IN BRIEF

BACTERIAL PATHOGENESIS

Prophages of *Staphylococcus aureus* Newman and their contribution to virulence

Bae, T., Baba, T., Hiramatsu, K. & Schneewind, O. *Mol. Microbiol.* **67**, 1035–1047 (2006)

Hospital-acquired infections of surgical wounds and those associated with indwelling medical devices are potentially life-threatening. The main cause of these infections is *Staphylococcus aureus*, which also causes numerous other pus-forming infections and toxinoses. Although most *S. aureus* virulence factors are chromosomally-encoded, recent studies have linked prophage functions to pathogenesis. Now the latest study from the Schneewind laboratory proves that *S. aureus* strain Newman (a human clinical isolate) prophages are essential for virulence in nematodes and rodents. There are four prophages that encode innate immune modulatory genes and toxins present in the genome of this strain. Intriguingly, the excision and loss of individual prophages altered virulence in an organ-specific manner, and loss of all four prophages rendered the strain avirulent.

TOXINS

Pseudomonas aeruginosa type III-secreted toxin ExoT inhibits host-cell division by targeting cytokinesis at multiple steps

Shafikhani, S. H. & Engel, J. *Proc. Natl Acad. Sci USA* 09 October 2006 (doi:10.1073/pnas.0605949103)

Acute infections caused by *Pseudomonas aeruginosa* commonly occur in immunocompromised individuals or those who have wounds. This important opportunistic pathogen also colonizes the lungs of cystic fibrosis patients. Damage to the host is dependent on the functions of effector proteins that are translocated into eukaryotic cells by the bacterial type III secretion system apparatus. Although the complement of effectors produced differs among clinical strains of *P. aeruginosa* most strains produce the toxin ExoT. This paper shows that both domains of the bifunctional ExoT protein are required to inhibit cytokinesis in host epithelia, which directly inhibits wound-healing in the host. This new virulence tactic serves to maintain the damaged host environment and facilitate bacterial proliferation.

VIRAL PATHOGENESIS

Insulin-degrading enzyme is a cellular receptor mediating varicella-zoster virus infection and cell-to-cell spread

Li, Q., Ali, M. A. & Cohen, J. I. *Cell* **127**, 305–316 (2006)

Varicella-zoster virus (VZV), a member of the α-herpesvirus family, causes chickenpox (varicella), which has a characteristic rash, then establishes a latent infection in the nervous system. Reactivation of VZV infection can subsequently cause shingles (zoster). Inside the body, virus transmission is by cell-to-cell spread. The glycoprotein E gene of VZV, which is essential for virus infection, and the herpes simplex virus-1 glycoprotein D gene, which codes for the protein that binds to host receptor proteins in this related virus, are found in the same region of the viral genomes. Here, the authors showed that VZV glycoprotein E binds to host-cell insulin-degrading enzyme (IDE). Downregulation of IDE affected transmission of cell-free and cell-associated VZV but did not block transmission completely, so the authors are still looking for additional host-cell receptors for this virus.

INFECTIOUS DISEASE

Probing pathogen proliferation

Despite a considerable body of knowledge on the molecular basis of bacterial virulence mechanisms, little is known about bacterial infection dynamics at the single cell level, including *in vivo* survival and replication within individual host cells or spread between cells in infected tissue. Reporting in *PLoS Biology*, Sam Brown and colleagues combine microscopy and modelling techniques to explore the key variables that underlie the dynamics of *Salmonella enterica* infection of phagocytic cells.

Previous work by the authors, using microscopy and a mouse model of infection, showed that the growth of *S. enterica* in the tissues of infected animals resulted from the continuous spread of microorganisms to new phagocytic cells, rather than increased bacterial replication within the initially infected host cells. Indeed, each infected phagocyte typically had a low bacterial count that was independent of microbial growth rate or the duration of infection. This finding raised the possibility that the observed variation in intracellular bacterial counts was due to differences in the inherent host-cell response to *S. enterica* invasion and replication. To explore this possibility and to explain the observed intra- and intercellular infection dynamics, a simple mathematical model was developed. Results obtained using this model indicated that many host cells contained just one bacterium, whereas other cells contained several — a finding that mirrored the experimental microscopic observations. Furthermore, it was also shown that it is not necessary to invoke variation in the host-cell response to explain the differences in the number

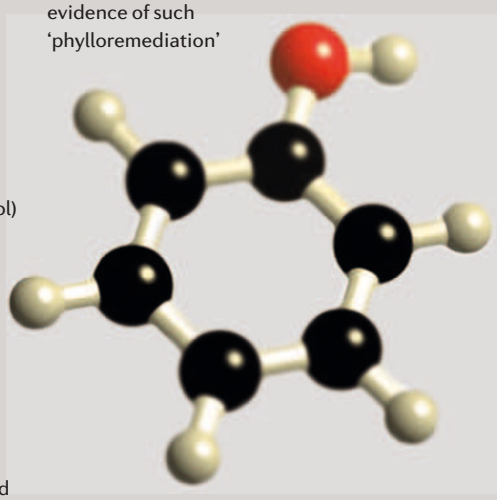
ENVIRONMENTAL MICROBIOLOGY

Phenol and the phyllosphere

Bacteria on the leaf surface — the phyllosphere — could potentially have a role in removing organic pollutants from the air, according to a recent paper in *Environmental Microbiology*.

Amarjyoti Sandhu, Larry Halverson and Gwyn Beattie used a bioreporter system comprising *Pseudomonas fluorescens* strain A506 harbouring a plasmid carrying a fusion between a phenol catabolic operon and green fluorescent protein (A506 (pPhenol)). The availability of airborne phenol to bacteria on the leaf surface was assessed by inoculating A506 (pPhenol) onto leaves, then exposing the leaves to gaseous phenol in closed chambers. The results showed that the cells of the reporter strain on leaves could detect the introduced phenol. Volatile organic compounds (VOCs) such as phenol are known to be taken up by sorption onto the leaf cuticle. Could the reporter strain detect phenol that had been absorbed in this manner? This was assessed by exposing leaves to phenol before inoculating the leaf surface with A506 (pPhenol), and the results indicated that phenol accumulates on the leaf surface and is available to the bacteria there.

Although previous work had provided evidence of such 'phylloremediation'



of microorganisms an infected phagocyte contains. The model was then used to investigate the origin of variability in host-cell response to infection, reaching the conclusion that stochastic rather than intrinsic differences between cells offered the best fit for the observational data.

Finally, using these insights into intra- and intercellular infection dynamics, the authors explored the effects of medical intervention. Using the model, the authors could demonstrate that inhibiting intracellular bacterial replication reduces the number of infective bacteria that trigger host-cell lysis and are released into the extracellular environment. In terms of therapy, an intriguing prediction from this analysis is that the efficacy of common extracellular antibiotics will be enhanced by the use of molecules that slow intracellular bacterial division.

David O'Connell

ORIGINAL RESEARCH PAPER Brown, S. P. *et al.* Intracellular demography and the dynamics of *Salmonella enterica* infections. *PLoS Biol.* 17 Oct 2006 (doi:10.371/journal.pbio.0040349)

of VOCs, Sandhu *et al.* directly measured phenol degradation by natural phyllosphere communities. Leaves were collected from trees growing in an area that was known to be high in VOCs. Unsterilized and surface-sterilized leaves were then exposed to radiolabelled phenol in closed chambers for 24 hours and the amount of phenol degradation was compared. The phenol degradation by the non-sterilized leaves was significantly greater than the degradation by the sterilized leaves, indicating that degradation of this VOC was enhanced by the presence of the phyllosphere communities.

This work indicates that plant leaves can accumulate phenol, which is subsequently available to bacteria in the phyllosphere for degradation. The authors are planning future studies to further probe the role of phylloremediation in the attenuation of natural airborne pollutants.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Sandhu, A., Halverson, L. J. & Beattie, G. A. Bacterial degradation of airborne phenol in the phyllosphere. *Environ. Microbiol.* 04 Oct 2006 (doi:10.1111/j.1462-2920.2006.01149.x)

NETWORK BIOLOGY

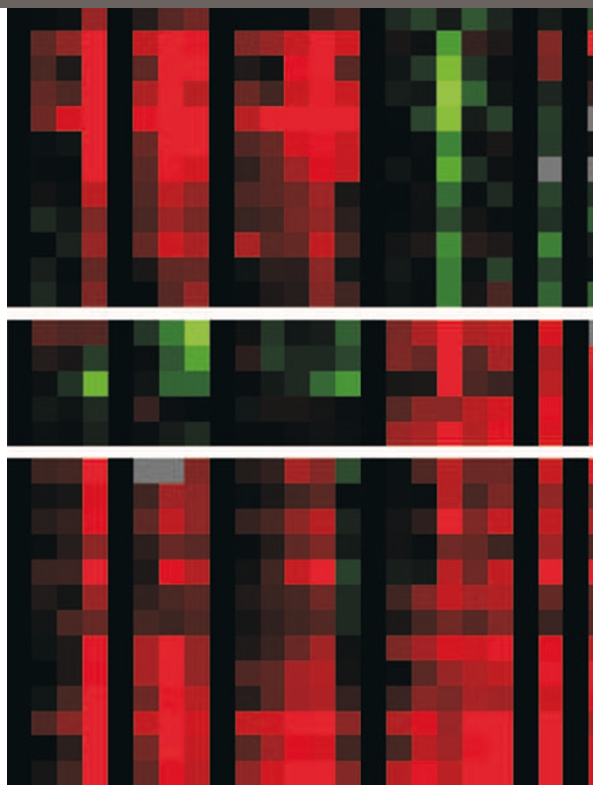
Wiring with a difference

The fact that changes in transcriptional logic bring about adaptive changes — as might occur when developmental modules are rearranged — is no longer front page news. Now, a study of mating type in two divergent yeast species shows the opposite principle: that phenotypes might stay the same during evolution, while the transcriptional logic is sometimes completely rewired.

The ascomycete yeasts *Candida albicans* and *Saccharomyces cerevisiae* each come in two varieties, **a** and α, depending on which allele they express at the mating-type (MAT) locus. Each mating type expresses a set of specific genes, which allows mating only between **a** and α types. In this respect the two yeast species are identical — however, they differ radically in how they regulate the expression of these antigens. In *C. albicans*, **a**-type genes are 'off' by default, and are turned 'on' in **a**-type cells; in *S. cerevisiae*, **a**-type genes are 'on' by default, and need to be repressed in α-type cells. The end result is the same — **a**-type genes are 'on' in **a** cells and 'off' in α cells — but the two yeasts use opposite means of achieving this pattern of expression. How did this transition take place, in the 200–800 million years since the two species shared a common ancestor? By combining microarrays (see image) and other bench experiments with comparative genomics in modern yeasts, Annie Tsong, Brian Tuch and colleagues have identified the *cis* and *trans* elements that were in place at the transition, and have traced the order in which the events took place.

A phylogenetic survey shows that the *C. albicans* style of activation is the ancestral state: in *C. albicans* and its ancestors, **a**-type genes are induced by an activator (**a**2) that is encoded by MAT**a**. The challenge is to explain how this activator was lost in the *S. cerevisiae* lineage and replaced by a repressor — α2, which is encoded by MATα.

The authors started out by identifying the **a**-type genes that were specifically activated in the *Candida* lineage and then characterizing the *cis*-regulatory motifs that allowed **a**-type activation. By combining this information with knowledge of the mating-type circuitry in *S. cerevisiae* and the genome sequence of 16 ascomycete yeasts, the authors concluded that the transition from activator to repressor occurred as follows. First, regulation of **a**-type genes became independent of **a**2; in the ancestral state, Mcm1 (a protein in the MADS-box family) required **a**2 to activate **a**-type genes, but this dependence was lost owing to sequence changes in the *cis*-elements, which allowed Mcm1 to operate on its own. As Mcm1 is constitutively active, **a**-type genes would have been inappropriately expressed in α cells: this situation would have favoured a second step, in which α2 stepped in as an Mcm1 cofactor, thereby allowing the evolution of α2-mediated repression. This step would have required the conversion of a *cis*-sequence that recognizes **a**2 to one that recognizes α2, which the authors think could have occurred simply through changes both in *cis* and in *trans*.



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Beyond the immediate implications for the wiring of yeast mating systems, this study stands out because of the molecular resolution at which it has defined an evolutionary transition. Importantly, proper gene regulation seems to be maintained at all steps during the transition. Large evolutionary transitions can be ordered, stable affairs, as long as they involve coordinated interactions between proteins, and between proteins and DNA that do not compromise fitness.

Tanita Casci Senior Editor,
Nature Reviews Genetics

ORIGINAL RESEARCH PAPER Tsong, A. E., Tuch, B. B. *et al.* Evolution of alternate transcriptional circuits with identical logic. *Nature* **443**, 415–420 (2006)