transport from these sites. In addition, they showed that the subversion of early secretory vesicles is needed to make a stable vacuole that is kept sequestered from the endocytic pathway.

Kagan and Roy have therefore shown that *L. pneumophila* subverts host cellular processes in a new way, and they suggest that understanding the mechanisms used by this bacterium to interact with tER sites and to recruit ER-derived vesicles might help us to identify host factors that regulate vesicular transport at these sites.

Rachel Smallridge

References and links

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FURTHER READING Roy, C. R. Exploitation of the endoplasmic reticulum by bacterial pathogens. *Trends Microbiol.* **10**, 418–424 (2002)

DNA REPAIR

Molecular mimickry

Germline mutations in the *BRCA2* gene cause increased susceptibility to breast and ovarian cancers, so much work is being done to understand the cellular role of BRCA2. It is known to interact with — and modulate the function of — RAD51, a protein involved in recombinational DNA repair. But what does this interaction mean at a functional level?

Reporting in *Nature*, Tom Blundell, Ashok Venkitaraman and colleagues now reveal the structural basis for the BRCA2-dependent regulation of RAD51. They describe the 1.7-Å crystal structure of a complex between BRC repeat 4 (BRC4) of BRCA2 and the RecA-homology domain of RAD51, and show that the BRC repeat mimics a conserved motif found in RAD51, so enabling BRCA2 to control the activity of RAD51.

When mammalian cells are exposed to DNA damage, RAD51 oligomerizes on damaged DNA ends to form a nucleoprotein filament that is essential for subsequent steps in recombinational DNA repair. To work out how this happens, the authors compared the BRC4–RAD51 structure with that of the bacterial RAD51 homologue, RecA, which also forms a helical filament. They discovered that a conserved sequence motif in BRC4 structurally mimics a seven-amino-acid sequence that is found at the interface between subunits in the RecA filament. They then used this information to show that RAD51 oligomerizes through a similar motif. This motif is conserved in RecA-like molecules from bacteria to humans, highlighting a common structural mechanism for the formation of such nucleoprotein filaments.

BRCA2 binds to RAD51 through six of its eight so-called BRC repeats (BRC1–8). From the structure of the BRC4–RAD51 complex, the authors show that these BRC repeats mimic the structure of the natural RAD51 motif that forms the interface between RAD51 subunits in the nucleoprotein filament. So BRCA2 copies a structure in RAD51 to control the oligomerization state of RAD51.

Does this study tell us anything about BRCA2's role in cancer? The authors show that several point mutations in *BRCA2*, which have previously been linked to cancer, impair the ability of BRCA2 to bind RAD51. RAD51 would therefore be unable to repair damaged DNA, which could explain the development of cancer. The importance of this interaction also means that the BRCA2–RAD51 interface could be a target for the development of small-molecule inhibitors as potential anti-cancer drugs.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Pellegrini, L. *et al.* Insights into DNA recombination from the structure of a RAD51–BRCA2 complex. *Nature* 2002 November 10 (DOI: 10.1038/nature 01230)

WEB SITE

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