New research, from scientists at Imperial College London, unravels how so-called bacterial persister cells manipulate our immune cells, potentially opening new avenues to finding ways of clearing these bacterial cells from the body, and stopping recurrence of the bacterial infection. The latest findings may help explain why some people suffer from repeated bouts of an illness, despite taking antibiotics.

In the study, funded by the Medical Research Council, the Lister Institute and EMBO, the scientists, studied bacterial cells of Salmonella called persisters. Whenever bacteria such as Salmonella invade the body, many of the bugs enter a type of standby mode in response to attack by the body immune system, which means they are not killed by antibiotics. These bacteria persister cells stop replicating and can remain in this dormant, 'sleeper-cell' state for days, weeks or even months. When antibiotic treatment has been stopped, if some of these bacterial cells spring back to life, they can trigger another infection. Dr Sophie Helaine, senior author of the research from the MRC Centre for Molecular Bacteriology and Infection in Imperial's Department of Medicine explained: "Persisters are often the culprit for repeat or hard-to-treat infections. The classic scenario is a person suffers some type of illness - such as a urinary tract infection or ear infection, and takes antibiotics that stop the symptoms, only for infection to return a few weeks later."

These persisters cells are formed when bacteria are taken up by macrophages, which are human immune cells that have a key role in protecting the body against infections by engulfing bacteria and viruses. Once inside the macrophage, the persister can exist in this state in which antibiotics can't kill it for weeks, or even months. Persisters were discovered in 1944 and were thought to be dormant inactive bacteria lying low in the body, acting as time bomb for relapse. In the latest research, the scientists reveal that the persisters, while hiding in the body's immune cells, are actually able to weaken the killing ability of the macrophages.

The work was conducted in collaboration with the Vogel lab at the Helmholtz Institute for RNA-based Infection Research in Germany, a site of the Helmholtz Centre for Infection Research. Dr Peter Hill, co-author of the research explained: "Previously, it was thought the persisters are completely dormant. However the reality we revealed here is much scarier. They chip away at the defences from the inside, weakening the power of the macrophages - which are a key part of our arsenal against infection. This means that once antibiotic treatment stops, they might have created a much more favourable environment for another bout of infection, or even..."
a completely new infection from another bacteria or virus."

Although scientists, studied Salmonella infection of mouse macrophages in this research, many types of bacteria that commonly cause illness are known to form persisters in humans, including E.coli and the bacillus responsible for tuberculosis and Salmonella itself. The scientists are now investigating whether there is any way of turning the tables against the bacteria, and if they can target the mechanism by which the persisters weaken our immune cells. Dr Helaine added: "Although these findings suggest the persisters have a more profound effect on our immune defences than previously thought, they also reveal a potential bacterial weakness. Persisters are hard to treat as they are invisible to antibiotics, but it may be this mechanism of weakening our immune cells could be a vulnerability of these persisters. We could potentially target this mechanism, and more efficiently clear hard-to-treat infections."

**Original publication:**

Stapels, Daphne A. C. and Hill, Peter W. S. and Westermann, Alexander J. and Fisher, Robert A. and Thurston, Teresa L. and Saliba, Antoine-Emmanuel and Blommestein, Isabelle and Vogel, Jörg and Helaine, Sophie; "Salmonella persisters undermine host immune defenses during antibiotic treatment"; Science; 2018