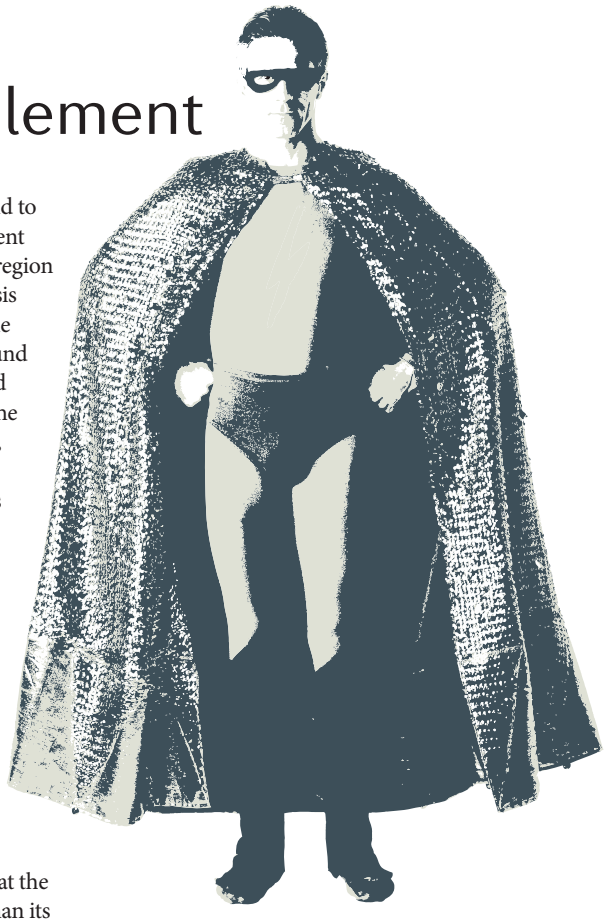
Nature Reviews Microbiology | AOP, published online 7 July 2008; doi:10.1038/nrmicro1953

IMMUNE EVASION

Cloaked against complement



The *Neisseria meningitidis* serogroup C conjugate vaccine (MCC) has proven extremely effective in reducing the incidence of meningococcal septicaemia and meningitis. The widespread use of this vaccine might, however, select for the emergence of a new virulent strain. In a study recently published in the *Journal of Experimental Medicine*, Uria *et al.* showed that strains of *N. meningitidis* that produce a larger capsule can survive in the presence of the antisera that are elicted by the MCC vaccine by avoiding complement-mediated lysis.

When *N. meningitidis*, an opportunistic pathogen that is a ubiquitous commensal of the upper respiratory tract, enters the bloodstream, bacterial replication can result in septicaemia, and if bloodborne bacteria spread to the cerebrospinal fluid an often-fatal meningitis can ensue. To probe whether variant strains can overcome the serum antibodies that are produced by vaccination and emerge to cause disease, Uria *et al.* isolated and characterized disease-causing strains that resisted killing by serum bactericidal antibodies.

Using sera from vaccinated individuals, Uria *et al.* screened 109 *N. meningitidis* strains that had caused disease in unvaccinated Spanish individuals and identified 3 strains (R1–R3) that were resistant to killing by bactericidal antibodies. *N. meningitidis* can evade complement by producing a capsule, so Uria *et al.* focused on capsule formation in these resistant strains. They showed that an R3 mutant that lacked capsule was more sensitive to antibody-mediated killing than the resistant progenitor. Resistant strains were found to harbour an insertion element (IS*1301*) in the intergenic region between the *cps* biosynthesis and export genes. The same insertion sequence was found in an identical position and orientation in all three of the resistant strains. Moreover, when a tagged version of the insertion sequence was transferred into a sensitive strain, the strain became resistant to antibody-mediated killing, proving that acquisition of this insertion sequence alone was sufficient to modulate resistance to serum antibodies.

Antisera elicted by resistant strains killed sensitive, but not resistant, strains, which indicated that the capsule structure, rather than its antigenicity, might have been altered. Surprisingly, cryo-transmission electron microscopy and NMR revealed that resistant strains had larger capsules than sensitive strains, but that the capsule polysaccharide was unchanged. Analysis of gene transcripts confirmed that *cps* genes were upregulated in resistant mutants. How does a thicker capsule, which contains more capsule antigen, resist antibody-mediated killing? After incubation with antisera, it was revealed that resistant strains had fewer complement factors deposited on their surfaces, which the authors attributed to inhibition of the alternative pathway of complement activation. Strikingly, strains R1–R3 also resisted killing by vaccine-elicted antisera against the unrelated *N. meningitidis* outer-membrane protein PorA, which led the authors to propose that increased capsule production and inhibition of the alternative pathway of complement activation could constitute a general mechanism of resistance to bactericidal antibodies.

Future studies will address how insertion of IS*1310* increases *cps* gene expression and whether IS*1310* has spread to other meningococcal strains.

Susan Jones

ORIGINAL RESEARCH PAPER Uria, M. J. *et al.* A generic mechanism for enhanced resistance against bactericidal antibodies in *Neisseria meningitidis*. *J. Exp. Med.* **205**, 1423–1434 (2008)