Bacterium Salmonella enterica regulates virulence according to iron levels found in its surroundings

May 10 2011

Salmonella enterica, one of the main causes of gastrointestinal infections, modulates its virulence gene expression, adapting it to each stage of the infection process, depending on the free iron concentration found in the intestinal epithelium of its host. Researchers at Universitat Autònoma de Barcelona (UAB) have demonstrated for the first time that the pathogen activates these genes through the Fur protein, which acts as a sensor of iron levels in its surroundings.

The research, published online in the journal *PLoS ONE* and entitled "Fur activates the expression of *Salmonella enterica* pathogenicity island 1 by directly interacting with the hilD operator in vivo and in vitro", was carried out by the Molecular Microbiology Group of the UAB Department of Genetics and Microbiology and coordinated by Dr Jordi Barbé. Dr Juan Carlos Alonso from the National Biotechnology Centre also collaborated in the research group.

Iron is an essential part of the development of almost all living organisms. This is why all organisms have developed an iron uptake system which guarantees that they can acquire it from their external environment. However, too much iron in the cell interior can have harmful effects and organisms have systems to control this as well.

In vertebrates, this control produces a first defence barrier known as nutritional immunity which limits the amount of free iron found in

biological fluids and prevents the development of pathogens. Only the upper intestinal track, given its anaerobic condition, presents appreciable levels of free iron. In the majority of gram-negative bacteria, such as *Salmonella enterica*, the control of iron levels is carried out by the Fur protein (Ferric Uptake Regulator), which interacts with the DNA and adjusts the production of uptake and storage systems of this element to the cell's cytoplasm.

Salmonella enterica is one of the most common bacterial pathogens associated with food-borne illnesses and is responsible for a number of diseases, from gastroenteritis to systemic infections affecting a wide variety of animals, including humans. During the first stages of infection, the bacterium enters the host through the intestinal epithelium thanks to the presence of a complex system of proteins called T3SS. The activation of T3SS however requires a large amount of energy and therefore depends on many systems to control and make sure its expression is produced just at the right moment.

The study published by UAB researchers indicates that one of the external signals controlling T3SS activation is the level of free iron of the host and that this control is carried out by the Fur protein. Thus, thanks to the Fur protein, when the bacterium detects that levels are high it interacts with its DNA and activates T3SS expression which allows it to invade the epithelium. Once it penetrates the epithelial barrier, however, the levels of free iron reduce drastically due to all of the iron secretion systems the host has at its disposal. In this case T3SS remains silent and thus avoids an unnecessary expenditure of energy.

The study demonstrates for the first time that Fur not only acts as an iron level sensor and regulator of this element in the cell's interior, but also helps the pathogen detect its location during the infection process, acting as a direct activator for the invasion. The research reinforces the idea that Fur is capable of modulating gene expression, adapting it to the

needs of each stage of the infection.

The results obtained demonstrate that delving deeper into the study at molecular level of the interactions between host - pathogen in relation to iron must lead in the future to the development of new strategies in the design of vaccines, as well as discover new targets for antibacterial action to fight against infectious diseases. In fact, the Molecular Microbiology Group of the UAB Department of Genetics and Microbiology has studied for years bacterial mechanisms of divalent cation uptake and its control systems. This line of research has given way to the publication of several scientific articles in prestigious journals, and has led to the patenting and licensing of a vaccine for the bacterial pathogen *Pasteurella multocida* based on its iron uptake methods.

Provided by Universitat Autonoma de Barcelona

Citation: Bacterium Salmonella enterica regulates virulence according to iron levels found in its surroundings (2011, May 10) retrieved 20 April 2024 from https://phys.org/news/2011-05-bacterium-salmonella-enterica-virulence-iron.html

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