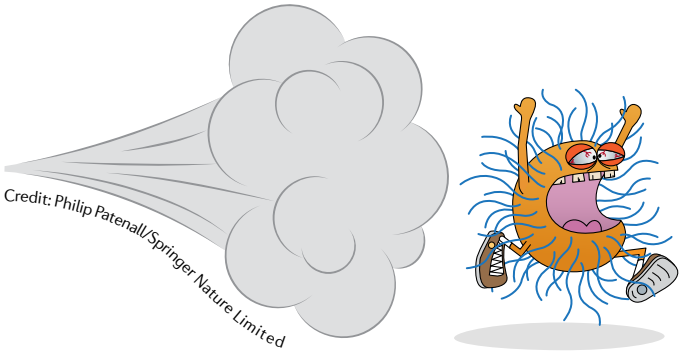

FUNGAL PATHOGENESIS

Spreading out of the lung

Environmental pathogens adapt to several conditions to switch from their ecological niche to their mammalian host. Phenotypic diversity is key to this transition and to facilitate spread to different host sites. The pathogenic fungus *Cryptococcus neoformans*, which is environmentally associated with trees and bird guano, enters the human lung and then disseminates to the brain causing meningitis. Evidence shows that *C. neoformans* populations found in the brain are homogeneous and small, but the phenotypic changes that lead to its extrapulmonary spread remain unclear. In a recent study, Denham and colleagues characterize an inducible cryptococcal morphotype that is critical for extrapulmonary organ entry.

The authors first performed inoculations in mice and microscopy to measure *Cryptococcus* spp. cell body and capsule size in different organs (lung, liver, spleen, brain and blood), and found that small *C. neoformans* cells detected in the lungs correlated with extrapulmonary dissemination. They named these small morphotypes 'seed cells'. To better replicate fungal entry into the bloodstream from the lungs, they isolated fungal cells from infected lung tissues and used them to intravenously inoculate mice. They observed that small ex vivo cells spread to other organs while intermediate and large cells remained in the lungs.

Next, the authors screened the binding of several host receptors to ex vivo cell subpopulations and found that small seed cells had increased mannose exposure compared with intermediate and large cells. This was linked to macrophage recognition and phagocytosis that likely supported fungal cell dissemination. Other fungal ligands, such as poly(I), and the capsule polysaccharide GXM were also involved in fungal entry into multiple organs.

The authors further demonstrated that, in addition to cell size, capsule morphology and culture conditions also influenced fungal distribution across organs. Transcriptomics and gene ontology term enrichment analysis of fungal cell populations revealed enhanced expression of phosphate acquisition genes in seed cells. Mutant strains unable to acquire phosphate could not adopt the seed cell morphotype, and phosphate availability was key to promote the switch of *C. neoformans* cells towards seed cells.

So, what is the source of phosphate that triggers seed cell formation? Phosphate is found in different environmental and host niches encountered by *C. neoformans*. The authors found that the nucleotide sugar UDP-GlcNAc, nucleoside triphosphates and pigeon guano, which are all rich in phosphate, triggered small cell morphogenesis and extrapulmonary organ entry of *C. neoformans* in vitro.

In sum, these findings underscore the importance of phenotypic heterogeneity in disseminated *C. neoformans* infection, in which seed cells form in response to phosphate to exit the lung and spread to other organs.

Agustina Taglialegna, Editor,
Nature Microbiology

ORIGINAL ARTICLE Denham, S. T. et al. A dissemination-prone morphotype enhances extrapulmonary organ entry by *Cryptococcus neoformans*. *Cell Host Microbe* https://doi.org/10.1016/j.chom.2022.08.017 (2022)

IN BRIEF

VIRAL PATHOGENESIS

The bodily distribution of monkeypox virus

Close contact during sex seems to be a key route for monkeypox virus (MPXV) transmission. In a recent study, Palich et al. investigated viral loads in clinical samples of men in Paris, France, with MPXV infection with the aim of understanding the distribution of MPXV in the human body and how this distribution may be influencing viral transmission. 356 samples from 50 men were collected from various anatomical sites including skin, anus, throat, blood, urine and semen at diagnosis and 2 weeks later. At diagnosis, MPXV was most frequently detected in skin, anus and throat samples, and viral loads were highest in skin and anus samples. At day 14, the proportion of positive samples substantially decreased relative to day 0 at all sites. High viral loads on the skin and mucosa suggest that transmission most likely occurs through direct contact as opposed to contact with bodily fluids or respiratory transmission.

ORIGINAL ARTICLE Palich, R. et al. Viral loads in clinical samples of men with monkeypox virus infection: a French case series. *Lancet Infect. Dis.* https://doi.org/10.1016/S1473-3099(22)00586-2 (2022)

ANTIMICROBIALS

Phages to the rescue

Extensively drug-resistant (XDR) *Pseudomonas aeruginosa* is a common cause of hospital-acquired infections, necessitating the development of novel treatment approaches. Now, a recent case report illustrates the potential of the therapeutic use of bacteriophages (phage therapy) for treating nosocomial *P. aeruginosa* infection. Van Nieuwenhuyse et al. report that a phage–antibiotic combination therapy was successful in treating XDR *P. aeruginosa* infection following liver transplantation in a toddler. 53 days post-transplantation, the toddler presented with severe sepsis caused by XDR *P. aeruginosa*, which was resistant to intravenous antibiotics, and the toddler was subsequently admitted to paediatric intensive care. The toddler was treated with an intravenous infusion of a cocktail of *Staphylococcus aureus* phage (ISP) and two *P. aeruginosa* phages (PNM and 14-1) for 86 days. Phage therapy in combination with antibiotics controlled bloodstream infection, enabling re-transplantation and eventual resolution of infection.

ORIGINAL ARTICLE Van Nieuwenhuyse, B. et al. Bacteriophage-antibiotic combination therapy against extensively drug-resistant Pseudomonas aeruginosa infection to allow liver transplantation in a toddler. *Nat. Commun.* **13**, 5725 (2022)

VIRAL INFECTION

Histone mimicry by SARS-CoV-2

Histone proteins are major determinants of gene regulation, and histone mimicry allows viruses to gain control of gene regulatory functions to support viral replication or suppress host antiviral responses. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to disrupt host cell epigenetic regulation, but the underlying mechanisms are unknown. In a recent study, Kee et al. uncover that the viral ORF8 protein mimics the H3 histone protein to disrupt epigenetic regulation. The authors found that, during infection, ORF8 associates with chromatin, disrupts the post-translational modification of histones and promotes chromatin compaction. Viruses that lacked *ORF8* or the histone mimic site had a reduced ability to disrupt host chromatin, and host cells infected with these viruses had an altered transcriptional response to infection and a lower viral genome copy number compared with wild-type viruses. These data may explain why SARS-CoV-2 viruses lacking *ORF8* have been associated with a reduced severity of COVID-19.

ORIGINAL ARTICLE Kee, J. et al. SARS-CoV-2 disrupts host epigenetic regulation via histone mimicry. *Nature* https://doi.org/10.1038/s41586-022-05282-z (2022)