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Press Release

A new way to inhibit inflammation

Tübingen immunologists identify enzyme regulator already targeted in cancer treatment

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Researchers at the University of Tübingen, working with colleagues in other parts of Germany and in the United States, have identified an enzyme as a kind of biological gauge regulating inflammation in the human body. Professor Alexander Weber of the Interfaculty Institute of Cell Biology says the enzyme – Bruton's tyrosine kinase or BTK – is switched on when an inflammation occurs in the body, playing a key role in the inflammation's subsequent development.

Inflammation is an important for recovery mechanism from many diseases. Yet in disorders like gout, Alzheimer's, atherosclerosis, heart attack or stroke, inflammation can also have negative effects and reinforce the damage done by the disease. Inflammation is driven – among other processes – by molecular machinery known as the inflammasome. First, immune cells are activated which release certain inflammation-promoting messenger proteins, called cytokines.

"Because there is a lot we don't know about how inflammasomes function, there are no currently available treatments to curb inflammation which would directly block this molecular machinery," Weber explains. Treatments available to date focus instead on later phases or symptoms of an inflammation. This gap in the treatment options motivated the Tübingen researchers to investigate inflammasomes more closely in the search for new ways to directly repress inflammation at the outset.

In the course of their work, Weber's team discovered the function of the BTK protein as a kind of biochemical faucet, turning on the flow of the inflammasome in human immune cells. "Bruton's tyrosine kinase has been known for many years as the genetic cause of the very rare Bruton syndrome, an immunodeficiency," says Xiao Liu, a doctoral candidate on the team. Bruton syndrome patients lack B lymphocyte white blood cells – and therefore antibodies which are normally produced by them – because BTK regulates their maturation and functions. Together with their colleagues in Bonn, Freiburg, Ulm and across the Altlantic in Baltimore, the Tübingen researchers demonstrated that BTK is a component of

inflammosomes; and that patients with a BTK mutation – Bruton syndrome – also have a defect in their inflammasome.

Weber says this might take us a step closer to a new approach to treating inflammation. Medications which inhibit the effects of BTK have been applied lately for treating a certain type of lymphoma caused by cancerous B lymphocytes. “We demonstrated that an experimental inhibition of BTK strongly reduced inflammation,” Weber says. The inflammatory cytokine Interleukin-1 is effectively blocked in immune cells of cancer patients on BTK inhibitors and in their cells the inflammasome is virtually shut down.

“This means that patients suffering the aftereffects of a stroke, heart attack, or who have gout may well benefit from the use of BTK inhibitors in the future,” Weber says, as the inflammasome appears to make the disease worse in such cases. “Our results and those provided by other colleagues are a good starting point to explore the possibilities in further experimental research and clinical studies,” the scientists say.

Publication:

Liu X, Pichulik P, Wolz OO, Dang TM, Stutz A, Page C, Delmiro Garcia M, Kraus H, Dickhöfer S, Daiber E, Münzenmayer L, Wahl S, Rieber N, Kümmerle-Deschner J, Yazdi A, Franz-Wachtel M, Macek B, Radsak M, Schulte S, Stickel JS, Hartl D, Latz E, Grimbacher B, Miller L, Brunner C, Wolz C, **Weber AN**. Human NLRP3 inflammasome activity is regulated by and therapeutically targetable via BTK. Journal of Allergy and Clinical Immunology 2017, http://dx.doi.org/10.1016/j.jaci.2017.01.017

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