Scientists re-establish dual toxin importance in C.diff

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(PhysOrg.com) -- Scientists at The University of Nottingham have re-established the lethal role of a toxin in the leading healthcare associated infection Clostridium difficile.

In a paper published in the prestigious journal *Nature*, the Nottingham team has proven that Toxin A -- one of two known disease causing factors in Clostridium difficile -- can kill on its own without working in tandem with the other associated virulence factor, Toxin B.

The results contradict those published last year in the same journal which suggested that only Toxin B was essential, and that Toxin A alone was not capable of causing the disease.

The new study has major implications for the development of new vaccines, drugs and diagnostic equipment for the prevention, treatment and detection of Clostridium difficile.

Professor Nigel Minton, head of the Clostridia Research Group in the School of Molecular Medical Sciences, University of Nottingham, said: “For many years it has been assumed by the scientific community that Toxin A and Toxin B worked hand-in-hand to cause fatalities by Clostridium difficile, although historically Toxin A was believed to be the most deadly factor.

“Last year a study was published that turned this on its head and appeared to prove that Clostridium difficile strains producing Toxin A

alone were innocuous, and that only Toxin B was essential for disease. This had significant implications — already we have seen a move within the diagnostics industry to develop new methods of diagnosing Clostridium difficile that rely entirely on targeting Toxin B.

“Our research, which has recreated that original experiment, but resulted in a different outcome —we were able to show in the laboratory that the mutated Clostridium difficile strain in which produced only Toxin A was deadly.”

Clostridium difficile infection is the most significant cause of hospital-acquired diarrhoea and is seven times more deadly than MRSA. The bacterium is present in the gut of up to three per cent of healthy adults and 66 per cent of infants. Usually it is kept in check by the healthy balance of bacteria in the gut but when this is disturbed by certain antibiotics, Clostridium difficile can multiply rapidly and produce toxins that cause illness and death. The disease is spread through spores, usually from poor hygiene.

Last year, a paper entitled ‘Toxin B is essential for the virulence of Clostridium difficile’ co-authored by a team led by Dr Dena Lyras at the Australian Bacterial Pathogenesis Program was published in Nature. It caused a stir among the scientific community by presenting evidence that the production of Toxin A alone by Clostridium difficile did not cause disease.

The latest work by Professor Minton’s¬ team, led by Dr Sarah Kuehne and Dr Stephen Cartman and funded by the Medical Research Council (MRC), recreated their experiment by using strains of Clostridium difficile from the same original source as the earlier study.

By using a gene knock-out system to permanently inactivate the toxin genes, they discovered that Clostridium difficile producing either one or

both of the toxins was deadly both in vitro and in vivo.

Professor Minton added: “Our results seemed to bear out some of the findings of the earlier study, in that the mutant strain producing Toxin B alone causes more severe disease. However, we found the mutant making only Toxin A will cause fatalities. As a result, we strongly believe that new strategies to improve the management of this disease should target both bacterial toxins.”

The Clostridia Research Group has developed a unique technology called the ClosTron, a gene knock-out technique that allows researchers to create extremely stable, permanent mutants of Clostridium difficile, including hyper-virulent strains. The group is working with pharmaceutical companies to develop new vaccines to protect against the disease and collaborating with industry on new diagnostic tools that will allow doctors to rapidly detect the bug at the patient’s bedside.

Other areas of work are focusing on understanding how spores change into cells to spread disease to find new ways of eradicating the illness, looking at natural viral predators as a method of protecting against infection and using advanced genetic tools to identify weaknesses in the bug that could be targeted with chemical drugs.

More information: The Nottingham paper ‘The role of toxin A and toxin B in Clostridium difficile infection’ is co-authored by Sarah A Kuehne, Stephen T Cartman, John T Heap, Michelle L Kelly, Alan Cockayne and Nigel P Minton.

Provided by University of Nottingham