It takes two to infect: Structural biologists shed light on mechanism of invasion protein

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Bacteria are quite creative when infecting the human organism. They invade cells, migrate through the body, avoid an immune response and misuse processes of the host cell for their own purposes. To this end every bacterium employs its own strategy. In collaboration with a British research group, structural biologists from the Helmholtz Centre for Infection Research in Braunschweig, Germany, and the University of Bielefeld, Germany, have now elucidated one mechanism of Listeria bacteria.

Two so-called invasion proteins are crucial for infection. Each binds a specific receptor on the surface of human cells, which stimulates the host cell to take up the pathogen. Normally, these receptor molecules exert a different function, for example the regulation of cell growth and wound healing. The group's results have now been published in the current issue of the Journal of Molecular Biology.

Spoiled meat is one of the sources for *Listeria* infections leading to listeriosis. Pregnant women, newborns and immune compromised people are susceptible for a severe progression of this disease. Firstly, the pathogen breaches the intestinal barrier and thus enters the body. The key for further spreading is the invasion protein internalin B that is located on the bacterial surface. On human cells, internalin B activates a receptor molecule called "Met", thereby signaling the host cell to take up the pathogen. Inside the cell, *Listeria* uses the host cell's nutrients and is somehow sheltered from an immune response.

Until now, the researchers did not know how the bacterial invasion protein activates the human receptor. To solve this question, the structural biologists from the HZI first analysed the crystal structures of the single internalin B molecule and of its complex bound to human Met. "In X-Ray structural analysis we noticed that in protein crystals two internalin B molecules align characteristically," says Hartmut Niemann, assistant professor at the University of Bielefeld. Professor Dirk Heinz, head of the structural biologists at the HZI, explains: "This gave rise to the idea of a dimer - two congregated internalin B molecules - playing a pivotal role in the activation of the Met receptor."

Minor changes in the internalin B molecule confirmed their hypothesis: inhibiting the congregation of two internalin B molecules prevented the activation of Met. On the other hand, strengthening the interaction resulted in particularly strong receptor activation.

These results may lead to the development of new protein drugs in the future. "Met plays a major role in the body, for example during wound healing," says Heinz. "Thanks to the extraordinary ability of the internalin B dimer to strongly activate Met, therapeutics for improved wound healing may result someday."

More information: Ligand-Mediated Dimerization of the Met Receptor Tyrosine Kinase by the Bacterial Invasion Protein InlB. Davide M. Ferraris, Ermanno Gherardi, Ying Di, Dirk W. Heinz and Hartmut H. Niemann. *J Mol Biol*. 2009 Nov 6. [Epub ahead of print]. doi:10.1016/j.jmb.2009.10.074

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