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Host or foreign -- the body's frontline defense mechanism understood

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Researchers at the University of Helsinki, Finland, have now described how the first line of defense of the human immune system distinguishes between microbes and the body's own structures. The basis of this recognition mechanism has been unclear since the key protein components were discovered over 30 years ago -- and has now finally been cracked.

This week, the highly-respected US Academy of Sciences journal (*PNAS*) published an article describing how the first line of defence of the human immune system distinguishes between microbes and the body's own structures. The basis of this recognition mechanism has been unclear since the key protein components were discovered over 30 years ago – and has now finally been cracked by a collaboration between high-level research groups at the University of Helsinki, Finland.

When a microbe has infected us, the first defence mechanism that attacks it is a protein-based marking and destruction system called complement. It usually suffices that foreign targets are marked as enemy while our own targets are left untouched, so that white blood cells attack only foreign targets like bacteria, viruses and parasites.

Researchers at the Haartman Institute and the Institute of Biotechnology at the University of Helsinki have, as a result of years of dedicated work, been able to show how complement dis-tinguishes foreign structures from our own structures – all days before antibodies have a chance to develop. The key to unlocking the problem was when the groups of

Sakari Jokiranta and Adrian Goldman in Helsinki, along with David Isenman's group in Canada, were able to solve the structure of two components of the system at atomic resolution. The structure revealed a stunning unexpected arrangement: factor H bound two of the C3bs, which mark foreign targets, in two different ways. Laboratory tests showed that this actually happened: to recognise our own cells, factor H binds not only C3b but also the cell surface at the same. Thus, the system mark only foreign structures for destruction by the white blood cells.

This new understanding of how host and foreign structures are distinguished by the front-line defence mechanism also explains how the severe and often fatal form of disease "Hemolytic Uremic Syndrome" (HUS) starts. This rare disease often occurs in children and can be caused by genetic defects in factor H or in C3b, or else by the disruption of factor H activity by antibod-ies. In Finland, too, some of these patients have had to have complete liver-kidney transplants because of the severity of the disease. Consequently, the research's surprising and wide-reaching result will be important not only in terms of advancing basic immunological research but also in the diagnosis and treatment of very sick children.

Provided by University of Helsinki