Discovery of how a gene that regulates factors involved in bacteria pathogenicity acts

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In a piece of work carried out by the Carbohydrate Metabolism Research Team of the Institute of Agrobiotechnology (a centre jointly owned by the NUP/UPNA-Public University of Navarre, the Spanish National Scientific Research Council-CSIC, and the Government of Navarre), the discovery has been made of the way in which the glgS gene (now renamed as the "surface composition regulator", scoR) acts in bacteria and how the mechanisms involved in bacterial infection can be altered by manipulating this gene, which indirectly affects glycogen production. The finding has been protected through the application for a patent and the exploiting of it is now pending a response from institutions or companies prepared to develop it. Thanks to this discovery, the researchers received the top prize in the 9th International Medical Congress in the category of "Genetics and Molecular Biology" held in Warsaw recently.

As Javier Pozueta, director of the Carbohydrate Metabolism Research Team that carried out the work, explained, "We can say that we may have found an additional way of combating bacterial infections and contamination by encouraging the formation of glycogen in bacteria. Now we know that by altering the glycogen producing machinery, we can in turn alter the capacity of the bacteria to move, stick to a cell or to the surfaces of tubes, catheters, etc."

The 9th International Medical Congress held in Warsaw from 9 to 12

May drew 1,400 researchers from all over the world and 700 pieces of work were presented. The researcher Mehdi Rahimpour attended on behalf of the research team of the Institute of Agrobiotechnology (IdAB). Together with Dr Manuel Montero, he was the main architect of the winning piece of research. The research has recently been published in the *Biochemical Journal* and is based on the PhD thesis that Rahimpour read last February at the NUP/UPNA-Public University of Navarre and for which he was awarded the maximum grade. This researcher, who is of Iranian origin, has studied the mechanism of the action of the glgS gene in *Escherichia coli* bacteria and in various *Salmonella* species, which in certain cases can cause diseases and acute symptoms in humans.

Glycogen is a reserve material that bacteria can avail themselves of. The team's researchers led by Prof Pozueta had previously identified and characterised the genes directly involved in glycogen production in *E. coli*. Contrary to what was believed, they were able to prove that the glgS gene did not play a part in this process. So what was it for? This was the subject of Mehdi Rahimpour's PhD thesis.

To immobilise bacteria

To understand the way in which the glgS gene acts, you have to bear in mind the structure of bacteria. As the researcher points out, bacteria have something akin to oars or arms (flagella) that are used for moving; they also have some appendices called fimbriae which enable them to stick or adhere to the cells which host them; and a protective capsule or shield made up of polysaccharides. To create all these elements and to enable the bacteria to move, they need energy (provided by the ATP molecule) and sugar. "GlgS acts as a brake," points out Rahimpour. We realised that by altering the expression of the glgS, the creation of these structures is altered and, indirectly, the production of glycogen because it also needs sugar and energy. In circumstances in which the creation of

flagella and components of the capsule is boosted, the bacteria consume large quantities of energy to move as well as sugars, so they will not have sufficient raw material available to produce glycogen. And vice versa: in circumstances in which the creation of flagella, fimbriae and components of the capsule is repressed, the bacteria will lose their capacity to move and become adhered to surfaces, and the surplus of energy and sugar will be devoted to producing glycogen.

In short, the research team has discovered that there is an inverse correlation between glycogen production and the production of structures involved in bacterial pathogenicity. "In our case we found that the alteration in the expression of glgS, which is only present in the group of enterobacteria (*E. coli*, species of the *Salmonella* genus, *Yersinia pestis*, etc.), has an effect on the production of structures involved in bacterial pathogenicity which, indirectly, affects the capacity to produce glycol gen. "The finding may provide clues to future strategies for combating bacterial infections by modulating glycogen production, a substance that many bacteria of all kinds can accumulate.

Resistance to antibiotics

In a world in which bacteria strains are becoming increasingly resistant to antibiotics, the researchers are sending an optimistic message: "by encouraging glycogen production in bacteria we may be able to hamper the creation of these structures and cause the bacteria to stop moving and proliferate in the medium and/or stick to surfaces and therefore would stop being pathogens."

The research team has protected the discovery relating to this procedure to try and combat bacterial infections. The next step is to find substances that boost glycogen production in bacteria. "We have incorporated a gene into the pathogenic bacteria that causes them to produce large quantities of glycogen; that way we can stop them "running" and reduce

their pathogenicity. But we want to go further: we want to find substances that once applied to wounds or surfaces or once administered to patients with bacterial diseases, will encourage the accumulation of bacterial glycogen and the resulting reduction in the capacity of the bacteria to become adhered, invade, proliferate."

More information: Rahimpour, M., Montero, M., Almagro, G., Viale, A.M., Sevilla, A., Cánovas, M., Muñoz, F.J., Baroja-Fernández, E., Bahaji, A., Eydallin, G., Dose, H., Takeuchi, R., Mori, H., Pozueta-Romero, J. GlgS, previously described as a glycogen synthesis control protein, negatively regulates motility and biofilm formation in Escherichia coli. *Biochem. J.* 452: 559-573. (2013) www.biochemj.org/bj/452/bj4520559add.htm

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