BACTERIAL PHYSIOLOGY

Under attack! SOS!

Like most cells, bacteria respond to adverse conditions by activating gene-expression pathways that increase their chances of survival. Such a pathway — the aptly named SOS response — is induced by genome damage or disruption of DNA replication, and results in the synthesis of DNA repair enzymes and the inhibition of bacterial cell division. Now, reporting in *Science*, Stanley N. Cohen and colleagues show that treatment of *Escherichia coli* with β-lactam antibiotics induces the SOS response, which decreases the lethal effects of these bactericidal drugs and enhances *E. coli* survival.

Previous studies have shown that overexpression of DpiA — the effector protein of the DpiBA two-component signal-transduction system in *E. coli* — inhibits DNA replication and therefore activates SOS-regulated genes. To characterize stimuli that activate the *dpiBA* operon, the authors transformed *E. coli* with a plasmid containing the *dpiBA* promoter fused to a *lacZ* reporter-gene fragment, and exposed these bacteria to various culture conditions. Suprisingly, Cohen and co-workers found that the β-lactam antibiotics — including ampicillin, cephalexin and pipericillin — induced expression of the *dpi–lacZ* reporter construct.

So what is the mechanism of *dpiBA* induction by β-lactam antibiotics? β-lactams bind to and inhibit the penicillin-binding proteins (PBPs). However, although ampicillin binds to all the PBPs, pipericillin and cephalexin bind to a specific PBP — PBP3. The authors therefore reasoned that inactivation of PBP3 might induce *dpiBA* expression. PBP3 is encoded by the temperature-sensitive *ftsI* gene and is required for the synthesis of the cell-wall septum that is formed during cell division. When *ftsI* was repressed by culture of *E. coli* at inhibitory temperatures, the marked increase in *dpi–lacZ* reporter-gene expression was comparable to that seen when the bacteria were exposed to ampicillin. Furthermore, a strain of *E. coli*

FUNGAL PATHOGENICITY

Magnaporthe blasts into roots

Understanding how a pathogen breaches host defences to enter cells and cause disease is an important step towards devising disease-prevention strategies. The rice blast fungus is a paradigm for mechanisms of leaf disease but can also enter plants through the roots. Reporting in *Nature*, Sesma and Osbourn describe the mechanism of root entry by rice blast — a completely new facet of this pathogen's life cycle.

Plant pathogens often have a core set of virulence factors but the disease that results is usually restricted to one tissue type — leaf, root or vascular tissue. *Magnaporthe grisea* is a leaf pathogen that destroys rice crops worldwide and enters leaves using a sophisticated method that increases turgor pressure in a melanized appendage (the appressorium) to force through the leaf surface and enable entry. It is in the same family as *Gaeumannomyces graminis*, a soil-borne fungus that causes cereal take-all disease, which is characterized by root rot.

Using microscopy of strains that were labelled with GFP, Sesma and Osbourn showed that *M. grisea* uses hyphopodia — simple penetration structures typical of take-all — rather than appressoria to penetrate roots. Outward signs of infection that are typical of root-infecting fungi, including microsclerotia, brown surface structures and swollen bundles of fungal hyphae with pores, were observed. Once inside the root, pathogenesis resembled that seen in leaves, with multiple thick intracellular hyphae and rapid invasion into the endodermis and stele. Mutants that lacked the ability to form functional appressoria still made hyphopodia and infected roots, indicating that leaf and root penetration mechanisms fundamentally differ.

What about root virulence factors? The wilt pathogen *Fusarium oxysporum* requires *FOW1* to efficiently infect roots and inspection of the genome sequence revealed that *M. grisea* has a *FOW1* homologue. It turns out that deletion of the *M. grisea FOW1* gene restricted root colonization and symptoms, but did not affect leaf pathogenesis. This confirmed that *M. grisea* not only infects rice roots, but shares virulence factors with other root-infecting fungi, and importantly, that leaf and root pathogenic strategies are distinct.

Not only do the rice roots have disease symptoms, in up to 10% of infected plants *M. grisea* was shown to spread and cause blast disease on aerial parts of the plant — the first time that systemic disease caused by *M. grisea* has been reported. Furthermore, plants harbouring an avirulence gene that prevents *M. grisea* from causing disease by leaf entry were also resistant to root infection, so the same gene-for-gene mechanisms mediate plant defence in leaves and roots.

Although these studies have not yet been evaluated in paddy fields, this research shows that soil-borne inocula and root infection might be important in diseases formerly only thought to affect aerial parts of plants, which has important implications for plant breeding and disease control.

Susan Jones

References and links

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that contained a *lacZ* reporter fused to an SOS-regulated promoter showed increased β-galactosidase synthesis on inhibition of the *ftsI* gene. This supports the hypothesis that defective septum synthesis caused by inactivation of PBP3 by β-lactams induces the SOS response.

The inhibition of cell division — an end-result of the SOS response — would allow microorganisms to 'shelter from antibiotic attack', as only dividing cells are vulnerable to the bactericidal effects of the β-lactams. This might contribute to bacterial persistence — a phenomenon in which small numbers of microorganisms survive despite antibiotic therapy. As the authors point out, the SOS response might therefore represent a novel therapeutic target "aimed at enhancing the efficacy of β-lactam antimicrobials".

Shannon Amoils

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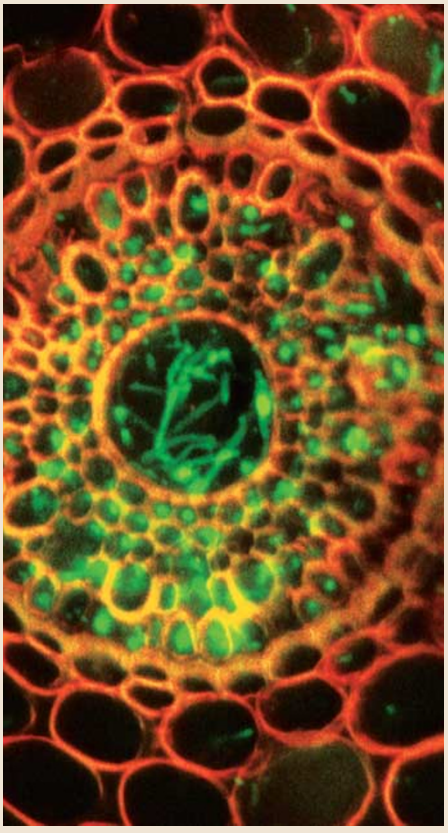
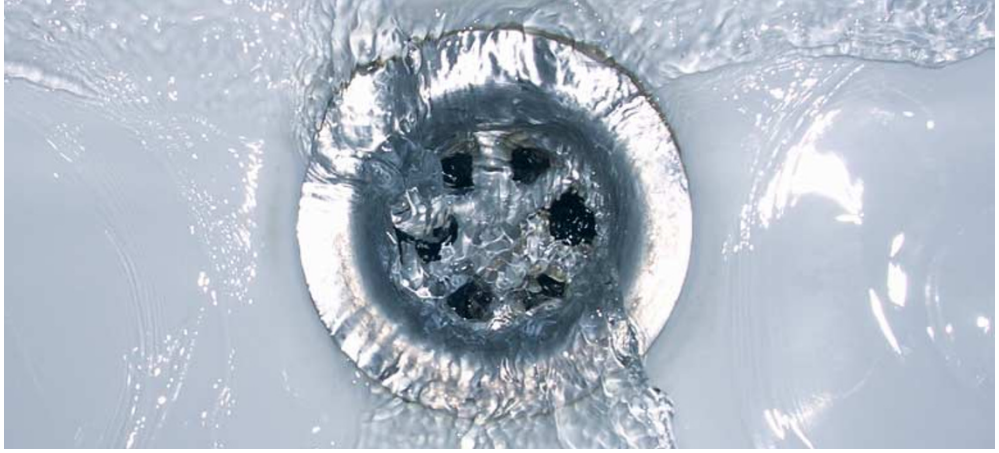


GFP-labelled rice blast fungus spreading through a rice plant. Image courtesy of Ana Sesma.



HIV

Getting to the bottom of CD4$^+$ T-cell loss

Previous studies of HIV pathogenesis have largely ignored events in the intestines of HIV-infected patients and have mostly concentrated on events in the blood, perhaps owing to the difficulty in obtaining intestinal lymphoid-tissue samples. However, two groups now report that the gastrointestinal tract has the most marked depletion of CD4$^+$ T cells, and this occurs rapidly and at all stages of HIV infection, regardless of administration of highly active antiretroviral therapy (HAART).

Given that the gastrointestinal tract and other lymphoid tissues harbour most of the body's CD4$^+$ T cells, and that in the gut a large number of these cells are activated and express the HIV co-receptor CC-chemokine receptor 5 (CCR5), the intestinal CD4$^+$ T cells are potentially highly susceptible to infection with HIV and are therefore of crucial importance in HIV pathogenesis. So, the authors of both studies set out to examine CD4$^+$ T-cell depletion in the intestines of patients with HIV.

Danny Douek's group compared T-cell depletion in intestinal tissue, lymph nodes and blood from untreated HIV-infected patients (at all stages of disease) and from HIV-uninfected individuals. As expected, the frequency of CD4$^+$ T cells was significantly lower in each compartment in HIV-infected patients compared with HIV-uninfected individuals; however, the greatest loss of CD4$^+$ T cells was seen in the gastrointestinal tract, even in acute infection. This preferential depletion of intestinal CD4$^+$ T cells was confirmed by histological studies, showing that lymphoid aggregates, which are abundant in normal intestinal-tissue samples, were largely absent in samples from patients with HIV. Further analysis revealed that the CD4$^+$ T-cell depletion in the gut was specific for those cells expressing CCR5 and the activation marker Ki67, which is consistent with the observation that HIV preferentially replicates in and causes the death of activated CD4$^+$ T cells.

It is well known that chronic infection with HIV results in a state of general immune activation. Accordingly, Douek's group observed that effector memory T cells accumulated abnormally in the lymph nodes of HIV-infected patients, possibly owing to the activation and recruitment of these cells to the site of viral replication. Moreover, this increased T-cell activation was associated with collagen deposition in the lymph nodes, a marker of inflammation associated with chronic immune activation. This led the authors to suggest that disrupted lymphoid architecture might disturb normal lymphoid-tissue homeostasis, which might then impair CD4$^+$ T-cell reconstitution of the gut following depletion by infection with HIV.

Martin Markowitz's group studied T-cell depletion in patients with acute or early HIV infection, and compared untreated patients with those who had received HAART. Consistent with observations by Douek's group, in primary HIV infection, they found that CD4$^+$ T-cell depletion was most marked in the gastrointestinal tract and that it occurred before changes observed in the blood. Specifically, deletion mainly occurred in the effector sites (the lamina propria), as opposed to the inductive sites (Peyer's patches and lymphoid follicles), of the gastrointestinal mucosa.

To examine whether HAART would allow the reconstitution of CD4$^+$ T cells in the gut, they studied patients who had initiated HAART during primary infection. However, although CD4$^+$ T-cell numbers in the blood of these patients were mostly restored following HAART, reconstitution in the gastrointestinal tract remained incomplete despite up to 5 years of fully suppressive therapy.

Both of these studies, which are in agreement with earlier studies of macaques infected with simian immunodeficiency virus, highlight the need for further investigation of the mucosal compartment, given its crucial role in HIV infection, replication and persistence.

Lucy Bird, Associate Editor Nature Reviews Immunology

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