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Press Release

Dangerous bacterium gets cold feet

Helmholtz scientists disarm plague pathogen's next of kin

In medieval Europe, the Black Death once decimated large parts of the population. Although in Europe no longer a genuine cause for concern, in Africa, South America, and India the Bubonic plague still to this day poses a viable threat to public health. The culprit behind the pandemic is a bacterium of the genus Yersinia. Each year in Germany, the pathogen's slightly less virulent relative is responsible for causing several thousand cases of diarrheal disease – often times with serious consequences. Scientists at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, working closely with their colleagues at the Ruhr University in Bochum, Germany, have identified a mechanism that enables these bacteria to turn on their weaponry once inside the host. It turns out that Yersinia possesses a built-in molecular thermometer that jump-starts the bacterial pathogenic program at precisely 37 degrees Celsius, which corresponds to normal human body temperature.

By inducing genetic mutations in the bacterium, the researchers have successfully managed to reset the thermometer to a lower temperature setting, thereby permanently disabling the bacterial disease-causing program. The next step now is to identify a substance capable of inducing these modifications and administer it, alongside traditional antibiotics, in the form of a drug as part of the general treatment plan.

The scientists used as their model organism Yersinia pseudotuberculosis, the plague pathogen's next of kin. In Germany, this bacterium mainly infects young children - most commonly through ingestion of raw or undercooked pork. "Upon entry, the change detected in the external temperature informs the bacterium that it is now inside the human body," explains Dr. Katja Böhme of the HZI Department of Molecular Infection Biology. "Using special surface receptors, Yersinia attaches itself to cells in the small intestine, thus forcing its entry into the underlying tissue," adds her colleague Rebekka Steinmann. Once the bacterium has successfully entered into the tissue, it switches on its own pathogenic program to produce factors that shield the bacterium from attacks leveled against it by the human immune system and even kill off immune system cells. The bacterium's molecular thermometer acts as the switch. Outside the host's body the regulator YmoA blocks the bacterium's anti-immune program. At body temperature, YmoA is inhibited, which jump-starts Yersinia's anti-immune programand readies the bacterium for attack. As a part of that program the gene encoding the chief regulator in charge of a wide range of pathogenic factors called LcrF is activated.

On the road to every cellular gene product, including Yersinia's multi-purpose weapon LcrF, the first step is the polymerization of a strand of mRNA, the molecular template and mobile transcript of a gene that the cell's protein synthesizing machinery can attach to. In the case of LcrF, however, if the strict temperature requirement of 37 degrees Celsius is not met, the mRNA template folds on itself and becomes tangled up, thus becoming useless and inaccessible for protein production. The consequence being that the bacterium's disease-triggering program remains switched off.

"We managed to interfere with LcrF's thermosensory control mechanism on two levels at once," explains Böhme. "First, we artificially increased the amount of YmoA, thus inhibiting expression of the gene coding for LcrF." This alone, however, proved not nearly enough to inactivate the whole pathogen as the researchers still detected some level of LcrF activity that they were able to trace back to previously assembled LcrF mRNA molecules still present in the bacterial cell. Computer simulation of the mRNA molecules documented the existence of certain regions within its structure that are important for molecular folding and unfolding. "We next switched out individual building blocks within the LcrF template, so that the molecule was now incapable of unfolding and thus remained in a state of inactivation even at the proper temperature setting of 37 degrees. This successfully interfered with the bacterium's ability to start up its anti-immune program, thus giving the immune system a chance to eradicate it," explains Steinmann.

Prior to this research, molecular thermometers have only been described in the context of a cell's adjustment to heat stress, but not as the control mechanism behind important pathogenic genes, where they are a new discovery. "This opens up a whole new approach to fighting infections," explains Professor Petra Dersch, head of Molecular Infection Biology at HZI. "A molecule that can hold strands of LcrF mRNA together like a molecular clothespin of sorts, preventing it from unfolding and becoming active, would basically inactivate Yersinia and surrender it to the immune system. In addition, such a molecule, because it specifically targets pathogenic Yersinia, would also be an effective weapon in our fight against the Bubonic plague."

A common dilemma in the ongoing fight against infectious diseases is the constant and rapid genetic mutation of many pathogens. This explains why researchers today are always on the lookout for universal weak spots – properties or mechanisms that are central and indispensible to the pathogen's ability to cause disease in the host. "Our goal is to take out pathogens without eliminating useful bacteria in the same sweep, a common problem with current antibiotics." According to Dersch, "molecular thermometers in charge of a pathogenic bacterium's degree of virulence represent ideal targets."

Original Publication:

Böhme K, Steinmann R, Kortmann J, Seekircher S, Heroven AK, Berger E, Pisano F, Thiermann T, Wolf-Watz H, Narberhaus F, and Dersch P (2012): Concerted actions of a thermo-labile regulator and a unique intergenic RNA thermosensor control Yersinia virulence. PLoS Pathogens, February 2012, Volume 8, Issue 2, e1002518.