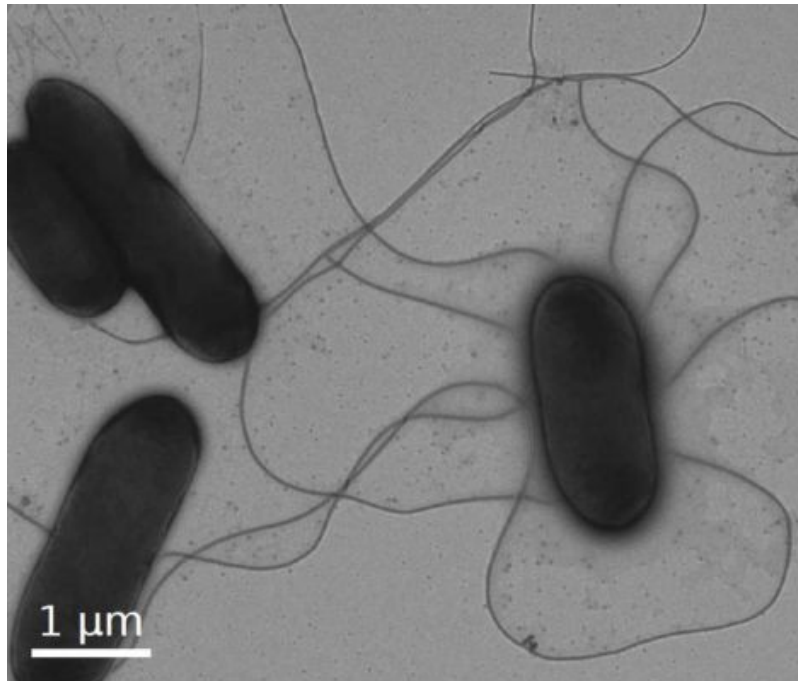


Researchers discover Achilles' heel of bacteria

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Salmonella and many other bacteria use long filaments - so-called flagella - for directed movement. (HZI/Manfred Rohde)

HZI researchers identify a protein in Salmonella that contributes to the assembly of the motility apparatus – a possible target for novel medications

Salmonellae are particularly resistant to antibiotics since they possess not only one, but two membranes that protect them from harmful substances. This makes them members of the so-called Gram-negative bacteria. Since Salmonella infections are becoming increasingly difficult to treat with antibiotics, researchers are looking for alternative agents to control these pathogens. One possible target is the motility apparatus of the bacteria: Many Gram-negative bacteria produce long filaments – so-called flagella, which they make rotate in order to move in a directed manner. In the absence of intact flagella, the bacteria cannot move towards food sources or preferred sites of infection in the host – in effect, they would no longer be infectious. Scientists of the Helmholtz Centre for Infection Research (HZI) in Braunschweig and their partners have discovered that a certain protein organises the first steps of the assembly of the flagellum. Once this protein was turned off, the bacteria were no longer able to produce flagella and would therefore be impaired in infecting a host. The scientists published their results in PLOS Biology.

In their search for food or a suitable host, many bacteria produce flagella – i.e. long filaments made up of thousands of proteins that the bacteria can use like a propeller for targeted movement. An early step in the production of a new flagellum is that various components in the cell membrane jointly form a pore from which the flagellum then grows. This pore functions as a protein channel and is the central component of a complicated, widespread protein transport system – the so-called type III secretion system. This complex system is responsible for transport of the building blocks of the flagellum and also in a needle-like structure that is found in many pathogenic bacteria: This molecular syringe is used by pathogenic bacteria to inject toxins into host cells during an infection, which makes the host cells die. Researchers

suspect that the layout of the syringe apparatus has developed from the flagellum in the course of evolution.

Both flagella and the molecular syringes are tools the bacteria need for successful infection. "If we managed to switch these tools off, the bacteria would be harmless to humans," says Dr Marc Erhardt, who is the head of the "Infection Biology of Salmonella" Young Investigator group at the HZI. Working collaboratively with cooperation partners from the University of Osnabrück, the Max-Planck-Institute for Infection Biology, the University of Tübingen and the German Center for Infection Research, Erhardt's team has studied the assembly process of flagella in detail using *Salmonella enterica* bacteria. "Many different proteins contribute to the assembly of the initial pore of the type III secretion system, but their individual role was not known," says Erhardt.

To start out, the researchers used fluorescent dyes to visualise the sites at which the different proteins reside. They noticed that one of the contributing proteins, abbreviated FliO, does not permanently reside at the anchoring of the flagellum. It moves freely in the cell membrane and migrates to the proper site only when a new pore is initiated. Then it forms a complex with the FliP protein, which is the major component of the protein channel. In one experiment, the researchers switched off the genetic information for FliO in the *Salmonellae*. The result: The bacteria were no longer able to produce functional pores and therefore no flagellum either. "Since the FliO protein itself is not a component of the pore, it appears to work more like an organiser: It helps other proteins to combine correctly for assembly of the pore," Marc Erhardt says.

In further studies, the researchers showed that the FliP protein formed complexes even without the FliO organiser. But these were disordered such that no further components could be added to the pore – and, ultimately, the complexes were discarded. Since FliO helps the individual FliP proteins form complexes correctly, it functions as a so-called chaperone. "This function of FliO was not known before," Erhardt says. It opens new targets for future agents that might be used against a whole range of pathogenic bacteria.

"An agent that prevents the formation of the pores of type III secretion systems would be a double success," Marc Erhardt says. "It would hit bacteria that produce flagella and also those that use molecular syringes." For example, *Salmonellae*, *Escherichia coli*, *Yersinia* and *Pseudomonads* are typical Gram-negative pathogens that use a syringe apparatus to infect their host. In contrast, bacteria of the genera, *Campylobacter* and *Helicobacter*, which cause intestinal and gastric diseases, do not possess molecular syringes. But they do form flagella and are therefore also a target for an alternative agent. "Another advantage of this type of agent as compared to an antibiotic would be that the pathogens stay alive and are therefore not under any pressure to develop resistance against the substance," says Erhardt. "In addition, the useful bacteria in the body would also survive."

The press release and a picture are also available on our website:

Original publication:

Florian D. Fabiani, Thibaud T. Renault, Britta Peters, Tobias Dietsche, Eric J.C. Gálvez, Alina Guse, Karen Freier, Emmanuelle Charpentier, Till Strowig, Mirita Franz-Wachtel, Boris Macek, Samuel Wagner, Michael Hensel, Marc Erhardt: A flagellum-specific chaperone facilitates assembly of the core type III export apparatus of the bacterial flagellum. *PLOS Biology*, 2017, DOI: 10.1371/journal.pbio.2002267

Helmholtz Centre for Infection Research:

Scientists at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, are engaged in the study of different mechanisms of infection and of the body's response to infection. Helping to improve the scientific community's understanding of a given bacterium's or virus' pathogenicity is key to developing effective new treatments and vaccines.

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