Mycoplasma genitalium's cell adhesion mechanism revealed

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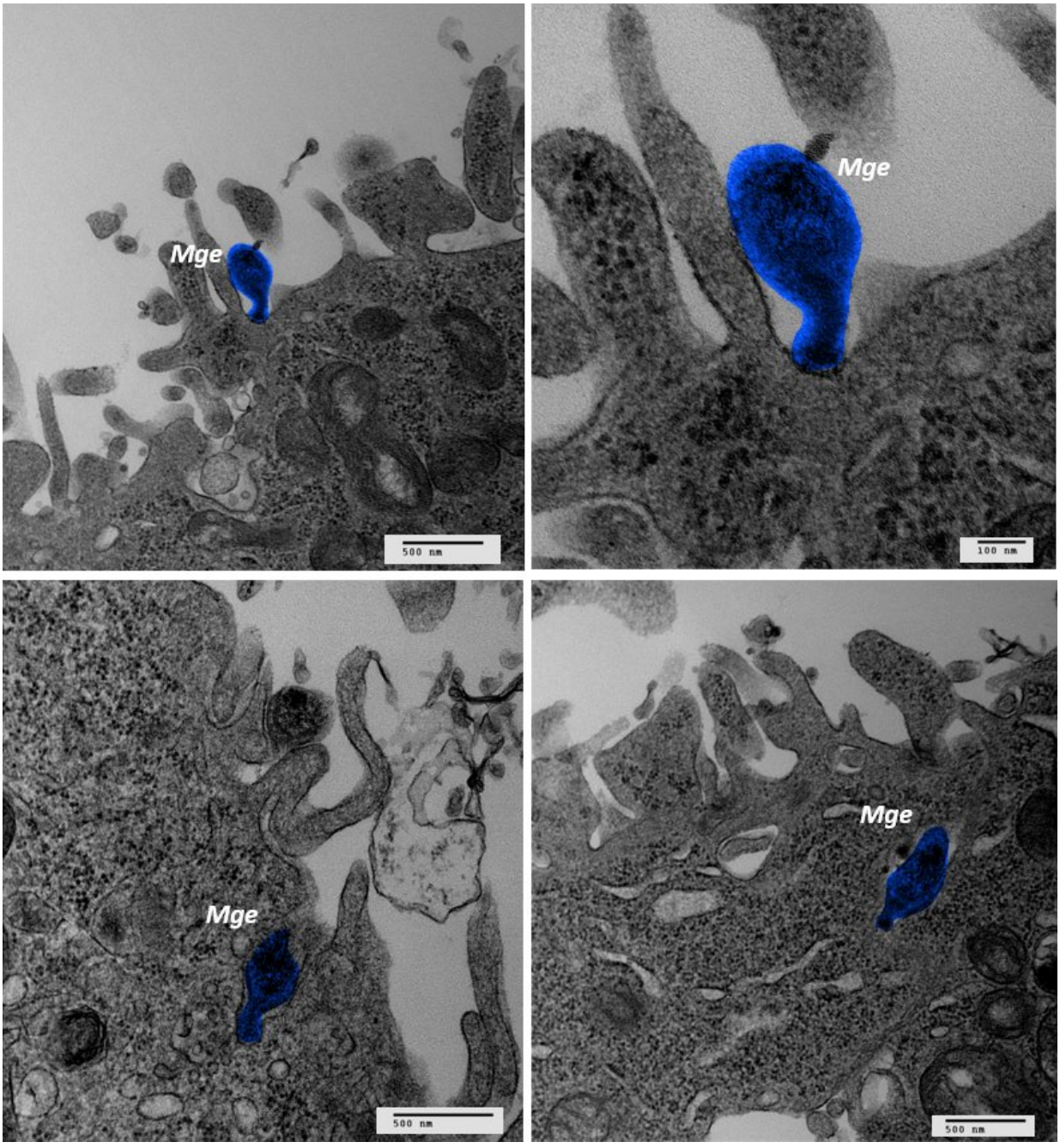

Transmission electron microscopy images in which the bacterium Mycoplasma genitalium (Mgen) can be observed adhered to the surface of a human cell (top images) and penetrating the interior of the cells (bottom images). Images have been edited to facilitate the identification of the mycoplasma (in blue). Credit: Universitat Autònoma de Barcelona

Researchers from the Molecular Biology Institute of Barcelona (IBMB-CSIC) and the Institute of Biotechnology and Biomedicine (IBB-UAB) have discovered the mechanism by which the bacterium Mycoplasma genitalium (Mgen) adheres to human cells. This adhesion is essential for the onset of bacterial infection and subsequent disease development.

The study, published in the journal *Nature Communications*, was led by Ignacio Fita, research lecturer of the Structural Biology Unit at the IBMB-CSIC, and Oscar Quijada and Jaume Piñol, researchers from the Molecular Biology Lab, IBB-UAB. The first author of the work is David Aparicio, postdoctoral researcher at the IBMB-CSIC.

Mgen is an emerging pathogen responsible for several infectious genitourinary disorders. In men, it is the most common cause of urethritis (15-20%) while in women, it has been associated with cervicitis, pelvic inflammatory disease (PID), premature birth and spontaneous abortions.

So far, it was known that adherence to the genitourinary tract was possible thanks to proteins known as adhesins, which recognise specific cell surface receptors. In the case of Mgen, these cell receptors are generically known as sialic acids. Other important pathogens such as the influenza virus also use sialic acids to adhere to cells.

In this study, IBMB-CSIC researchers determined the three-dimensional structure of the Mgen's P110 adhesins interacting with these cell receptors.

"We made a protein crystal of the P110 adhesin bound to sialic acids and used X-rays to determine the exact position of the atoms within the protein, and we were able to decipher the three-dimensional structure," explains IBMB researcher David Aparicio. The experiments were conducted at the Xaloc light line of ALBA Synchrotron located in Cerdanyola del Vallès using X-ray crystallography.

At the same time, IBB-UAB scientists conducted in vivo studies with human cells and demonstrated that mutations in specific sites of the P110 protein prevent the adherence of Mgen. These results were fundamental to confirm the information obtained from the three-dimensional structure.

The results allow a better understanding of the molecular bases of the Mgen interaction with human cells. "On the one hand, we have obtained key information on the process of colonisation, that is how the pathogen comes into contact with the host cells. On the other hand, it allows us to develop alternative drugs capable of blocking Mgen's cell adhesion, such as molecules mimicking the human cell receptors, or stimulating the formation of antibodies which can inhibit the function of these adhesins," explains IBB research Oscar Quijada.

The research has led to an international patent application and a new collaboration with the Microbiology Department and research group from the Vall d"Hebron Campus with the aim of fighting against the emergence of new resistances.

Antibiotic Resistance

Currently, Mgen infections are as frequent as gonorrhoea infections, one of the most common sexually transmitted diseases. In addition, Mgen is becoming a superbug capable of resisting all available antibiotics, which will soon leave humans with no alternative therapies to fight infections. Understanding the mechanism behind the infection can help to define new treatments which can fight it.

Antibiotic resistance is rising to dangerously high levels. Through genetic changes, many bacteria have developed the capacity to become resistant to antibiotics and continue to reproduce themselves. Although this is a natural process, inadequate use and abuse of these drugs are accelerating the process.

Given that Mgen is becoming resistant to all available antibiotics, finding an alternative therapeutic strategy is of utmost importance. The results obtained are essential for the design of new drugs thanks to the ability to define adhesion at molecular level.

More information: David Aparicio et al. Mycoplasma genitalium adhesin P110 binds sialic-acid human receptors, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06963-y

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