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Overlooked molecules could revolutionize our understanding of the immune system

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Thousands of new immune system signals have been uncovered with potential implications for immunotherapy, autoimmune diseases and vaccine development.

The researchers behind the finding say it is the biological equivalent of discovering a new continent.

Our cells regularly break down proteins from our own bodies and from foreign bodies, such as viruses and bacteria. Small fragments of these proteins, called epitopes, are displayed on the surface of the cells like little flags so that the immune system can scan them. If they are recognised as foreign, the immune system will destroy the cell to prevent the spread of infection.

In a new study, researchers have discovered that around one third of all the epitopes displayed for scanning by the immune system are a type known as 'spliced' epitopes. These spliced epitopes were thought to be rare, but the scientists have now identified thousands of them by developing a new method that allowed them to map the surface of cells and identify a myriad of previously unknown epitopes.

The findings should help scientists to better understand the immune system, including autoimmune diseases, as well as provide potential new targets for immunotherapy and vaccine design.

The research was led by Dr Juliane Liepe from Imperial College London

and Dr Michele Mishto from Charité - Universitätsmedizin Berlin in Germany in collaboration with the LaJolla Institute for Allergy and Immunology and Utrecht University, and it is published today in *Science*.

Co-author of the study Professor Michael Stumpf from the Department of Life Sciences at Imperial said: "It's as if a geographer would tell you they had discovered a new continent, or an astronomer would say they had found a new planet in the solar system.

"And just as with those discoveries, we have a lot of exploring to do. This could lead to not only a deeper understanding of how the immune system operates, but also suggests new avenues for therapies and drug and vaccine development."

Prior to the new study, scientists thought that the machinery in a cell created signalling peptides by cutting fragments out of proteins in sequence, and displaying these in order on the surface of the cell. However, this cell machinery can also create 'spliced' peptides by cutting two fragments from different positions in the protein and then sticking them together out of order, creating a new sequence.

Scientists knew about the existence of the spliced epitopes, but they were thought to be rare. The new study suggests that spliced epitopes actually make up a large proportion of signalling epitopes: they make up around a quarter of the overall number of epitopes, and account for 30-40 per cent of the diversity - the number of different kinds of epitopes.

These extra epitopes give the immune system more to scan, and more possibilities of detecting disease. However, as the spliced epitopes are mixed sequences, they also have the potential to overlap with the sequences of healthy signallers and be misidentified as harmful.

This could help scientists understand autoimmune diseases, where the immune system turns against normal body tissues, such as in Type 1 diabetes and multiple sclerosis.

The study's lead author, Dr Juliane Liepe from the Department of Life Sciences at Imperial, said: "The discovery of the importance of spliced peptides could present pros and cons when researching the immune system.

"For example, the discovery could influence new immunotherapies and vaccines by providing new target epitopes for boosting the immune system, but it also means we need to screen for many more epitopes when designing personalised medicine approaches."

More information: "A large fraction of HLA class I ligands are proteasome-generated spliced peptides" science.sciencemag.org/cgi/doi… 1126/science.aaf4384

Provided by Imperial College London