and *mecI*, respectively and which also regulate *blaZ*, the gene encoding β-lactamase. Katayama and colleagues found that the *bla* regulatory regions did have a permissive effect on *mecA* acquisition in naive strains, although this effect was not as strong as that of the *mec* genes.

Horizontal transfer of the *mec* element has long been recognised as a major contributor to the evolution of MRSA strains, yet the clonal restriction of *mecA* distribution has always been puzzling. This work highlights the important contribution of the genetic background of the host staphylococcal strain to this process.

Sheilagh Clarkson

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This *in vitro* demonstration of the inhibition of HIV-1 infectivity by a recombinant constituent of the vaginal microflora is an important proof-of-principle study in the search for novel methods to halt the HIV epidemic. As yet, the engineered lactobacilli are a long way from clinical development. However, Lee and colleagues have already gone on to achieve stable integration of the 2D CD4 coding sequence into the *L. jensenii* chromosome, thereby circumventing the problem that the antibiotic-resistance genes present on the expression plasmid would pose for clinical trials. The fact that in a recent issue of *PNAS* another team report on BMS-378806, a new small-molecule inhibitor that blocks the docking of HIV-1 to CD4, reflects the fact that the efforts of HIV researchers to thwart HIV-1 are not wholly devoted to the search for a vaccine, and all aspects of the infection and transmission cycle are being investigated for potential new targets.

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FUNGAL VIRULENCE

Stuck on you

New research published in Genes and Development from the Cormack lab shows that *Candida glabrata* has at least two groups of adhesin virulence genes located in subtelomeric regions that are regulated by a defined mechanism of transcriptional silencing.

Candida is responsible for 8% of serious nosocomial infections in the United States. In common with other *Candida* species, *C. glabrata* usually populates mucosal surfaces, but can breach the mucosal barrier when host defences are lowered and cause life threatening systemic infections. Unlike the diploid opportunistic pathogen *Candida albicans*, *C. glabrata* is haploid, which makes genetic manipulations far more straightforward. Previous work identified an adhesin protein — Epa1 — which enables *C. glabrata* to stick to epithelial cells. Epa1 is a member of a large class of cell wall proteins that are found in many fungi, including *Saccharomyces* and *Aspergillus* species.

When the *EPA1* gene was deleted from the chromosome, the resulting mutant lost virtually all ability to attach to epithelial cells in the lab. So, *EPA1* was an excellent candidate for a virulence gene. However, when the same mutant was tested for pathogenicity in mouse models of candidiasis it was still virulent. Pathogens like *C. albicans*, *Trypansoma brucei* and *Plasmodium* species commonly encode families of virulence genes. So, one possible solution to this conundrum was that *C. glabrata* might have a family of adhesins. The hunt was on for *EPA1* homologues and now De Las Peñas *et al.* report the characterisation of 5 homologues of *EPA1* in *C. glabrata*.

The 5 *EPA1* homologues are located in two separate subtelomeric clusters. Although *Saccharomyces cerevisiae* and *C. glabrata* have largely similar genetic organisation (with syntenic gene arrangement) the subtelomeric regions, including the *EPA* genes, are completely different. Knocking out both subtelomeric *EPA* clusters reduced virulence of the resultant mutant strain in a mouse model. Genomic sequencing studies have subsequently uncovered additional potential *EPA1* homologues, so the family is growing.

Curiously, De Las Peñas *et al.* found that only *EPA1* was expressed *in vitro*. Not only were the other *EPA* genes repressed, but a marker gene — *URA3* — was repressed when inserted at either subtelomeric locus. So, both subtelomeric *EPA* clusters are regionally silenced. This study also showed that a key component of the transcriptional silencing machinery in *S. cerevisiae* — *SIR3* — regulates transcriptional silencing of the *EPA* genes in *C. glabrata*. Even though the telomere gene complements of these two fungi are different, the gene silencing mechanism is conserved between these species.

The subtelomeric location of the adhesin genes, coupled with a defined silencing mechanism, means that *C. glabrata* is the first pathogen for which the mechanism of transcriptional silencing of virulence factors has been defined. Intriguingly, regulation of subtelomeric silencing in *S. cerevisiae* has been linked to cellular stresses. Since cellular stress is likely to be common during infection, this raises the exciting possibility that *C. glabrata* virulence factors could be switched on and off during infections.

Susan Jones

References and links

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