MiSAC matters
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Pathogenic bacteria: wolves in sheep's clothing

Christoph M. Tang

The world is full of microbes. Bacteria are the most populous free-living organisms on planet earth, yet they often go unnoticed. Most of them live in the environment, but our bodies are home to the densest communities of bacteria on the planet. Our skin, mouths and intestines teem with trillions of bacteria, with which we have enjoyed a long and often mutually beneficial relationship.

However, a subset of these unicellular, microscopic organisms - the pathogens - have plagued humans for millennia. Many of these bacterial pathogens have specific properties that make them especially adept at causing disease. For example, they can acquire nutrients from different habitats in the human body allowing them to grow in places where they are not wanted; they can bind to specific tissues protecting them from elimination, and they have weapons that enable them to cause damage.

To defend ourselves, we have evolved a sophisticated immune system to recognise, respond to, and kill invading pathogens. Our immune system is in a constant state of vigilance, and can call upon an array of weapons. These include phagocytic cells (from the Greek 'phagos' to eat) which engulf and destroy bacteria, and antibodies which specifically recognise molecules on the surface of bacteria, bind them, and target them for removal either by sending them to phagocytic cells or by recruiting antimicrobial proteins directly to the pathogen surface. In return, it appears that each bacterial species has evolved its own special tricks to escape the immune system enabling them to persist in our bodies and inflict harm on us. This is especially well illustrated by the important human pathogen, *Neisseria meningitidis* (**Figure 1**).

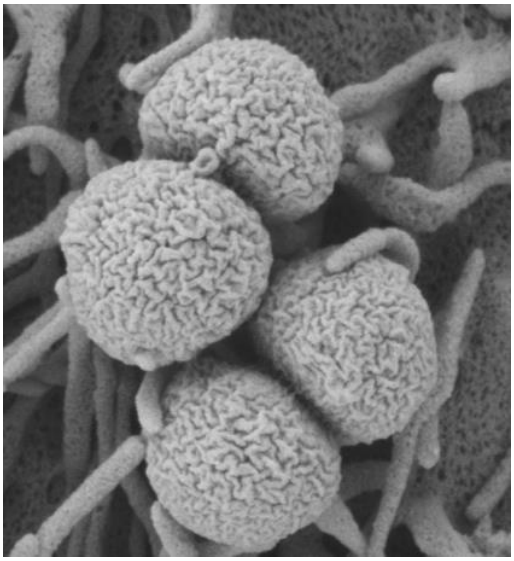

Figure 1. Scanning Electron Microscopy image of *Neisseria meningitidis* attached to a human cell. The bacteria are usually in pairs (diplococci). They bind to cell membranes using structures known as Type four pili and become enmeshed with cell membrane protrusions. Image credit R. Custodio and E. Johnson, SWDSP, Oxford.

N. meningitidis (the meningococcus) will be familiar to many as the cause of bacterial meningitis, a feared infection that can strike children and young adults rapidly. The meningococcus is found in the upper airways of healthy individuals but can spread into the bloodstream, where it can replicate quickly to very high levels (up to 10^{12} bacteria in an affected individual) and liberate toxins, mainly by shedding parts of its cell membrane. It is these accumulated toxins that are responsible for the severity of meningococcal infection.

How does *N. meningitidis* avoid immune surveillance and attack? Examples of some of the immune evasion strategies employed by this bacterium are shown in **Figure 2**. The meningococcus produces a sugar coat called a capsule. This shields some of the bacterial surface molecules from recognition and binding by antibodies. One important way antibodies can destroy microbes to which they are bound is by localising components of the complement system to the microbe's surface. The complement system is a key part of our immune system; it is a collection of proteins that work together to kill invading pathogens by making holes (pores) in their membranes. However, antibodies bound to the meningococcal capsule are away from the bacterial surface, making it difficult for the complement system to be active.

In addition, in some strains, the capsule acts as molecular camouflage. The structure of the capsule of meningitis B, the leading cause of meningococcal disease in the UK, is identical to a molecule found in the human body. As we develop, our immune system learns to ignore molecules on our own cells through a process called tolerance. This is to avoid our immune system attacking 'self' antigens. Thus, by synthesising and covering itself in a mimic of a human molecule, meningitis B bacteria can pass under the radar of immune surveillance.

The meningococcus has another trick. It can attract our own molecules that switch off immune responses and bind them to its own surface. For example, Factor H (fH) is a human molecule that turns off the complement system. *N. meningitdis* has a protein on its surface that binds human factor H, called fHbp (Factor H binding protein). The bound fH not only acts as a camouflage but also helps the bacterium defend itself against complement-mediated killing.

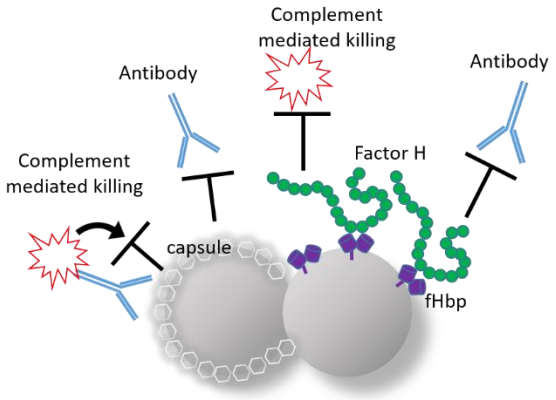

Figure 2. Examples of immune evasion strategies of *Neisseria meningitidis.*

Is it possible to combat such a devious pathogen as *N. meningitidis*? Thankfully yes. By targeting the very molecules on the bacterial surface that confuse the immune system, we have been able to generate a series of vaccines against most strains of *N. meningitidis*. Current research aims to improve these vaccines and ensure that they are available to all those who need them, providing hope that we will one day be able to eliminate this wolf in sheep's clothing.

AUTHOR PROFILE

Christoph Tang is Professor of Cellular Pathology at the Sir William Dunn School of Pathology and Fellow of Exeter College at the University of Oxford. He qualified in Medicine in Liverpool and was awarded a PhD at the Royal Postgraduate Medical School. Professor Tang leads the Bacterial Pathogenesis Group at the Dunn School. His group studies the fundamental mechanisms that human bacterial pathogens use to adapt to microenvironments and applies this understanding to vaccine development.