PRESS RELEASE

Central mechanism of inflammation decoded

Bonn researchers use nanobodies to elucidate pore formation by gasdermin D in cell membranes

Bonn, September 26 - The formation of pores by a particular protein, gasdermin D, plays a key role in inflammatory reactions. During its activation, an inhibitory part is split off. More than 30 of the remaining protein fragments then combine to form large pores in the cell membrane, which allow the release of inflammatory messengers. As methods for studying these processes in living cells have so far been inadequate, the sequence of oligomerization, pore formation and membrane incorporation has remained unclear. An international research team led by the University Hospital Bonn (UKB) and the University of Bonn has succeeded in answering this question with the help of antibody fragments, so-called nanobodies, which they have identified. They hope that this will lead to potential therapeutic applications. Their results have now been published in the journal "Nature Communications".

Inflammasomes, large multiprotein complexes of the innate immune system, activate and control inflammatory reactions in our body. An important step of the signaling cascade triggered by them is the cleavage of the protein gasdermin D (GSDMD). The active part of GSDMD, the so-called N-terminal domain (NTD), can then form pores in cellular membranes, which on the one hand enable the release of pro-inflammatory cytokines and on the other hand trigger pyroptosis - a form of cell death that further fuels inflammation. "But how exactly and where GSDMD assembles into pores, and whether this step can be inhibited, was previously unclear," says Prof. Florian I. Schmidt from the Institute of Innate Immunity at UKB, who is a member of the Cluster of Excellence ImmunoSensation^2 and the Transdisciplinary Research Area (TRA) "Life & Health" at the University of Bonn.

To clarify these open questions, Prof. Schmidt's research team used protein inhibitors that they derived from particular antibodies found in alpacas. These so-called nanobodies are around ten times smaller than normal antibodies. By binding to proteins, they can disrupt their function or mark certain molecules and thus make them visible. The Bonn researchers identified six nanobodies against GSDMD. In their study, they introduced the genetic information of two representatives into human macrophages, which belong to the white blood cells.

No pore formation in the cell membrane without oligomerization

"We have discovered that the nanobodies inhibit pore formation and thus prevent cell death and cytokine release," says first author Lisa Schiffelers¸ a doctoral student at the University

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of Bonn in Prof. Schmidt's working group at the UKB. The Bonn researchers also determined how this works: The nanobodies prevent the oligomerization of the GSDMD NTD - meaning that individual subunits do not combine to form a larger structure. On the other hand, they do not prevent the GSDMD NTD from inserting into the cell membrane. "This allows us to conclude that GSDMD NTD first intercalates into the cell membrane and only then oligomerizes," says Schiffelers. The Bonn researchers were also able to identify the target membrane beyond doubt. "GSDMD NTD inserts into the plasma membrane, i.e. the outermost membrane of the cell, as we already suspected, but not initially into the mitochondria, as postulated elsewhere," says Prof. Schmidt,. It was very surprising for the Bonn researchers that the nanobodies also inhibit cell death of macrophages when they are added externally as a purified protein. "This is because a first round of formed pores allows the nanobodies to enter the cell. There, further pore formation is prevented, while the cell's own processes remove the existing pores," says Schiffelers.

The Bonn researchers, who have filed a pending patent application for GSDMD nanobodies, assume that these results show a conceptual way in which nanobodies acting on GSDMD can also be used to treat diseases based on pore formation and pyroptosis. These include sepsis and many other autoinflammatory diseases. "Yet, as our nanobodies only recognize human GSDMD and not GSDMD from mice, they have not yet been tested in animal experiments. Only with those, we can really test whether these antibodies are therapeutically effective," says Prof. Schmidt. "In the meantime, we have also discovered nanobodies against mouse GSDMD that will allow us to carry out precisely these tests. This is the subject of ongoing research."

Participating institutions and funding:
In addition to the UKB and the University of Bonn, the Walter and Eliza Hall Institute of Medical Research (Australia) and the Whitehead Institute for Biomedical Research in Cambridge (USA) were also involved in the study. The study was funded by the German Research Foundation (DFG) via the Cluster of Excellence ImmunoSensation^2 at the University of Bonn, the Emmy Noether Research Group of Prof. Florian Schmidt at the UKB and the Collaborative Research Center (SFB)1403.

Prof. Florian I. Schmidt is cofounder of Odyssey Therapeutics, which was not involved in this study.

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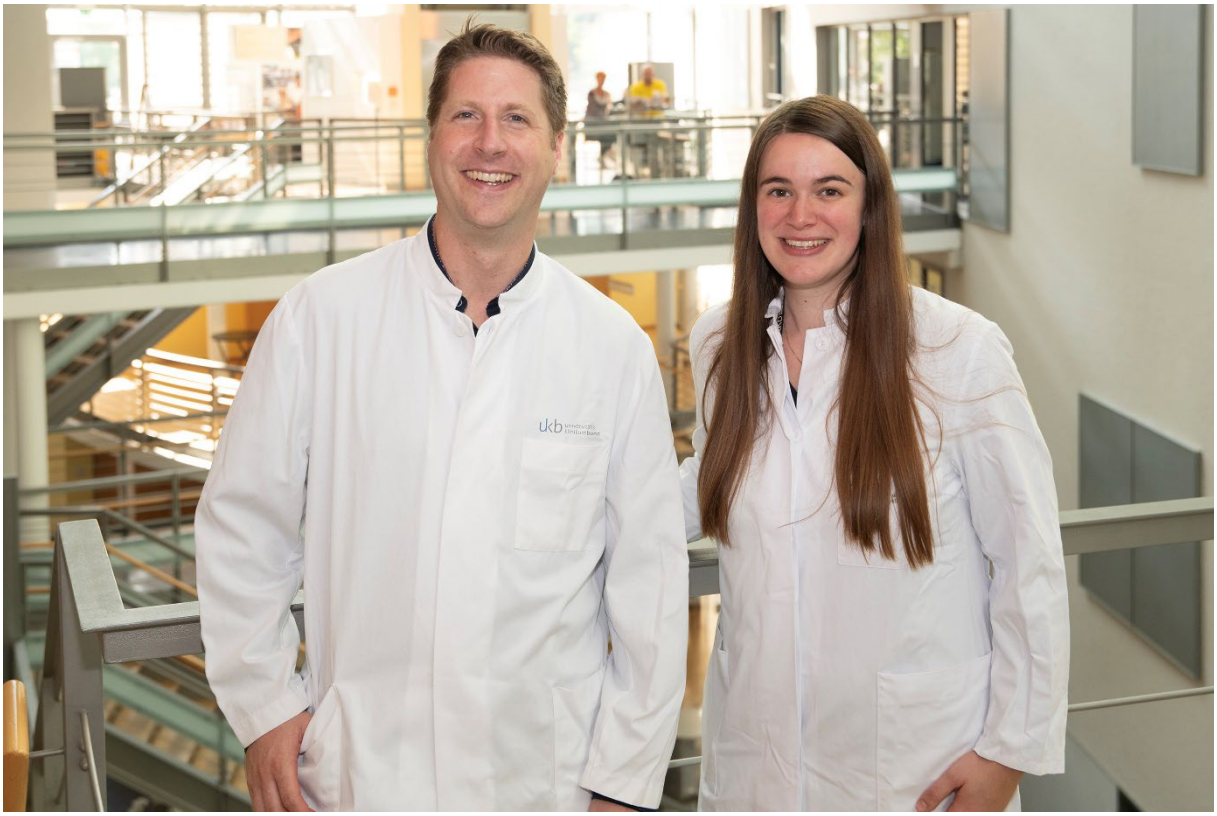

Caption: Central mechanism in inflammation decoded:
(from left) Prof. Florian I. Schmidt and Lisa Schiffelers use nanobodies to clarify the formation of pores by gasdermin D in cell membranes

Picture credits: University Hospital Bonn (UKB) / Rolf Müller

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About Bonn University Hospital: The UKB treats around 500,000 patients per year, employs around 9,500 staff and has total assets of 1.8 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals (UK) in NRW in the Focus Clinic List, had over 100 million third-party funds in research in 2023 and has the second highest case mix index (case severity) in Germany. The F.A.Z. Institute awarded the UKB first place among university hospitals in the category "Germany's Training Champions 2024".