Scientists unlock the secrets of C. difficile's protective shell

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C. difficile infections are commonly caught in hospitals and can be fatal for patients with weakened immune systems.

The detailed structure of a protective 'jacket' that surrounds cells of the *Clostridium difficile* superbug, and which helps the dangerous pathogen stick to human host cells and tissues, is revealed in part in the 1 March issue of *Molecular Microbiology*.

Scientists hope that unravelling the secrets of this protective layer's molecular structure might reveal possible targets for new drugs to treat *C. difficile* infections.

The 'jacket' is a surface layer, or 'S-layer', made of two different

proteins, with half a million of each covering every *C. difficile* cell. The S-layer is believed to help *C. difficile* cells colonise the human gut, where they release sickness-causing toxins.

The new research was led by scientists from Imperial College London, funded by the European Union Seventh Framework Programme and the Medical Research Council. They used X-ray crystallography techniques to produce the first ever high-resolution images of the structure of LMW-SLP, one of the two proteins that make up *C. difficile*'s S-layer. The team also produced lower resolution images of the two S-layer proteins linked together into the 'building block' which makes up the layer over all.

Understanding exactly how the S-layer is formed, and how it works, could reveal new ways of fighting *C. difficile* infections, because without the S-layer, the pathogen cells cannot function, and die. The team behind the new study say that the long term aim is to use this structural knowledge to design a drug that will target the S-layer, leading to cell death, and the defeat of infection.

In addition, the research team behind today's study say that understanding the S-layer could be the key to developing a preventative vaccine for *C. difficile*. This is because the protein outer-shell of the pathogen is 'seen' and recognised as dangerous by the human immune system, triggering an immune response. This means that in the future, if the structure of these proteins is fully understood, they could one day be administered as a vaccine to pre-prepare the body to fight infection.

Professor Neil Fairweather, from Imperial College London's Department of Life Sciences, explains that his group's findings are an important in developing new treatments for *C. difficile* infections:

"This is the first time anyone has gained detailed information about the

molecular structure of *C. difficile*'s protective 'jacket', because analysing the two protein components is painstakingly difficult work. We're confident that continuing this work to better understand the formation of this protective coat and its exact function will reveal new targets for effective drugs to beat this dangerous pathogen, and could even lead to an effective vaccine."

The team's next steps will be to produce a high resolution image of the structure of the whole S-layer, and to further analyse the areas where the two proteins link together in the layer.

Clostridium difficile is a bacterial pathogen that is present naturally in the gut of about three percent of adults, and 66 percent of children. It does not cause problems in healthy people, but antibiotics used to treat other health problems can sweep away the 'good' bacteria in the gut, leaving *C. difficile* free to multiply dramatically causing severe diarrhoea and inflammation.

Because *C. difficile* is usually caused by taking antibiotics, most cases happen in hospitals or care homes. *C. difficile* is naturally resistant to lots of antibiotic treatments, and can recur once contracted. There are now more cases of *C. difficile* than MRSA in the UK, and in 2007 over 8000 deaths were associated with *C. difficile*.

More information: 'Structural insights into the molecular organization of the S-layer from Clostridium difficile', *Molecular Microbiology*, published online 29 January 2009.

Source: Imperial College London