Study makes breakthrough in understanding of proteins and their impact on immune system

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Researchers at the University of Birmingham have made a breakthrough in the understanding of how our genetic make-up can impact on the activity of the immune system and our ability to fight cancer.

The study, conducted in conjunction with researchers from Birmingham's Queen Elizabeth Hospital, was published in *Science Signaling* and focusses on a protein called ULBP6.

Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. Proteins do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Lead author of the study Professor Paul Moss from the University of Birmingham's Institute of Immunology and Immunotherapy, said: "We worked on a protein called ULBP6 which leads to the removal of damaged cells and an interesting observation has been that there are two types of this protein found in different people.

"This is important as previous studies have shown that the type of protein that we inherit from our parents can influence our risk of autoimmune disease and affect how we respond to some forms of cancer treatment."
"The ULBP6 protein is found on the surface of damaged cells, including several types of cancer cells, and acts as a 'flag' to signal to white cells in our immune system that the damaged cell should be killed.

"Interestingly, there are two major types of this protein in the population and people who inherit a certain subtype have been shown to have a poor outcome after stem cell transplantation, a procedure used to treat leukaemia, which is commonly referred to as 'bone marrow treatment'."

Professor Ben Willcox, also from the University of Birmingham's Institute of Immunology and Immunotherapy, said: "The two types of ULBP6 differ only by two amino acids out of a total of around 180 and it has surprised us that this can have such an important influence on patient outcomes.

"In the study we found that one form of ULBP6 forms a very strong bond indeed with its receptor NKG2D on the immune system. In addition, when the protein is released into the local environment it can act to block the signalling pathway.

"The 'sticky' form of ULBP6 binds over 10 times more strongly to NKG2D but a major surprise was that this acted to reduce killing by the immune system rather than increase it. We now want to understand how this information might be used to improve the outcome of patients undergoing stem cell transplantation."

The study was funded by the Bloodwise and the Wellcome Trust. Bloodwise, the UK's specialist blood cancer charity, funds world-class research and offers expert information and support to anyone affected by leukaemia, lymphoma, myeloma and other blood cancer related disorders.

Alasdair Rankin, Director of Research at Bloodwise, said: "For some
people with leukaemia and other types of blood cancer, stem cell transplantation can mean the difference between life and death. But a stem cell transplant is a gruelling procedure which sadly does not always work, so we need research to improve success rates.

"This research will not change care today, but it helps us understand why transplants work less well in some people, which is an important step on the path to developing better transplant therapy for more people living with blood cancer."

Wellcome Trust is a global charitable foundation, supporting scientists and researchers to take on big problems, fuel imaginations, and spark debate.

**More information:** A disease-linked ULBP6 polymorphism inhibits NKG2D-mediated target cell killing by enhancing the stability of NKG2D-ligand binding. *Science Signaling*, [DOI: 10.1126/scisignal.aai8904](https://doi.org/10.1126/scisignal.aai8904)

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