FUNGAL GENETICS

Fungal resistance needs a little extra

DOI:

10.1038/nrmicro1500

URLs

Online Links

Candida albicans

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prj&cmd=Retrieve&dopt=Overview&list_uids=9526

Saccharomyces cerevisiae

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&prj&cmd=Retrieve&dopt=Overview&list_uids=9518

Work in Judith Berman's laboratory at the University of Minnesota has identified common genome rearrangements associated with azole resistance in *Candida albicans*, according to a recent *Science* paper.

The *C. albicans* genome is known to tolerate aneuploidy — the gain or loss of chromosomes or chromosome fragments. Traditionally, changes in fungal karyotype are detected using CHEF (contour-clamped homogeneous electric field) whole-chromosome gels and quantitative Southern blots. However, the Berman laboratory recently adapted a technique, which was originally used to detect changes in the gene copy number at all loci in the *Saccharomyces cerevisiae* genome, to make it suitable for use in *C. albicans*. The technique involves comparative genome hybridization (CGH), in which digested genomic DNA from test and control isolates is differentially labelled with fluorescent dyes then hybridized to *C. albicans* whole-genome microarrays.

Anna Selmecki and Anja Forche from the Berman group used this CGH technique to take an in-depth look at the genome rearrangements present in clinical isolates of *C. albicans* resistant to the azole fluconazole. Aneuploidy was seven times more common in fluconazole-resistant isolates than in fluconazole-sensitive isolates, with chromosome 5 most frequently involved. Moreover, a specific segmental aneuploidy, an isochromosome comprising the two left arms of chromosome 5, was detected only in fluconazole-resistant isolates. The isochromosome, i(5L), was present both as an independent chromosome and fused to full-length chromosome 5.

So, what genes could be responsible for the resistance? The left arm of chromosome 5 carries the *ERG11* gene, which encodes the target of fluconazole, and *TCA1*, which encodes a transcription factor that upregulates the expression of an efflux pump on chromosome 3, in addition to two ORFs encoding predicted efflux pumps. Analysis of the transcript profiles showed that the increased copy number associated with the aneuploidy correlates with increased gene expression.

Further analysis showed that

strains carrying i(5L) had a growth advantage in the presence of fluconazole compared with strains lacking i(5L), and that the loss of i(5L) was accompanied by a concomitant loss of fluconazole resistance. The authors therefore suggest that agents that block or reduce isochromosome formation could be useful adjuncts to current azole therapeutic regimes.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Selmecki, A., Forche, A. & Berman, J. Aneuploidy and isochromosome formation in drug-resistant *Candida albicans*. *Science* **313**, 367–369 (2006)