Shedding more light on how the body controls our immune systems

January 5 2022

Credit: Andrea Piacquadio from Pexels

The membrane attack complex (MAC) is a set of proteins typically formed on the surface of pathogen cell membranes. They punch tiny holes in an invading bacteria's membrane. The bacteria ultimately dies if

enough holes are punched. When an invader is discovered, our immune system produces many MACs. Those that do not reach their targets end up in the bloodstream where they can have detrimental effects.

If left unchecked, MACs directly lead to collateral damage to healthy cells and cause human disease. Controlling MAC activity requires deep insight into their structure and function.

Understanding how MAC activity is controlled

Special chaperone proteins called clusterin and vitronectin help to prevent MACs from causing unwanted attacks. However, the scientific community does not know how. This understanding has been missing until now.

Researchers supported by the EU-funded Controlling MAC and EPIC-XS projects have uncovered how these special proteins in the blood stop the immune system from damaging our own cells with overproduced molecules. The results were published in the journal *Nature Communications*. They captured and examined in exceptional detail MAC precursor molecules confined to the chaperone proteins. This revealed how the chaperones prevent MACs from becoming completely functional.

In search of the control mechanisms

"When a pathogen is detected, our immune system goes into overdrive to make MACs and not all of them reach their bacterial targets. Here we discovered how chaperones in the blood capture rogue molecules and prevent them from damaging human cells," explained lead researcher Dr. Doryen Bubeck from Controlling MAC project coordinator Imperial College London (ICL) in a news release. "Seeing how these proteins stop

MAC provides the first clues into how this branch of the immune system can be controlled and shows us how these chaperones might capture other harmful proteins in the blood."

The findings showed that clusterin binds to a precursor version of the MAC dissolved in our bloodstream. It then keeps the MAC from increasing more of the components it requires to completely accumulate and punch holes.

The research could also indicate how special chaperone proteins can inhibit the accumulation of other harmful molecules, such as those linked to Alzheimer's disease. First author Anaïs Menny, also from ICL, noted: "If clusterin uses the same method to recognize and prevent beta-amyloid accumulation as it does for MACs, then we could get some really interesting insights into how the early precursors to Alzheimer's disease arise."

The main objective of Controlling MAC (Structural basis of controlling the membrane attack complex) is to explore the molecular mechanisms that support MAC assembly. It ends in June 2025. EPIC-XS (European Proteomics Infrastructure Consortium providing Access) is providing access to state-of-the-art proteomics facilities and advancing novel proteomics and bioinformatics approaches. Proteomics is the large-scale study of proteins. The project will be completed in December 2022.

More information: Anaïs Menny et al, Structural basis of soluble membrane attack complex packaging for clearance, *Nature Communications* (2021). DOI: 10.1038/s41467-021-26366-w

Controlling MAC project: cordis.europa.eu/project/id/864751

EPIC-XS project website: epic-xs.eu/

Provided by CORDIS