Possible substitute for antibiotics to treat dangerous infections

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Research team. From left: Daniel Butler, Manoj Puthia, Theresa Rosenblad (in the back), Caterina Cafaro, Ines Ambite, Catharina Svanborg, Aftab Nadeem, Nina Filenko. Credit: Lund University

Infections continue to threaten human health. With remarkable genetic flexibility, pathogenic organisms outsmart available therapies. Fortunately, microbial versatility is matched by the host immune system, which evolves in dialogue with the microbes. Therapies that enhance the beneficial effects of the immune response represent a promising, but under-explored, therapeutic alternative to antibiotics.

A recently published paper identifies a new therapeutic target for the treatment of bacterial infections that regulates the immune response. Researchers at Lund University in Sweden have now found an "off" switch for destructive inflammation in infected kidneys that does not impair the anti-bacterial defense.

The challenge is to strengthen the good, antibacterial defence without causing tissue damage. Inflammation accompanies most infections and symptoms like fever and pain are the price to pay for an effective defense.

"Here we address how to avoid the exaggerated immune response to severe infections, which can lead to tissue destruction and even organ failure" says Manoj Puthia, researcher at Lund University, Sweden and lead author of the study.

"We knew that specific transcription factors regulate innate immune responses to bacterial infection and that the outcome of infection be beneficial or destructive, depending on how these regulators work" says Professor Catharina Svanborg. "We have also identified genetic variants in susceptible patients that support this concept. "

Using mice lacking the closely related transcription factors IRF-3 or IRF-7, we were surprised to find that IRF-3 and IRF-7 control different facets of the immune response to kidney infection and that this determines the susceptibility to acute pyelonephritis, which is a severe,

potentially life-threatening bacterial infection of the urinary tract.

In contrast to mice lacking IRF-3, which became very ill, Irf7-/- mice were protected from infection and chronic inflammation, suggesting that suppression of Irf7 might be beneficial.

"Based on these findings identifying Irf7 as an immunotherapeutic target, we used siRNA therapy to silence Irf7 and were able to demonstrate protection in susceptible mice," says Dr. Puthia.

Infections remain the major cause of the deaths worldwide, especially in developing and poorly developed areas. While antibiotics have greatly reduced illness and mortality, many pathogens have developed resistance and we are facing a global crisis.

"We propose to fight infections by learning from the innate immune system. We also need to define why the immune system is not protecting certain patients and learn to replenish these defects by boosting the "good" immune response."

More information: M. Puthia et al, IRF7 inhibition prevents destructive innate immunity—A target for nonantibiotic therapy of bacterial infections, *Science Translational Medicine* (2016). DOI: 10.1126/scitranslmed.aaf1156

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