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When challenged with a pathogen, the host tries to maintain cellular integrity by mounting an immune response to restrict pathogen growth while repairing any cellular damage. A new paper in *Cell Host & Microbe* reveals that the insect pathogen *Pseudomonas entomophila* prevents both of these processes by arresting protein synthesis in the gut of its *Drosophila melanogaster* host.

Although oral infection with *P. entomophila* stimulates local and systemic expression of antimicrobial peptide genes, the infection is lethal, suggesting that there is a block in the immune response to infection and that this block occurs downstream of transcription. In addition, *P. entomophila* infection damages the gut epithelium, and there is a lack of epithelial renewal, indicating that the cellular repair pathways in the gut might also be inhibited. Bruno Lemaitre, Nicolas Buchon and colleagues began investigating these phenomena using transgenic *D. melanogaster* expressing a *Diptericin–lacZ* reporter gene. Although this reporter gene was transcribed in *P. entomophila*-infected *D. melanogaster*, there was a block in LacZ protein expression, whereas this block was not detected in flies infected with the non-lethal pathogen *Erwinia carotovora* subsp. *carotovora* str. 15 (Ecc15). The uncoupling of transcription and translation was not specific for genes encoding antimicrobial peptides, as a methionine analogue incorporation assay (which measures total protein synthesis) revealed that *P. entomophila* infection induces global suppression of translation in the *D. melanogaster* gut.

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How is this block in translation achieved? In eukaryotes, cap-dependent protein synthesis is typically regulated through eukaryotic translation initiation factor 2α (eIF2α) phosphorylation, which suppresses translation. Initial western blot analysis showed that eIF2α in the *D. melanogaster* gut was phosphorylated following infection with *P. entomophila* but not Ecc15. Phosphorylation of eIF2α can be achieved by various stress-responsive kinases, including GCN2. The authors again used the *Diptericin–lacZ* reporter construct to analyse translational activity and found that RNAi-mediated inactivation of GCN2 in the *D. melanogaster* gut removed the translational block. Another key component of protein synthesis in eukaryotes is the translational repressor eIF4E-binding protein 1 (4E-BP1), which is targeted by the kinase TOR (target of rapamycin); when TOR is inactive, 4E-BP1 is hypophosphorylated, and cap-dependent translation is inhibited. The authors found that at 16 hours after infection *P. entomophila* causes a reduction in 4E-BP1 phosphorylation and that this involves inhibition of TOR kinase activity. So, the translational arrest induced by *P. entomophila* infection involves activation of the kinase GCN2 and inhibition of the TOR pathway. Examination of epithelial turnover in *D. melan ogaster* in which GCN2 had been inactivated by RNAi also revealed that this translational arrest does inhibit epithelial renewal.

Translation inhibition is connected to oxidative stress, and *P. entomophila* infection is known to induce a strong oxidative burst in the host. In *D. melanogaster* fed *P. entomophila* in conjunction with antioxidants, the inhibition of translation was alleviated; conversely, in *D. melanogaster* fed Ecc15 plus paraquat (a potent inducer of reactive oxygen species), translation was inhibited. Thus, the translational arrest that follows *P. entomophila* infection is dependent on the host-generated oxidative burst. Finally, the experiments also revealed a role for monalysin, a *P. entomophila* pore-forming toxin that belongs to the aerolysin family, although further work is required to elucidate the precise mechanisms involved.

Inhibiting host translation is a strategy that is most often associated with viruses. However, over the past 12 months, the protozoan parasite *Leishmania major* and bacterial pathogens including *Legionella pneumophila* and now *P. entomophila* have also been shown to target translation. The authors conclude with the suggestion that "inhibition of protein synthesis could play a central role in host-pathogen interactions".

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ORIGINAL RESEARCH PAPER Chakrabarti, S. *et al.* Infection-induced host translational blockage inhibits immune responses and epithelial renewal in the *Drosophila* gut. *Cell Host Microbe* **12**, 60–70 (2012)