Online links

Brucella abortus:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=9619

BACTERIAL VIRULENCE

Circular virulence for *Brucella*

A constituent of the *Brucella* outer membrane is an important virulence factor for this facultative intracellular pathogen, according to a report recently published in *Nature Immunology*.

Brucella evade the host innate immune response by establishing a replication-competent, protective intracellular niche within host cells such as macrophages. After entering host cells, some *Brucella* escape the endocytic pathway and a *Brucella*-containing vacuole (BCV) is formed. As the BCV matures, endolysosomal fusion is avoided, and association with the endoplasmic reticulum (ER) creates a replication-competent niche. Although some of the molecular determinants of this intracellular survival pathway are known, many details remain to be elucidated.

The cyclic β-1,2 glucans (CβGs) belong to a family of osmoregulated periplasmic glucans (OPGs), which are constituents of the Gram-negative outer membrane. It has been difficult for researchers to assign a specific function to OPGs, as mutations in OPG synthesis are associated with a range of different phenotypes. *Brucella* CβGs belong to OPG family II but are distinct from the other members of this family in that they are not osmoregulated and contain no *O*-substitutions.

Given that lipid rafts are present in phagosome membranes and that CβGs have similarities to the cyclic oligosaccharides cyclodextrins, synthetic versions of which can damage membranes and selectively extract cholesterol, a key constituent of lipid rafts, Jean-Pierre Gorvel and colleagues hypothesized that *Brucella* CβGs might have a role in targeting lipid rafts. Initial investigations revealed that, although purified CβGs were less potent than synthetic methyl-β-cyclodextrin at perturbing the membrane integrity of whole cells, there was some evidence that CβGs interacted with cholesterol and could perturb lipid rafts.

Encouraged by these initial findings, the authors went on to look at the intracellular effects of mutations in the CβG synthetase gene (*cgs*) in *Brucella abortus*. *cgs*-deficient mutants of *B. abortus* were unable to replicate in HeLa cells or peritoneal macrophages and could be rescued by the addition of exogenous CβG. Analysis of the acquisition of lysosomal and ER markers revealed that CβG is necessary for BCVs to avoid fusion with lysosomes and to interact with the ER. Further analysis of the acquisition of lipid raft markers by vacuoles that contained *cgs*-deficient bacteria demonstrated that intracellular lipid rafts are associated with BCVs and that *Brucella* can locally modify the organization of these rafts. Gorvel and co-workers were also able to establish that CβG prevents lysosome fusion independently of the VirB/D4 type IV secretion system.

So, a specific function has now finally been assigned to a class of OPGs — *Brucella* CβGs function as a virulence factor, modifying the organization and composition of phagosomal lipid rafts to avoid fusion between the BCV and the host endocytic pathway.

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References and links

ORIGINAL RESEARCH PAPER Arellano-Reynoso, B. *et al*. Cyclic β-1,2-glucan is a *Brucella* virulence factor required for intracellular survival. *Nature Immunol.* **6**, 618–625 (2005)