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BACTERIAL PATHOGENESIS

Bacteriophages, the glue that holds bacteria together

> a high bacterial load at the site of colonization may be promoted by bacteriophage-driven aggregation

Neisseria meningitidis, a commensal bacterium that colonizes the mucosa of the nasopharynx, can invade the bloodstream and cross the blood–brain barrier to cause septicaemia and meningitis. Previous comparative genomic analyses of *N. meningitidis* strains that differ in their potential to cause invasive infections found that the meningococcal disease-associated prophage (MDAΦ), a bacteriophage that is integrated into the genome of some *N. meningitidis* strains, was associated with invasive infections, but how this bacteriophage promoted invasion was unknown. In a recent study, Bille, Meyer *et al.* provide a mechanism by which MDAΦ may enhance the translocation of *N. meningitidis* into the bloodstream.

First, the authors investigated whether MDAΦ contributes to increased virulence during sepsis by comparing the growth of wild-type *N. meningitidis* strains and strains that lacked the prophage (ΔMDAΦ) in the bloodstream of humanized mice. The authors did not observe any significant differences in growth between the two strains during the course of infection or in competition experiments. Both of the strains were also equally resistant to complement in human serum, which led them to conclude that the MDAΦ prophage does not contribute to the virulence of *N. meningitidis* during sepsis.

The authors hypothesized that MDAΦ contributes to pathogenesis in the nasopharynx by enhancing translocation of the bacterium into the bloodstream. To investigate this, the biomass of fluorescently labelled *N. meningitidis* cells and isogenic ΔMDAΦ cells that adhered to a monolayer of pharyngeal tumour cells was measured and compared. Although the knockout strain did not differ in growth rate compared with the parental strain, the biomass of the knockout strain that covered the cell monolayers was reduced by up to 50%, which suggests that MDAΦ enhances the colonization of *N. meningitidis* on epithelial cells. Epithelial colonization was reliant on the production of bacteriophage particles, as strains in which two MDAΦ genes (genes required for the production of bacteriophage particles) were deleted colonized monolayers to similar levels as the ΔMDAΦ strain. Adding exogenous bacteriophages to ΔMDAΦ cells was not sufficient to promote colonization, which indicates that this phenotype is dependent on the intracellular production of bacteriophages. Remarkably, the effect on colonization was specific to epithelial cells, as MDAΦ did not enhance bacterial colonization on endothelial cells that line the interior surface of blood vessels.

As type IV pili are known to promote the colonization of *N. meningitidis* and the formation of bacterial aggregates, the authors investigated the relationship between pili and MDAΦ in the biomass of colonizing bacteria. Immunofluorescence experiments revealed that bacterial cells that strongly adhered to epithelial cells expressed type IV pili on the surface but did not produce MDAΦ particles; by contrast, bacterial cells in the upper part of the biomass produced MDAΦ but not pili. The lack of appendages would suggest that these cells do not adhere; however, using immunogold electron microscopy, the authors were able to show that bacteriophages associate with the cell wall of bacteria and form bacteriophage–bacteriophage interactions that result in the formation of bundles of bacteriophage filaments and thus increase the density of bacteria.

In summary, the data suggest that a high bacterial load at the site of colonization may be promoted by bacteriophage-driven aggregation, which, in turn, increases the probability of bacterial translocation into the bloodstream and possibly enhanced dissemination in the general population.

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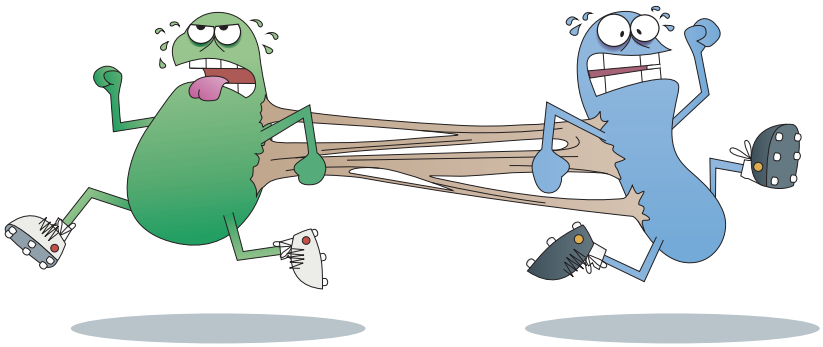

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