cap opens the gated ends of the proteasome and aids the unfolding and transfer of protein substrates into the core for degradation. 19S regulatory caps have so far not been found in prokaryotes, and how prokaryotic proteasomes regulate the degradation of substrates is not known.

The *M. tuberculosis* proteasome is essential for resistance to reactive nitrogen intermediates (RNI), and a screen for mutant strains with increased susceptibility to RNI identified Mpa and PafA as proteins that are functionally linked to the *M. tuberculosis* proteasome. Various *mpa*-mutant strains (including a C-terminal Mpa mutant) and a *pafA*-null strain were shown to have increased amounts of Mpa, which implies a defect in Mpa degradation in these mutants. The mycobacterial enzymes FabD and PanB also accumulated in an *mpa*-null and a *pafA*-null strain, and inhibition of the proteasome resulted in accretion of Mpa, FabD and PanB, providing compelling evidence that these proteins are natural proteasome

substrates and that Mpa and PafA work together with the proteasome to regulate the steady state levels of these proteins. These studies identify Mpa as both a substrate and a cofactor of the *M. tuberculosis* proteasome, and further analysis indicated that the C terminus of Mpa is essential for its function in the proteasome-degradation pathway.

Mpa is a hexameric AAA+ ATPase, homologous to the ATPases found in the eukaryotic 19S regulatory cap, and the authors propose that, in the presence of cofactors such as PafA, the C terminus of Mpa might open the gate of the proteasome core, allowing the entry of substrates into the catalytic chamber. In addition, Mpa is itself degraded by the proteasome, which represents a hitherto unknown mechanism of proteasomal autoregulation.

Shannon Amoils

ORIGINAL RESEARCH PAPER Pearce, M. J. et al. Identification of substrates of the *Mycobacterium tuberculosis* proteasome. *EMBO J.* **25**, 5423–5432 (2006)

correlation with several measures of innate and adaptive immune stimulation. Brechley et al. went on to investigate the effects of highly active antiretroviral therapy (HAART) and found that after 48 weeks on a HAART regimen, the plasma LPS levels decreased, indicating that a reduction in HIV replication is associated with the restoration of mucosal immune protection in the gut. Finally, sooty mangabeys are natural hosts for SIV and chronic SIV infection in these monkeys is non-pathogenic. SIV-infected sooty mangabeys show low plasma LPS levels, indicating that in this benign infection microbial translocation does not occur.

These data are consistent with a model in which the continuous replication of HIV during chronic infection prevents the repair of the breach in the gut mucosal barrier that occurs during acute infection. This allows microorganisms to translocate from the intestinal lumen and cause systemic immune activation. The authors conclude by suggesting that these findings could lead to the development of new HIV therapeutics.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Brechley, J. M. et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature Med.* 19 Nov 2006 (doi: 10.1038/nm1511)

FURTHER READING Brechley, J. M., Price, D. A. & Douek, D. C. HIV disease: fallout from a mucosal catastrophe? *Nature Immunol.* **7**, 235–239 (2006)

Infected cob of corn arranged on a Mexican pottery plate. Tumours induced by *Ustilago maydis* have been regarded as the favourite food of Aztec gods and are still a delicacy in Mexican cuisine. Image courtesy of Cristina G. Reynaga-Peña.

GENOMICS

Beat it — or eat it!

Most people lose their appetite when confronted with a picture of smut-disease infested corn, but well-cooked fungus-infected kernels are considered a delicacy in Mexico. Although there is no accounting for taste, the fungus causing these bizarre-looking tumours, *Ustilago maydis*, can be easily genetically manipulated and has been used as a model system to understand not only fungal pathogenesis but also, much like baker's yeast, to investigate basic processes in eukaryotic cell biology.

In a recent paper published in *Nature*, Joerg Kamper and colleagues present the genome sequence of this organism. In comparison to other plant-pathogenic fungi, its genome is relatively small (20.5 Mb), which can be explained by a comparably low number of introns and the virtual absence of both large-scale gene duplications and repetitive elements. In accordance with its biotrophic lifestyle *U. maydis* has only a few virulence factors that are common to other fungal pathogens, such as antibiotics, mycotoxins and plant-wall-degrading enzymes. But the genome sequence revealed some surprises: of 426 predicted secreted proteins, 298 could not be ascribed a function by protein homology and of those almost 20% were arranged in 12 large clusters that were scattered all over the genome. The transcription of the cluster genes, but not the flanking genes, was increased during the infection process, which prompted the authors to speculate that these clusters might be involved in pathogenesis. Indeed, deletion of five of the clusters resulted in marked alterations in virulence; two mutant strains produced fewer (and smaller) tumours during infection, two different mutant strains were arrested for growth during specific stages of pathogen development, and one mutant strain was hyper-virulent.

While the detailed analysis of these genetic loci awaits further investigation, initial characterization has revealed their importance in the biotrophic lifestyle of this pathogen. Future research will clarify whether these clusters, akin to pathogenicity islands in bacteria, are a common feature of biotrophic and maybe even symbiotic fungi.

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Associate Editor, *Nature*

ORIGINAL RESEARCH PAPER Kamper, J. et al. Insights from the genome of the biotrophic fungal plant pathogen *Ustilago maydis*. *Nature* **444**, 97–101 (2006)