Biochemists identify molecular structures which allow the immune system to tell friend from foe

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To repel an infection, the body's immune system has to tell the enemy – bacteria or other invaders – from cells of its own body. To achieve this distinction, the immune system utilizes characteristic molecular patterns displayed on the surface of each cell. One of these molecular patterns has now been identified by Dr. Bärbel Blaum and Professor Thilo Stehle of Tübingen's Interfaculty Institute of Biochemistry, working in cooperation with researchers in the UK and in the US state of Colorado. Using techniques of structural biology, the researchers identified the key determinants of a recognition process that relies chiefly on sialic acid, a glycan that is expressed on all human cells.

Human cells are covered in complex glycans – long and often branching chains of various sugars. For the self-recognition process under investigation, the chemically most important part of these glycans is sialic acid. Researchers have known since the late 1970s that sialic acid is important for regulating the complement system, part of our innate immune defense. The complement system is made up of a number of proteins circulating in the blood which set off a cascade reaction to destroy invaders. Up to now, it was not clear how sialic acid was able to hinder the complement system, keeping the complement system from attacking the body's own cells.

The Tübingen researchers identified and crystallized a complex that forms the contact point between the healthy human cell and the

complement system. Using nuclear magnetic resonance spectroscopy and X-ray structure analysis, they were able to solve the molecular structure of the complex. It is composed of a glycan containing sialic acid and two domains of the complement system regulator, factor H. "On healthy human cells, the recognition of sialic acid by factor H stops the complement cascade short, so that cells with these sugar structures remain undamaged," says Bärbel Blaum.

The researchers suspect that in one rare but serious kidney disease (atypical hemolytic-uremic syndrome, aHUS) this recognition mechanism is impaired. "We know from genetic studies that a part of factor H is damaged in some aHUS patients – and it now turns out that this damage is often located in the sialic acid binding site in factor H," Blaum says. Having a clear picture of the recognition pro-cess will also help researchers to better understand the strategies used by disease-causing bacteria which hide from the immune system by hijacking factor H with its sialic acid binding site to disguise themselves as human cells.

More information: Bärbel S Blaum, Jonathan P Hannan, Andrew P Herbert, David Kavanagh, Dušan Uhrín & Thilo Stehle: "Structural basis for sialic acid-mediated self-recognition by complement factor H." *Nature Chemical Biology*, DOI: 10.1038/nchembio.1696

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