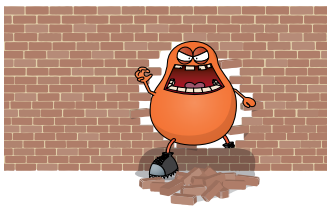
Bacterial physiology

Leaving the wall behind to escape



Bacteriophages (phages) are obligate predators of their bacterial hosts that typically sustain two distinct life cycles — a lytic cycle and a lysogenic cycle. During the lytic cycle, the phage genome is injected into the host cell, replicated and packaged into progeny phages that are released through bacterial host cell lysis. However, the cell wall and cytoplasmic membrane represent natural barriers for progeny release. To overcome this, tailed phages have evolved peptidoglycan hydrolases (termed endolysins) that mediate host cell lysis through the hydrolysis of the cell wall. Previous studies have shown that bacteria can transiently enter a cell wall-deficient L-form state in the presence of certain triggers such as lytic enzymes. Due to the lack of a cell wall and the associated polymers, L-forms are intrinsically resistant to lytic enzymes or antibiotics that target the cell wall. However, whether phage exposure can lead to the emergence of the L-form state is elusive. In this new study, Loessner and colleagues show that *Listeria monocytogenes* and *Enterococcus faecalis* can evade phage predation by transient conversion to a cell wall-deficient L-form state.

The authors first showed that repeated phage infection cycles trigger bacterial L-form switching in both *L. monocytogenes* and *E. faecalis* under osmoprotective conditions, and that the walled phenotype could be quickly reverted following removal of the selective pressure.

Next, the authors reported that the phage-encoded endolysin promotes L-form conversion.

Having established the peptidoglycan hydrolase as the transforming agent, the authors set out to gain mechanistic insights into the switching process. On the basis of their results, the authors propose that L-form switching comprises three distinct steps: first, endolysin induces punctured lesions in the cell wall and small membrane protrusions extrude through these holes; next, the protrusions fill with cytosolic content, driven by the internal turgor pressure of the cell; and finally, scission of the membrane bleb leads to the formation of an independent, viable L-form cell.

Importantly, the authors reported that only non-infected bystander cells, and not the phage-infected bacteria, can switch to L-forms. L-form conversion leads to the loss of the cell wall-associated phage receptors, and the authors hypothesize that L-forms are resistant to phage infection. Indeed, even after prolonged periods of incubation with excess amounts of phage, L-form bacteria did not exhibit signs of productive phage infection, which suggests that L-form conversion represents a protective mechanism.

To test whether phage-induced L-forms could be relevant in natural environments, the authors challenged the urinary tract pathogen *E. faecalis* with phages in sterile-filtered human urine (which provides an osmoprotective environment) and found substantial induction of L-forms. Finally, most *E. faecalis* L-forms underwent reversion to the walled state. These findings may have implications for the development of phage therapy for pathogens causing urinary tract infections.

> "phage exposure can lead to the emergence of the L-form state"

In sum, the results of the study show that L-form switching during phage exposure presents an evasion mechanism to prevent killing and ensure survival at the population level — the complete loss of peptidoglycan and potential surface receptors such as teichoic acids prevent phage binding and thus infection. Future experiments are now needed to establish how widespread this phenomenon is and the possible roles of phage-induced L-forms in the clinical setting.

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Viral infection

Early treatment for COVID-19

Type III interferons (also termed IFNλ) are the first line of defence against upper respiratory tract infections. Administered interferons can be used as a prophylactic or therapeutic agent against viral infections. It was previously shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces the expression of type III interferons following infection, and previous studies were undertaken to establish the efficacy of exogenous pegylated IFNλ in the treatment of patients with COVID-19. Now, Reis et al. have conducted a randomized, controlled, adaptive platform trial mostly involving vaccinated adults with SARS-CoV-2 infection in Brazil and Canada to further evaluate the efficacy of a single dose of pegylated IFNλ administered within 7 days following the onset of symptoms. The authors reported that the incidence of hospitalization or an emergency department visit due to COVID-19 was significantly lower among patients who received a single dose of pegylated IFNλ than among those who received placebo. This effect was consistent across SARS-CoV-2 variants and was independent of the vaccination status of the participants. The results support the notion that a single-dose regimen of pegylated IFNλ could be introduced as an early outpatient treatment option.

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Original article: Reis, G. et al. Early treatment with pegylated interferon lambda for Covid-19. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2209760 (2023)