UKB NEWS

New findings on blood clotting

Bonn researchers decipher structure of coagulation factor XIII using cryo-electron microscopy

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Bonn, December 11 - A deficiency in blood plasma coagulation factor XIII leads to a disruption in the cross-linking of fibrin, the "glue" in blood coagulation. The enzyme therefore plays an essential role in blood clotting. Researchers at the University Hospital Bonn (UKB) and the University of Bonn, together with Thermo Fisher Scientific in the Netherlands, deciphered the previously unknown structure of the Factor XIII complex using cryo-electron microscopy (cryo-EM), even at the atomic level. This enabled them to visualize the effects of disease-causing, clinically relevant factor XIII mutations in the structure of the coagulation complex. Their results have now been published in the print edition of the journal "Blood".

An injury triggers a cascade-like process that ends with the formation of a blood clot, also known as a thrombus. Fibrin solidifies - triggered by the activated factor XIII, which is an enzyme that catalyzes the formation of the cross-links required for this. A congenital or acquired deficiency of this coagulation factor disrupts the fibrin cross-linking necessary for wound healing and can lead to considerable bleeding complications in those affected. "Our discovery of the structure of factor XIII marks the culmination of a decade-long research journey to unravel the disease-causing mechanisms at the molecular level associated with heterozygous FXIII mutations in mild deficiency of this coagulation factor," says corresponding author PD Dr. Arijit Biswas, research group leader at the Institute of Experimental Hematology and Transfusion Medicine (IHT) at the UKB. Prof. Dr. Johannes Oldenburg, Director of the IHT and member of the Cluster of Excellence ImmunoSensation^2 at the University of Bonn, adds: "The structural findings we have discovered confirm the clinical effects of these mutations."

Heterotetramer forms a "crown-like" arrangement

Cryo-EM can be used to observe proteins in a shock-frozen state in their natural environment. Using this relatively new technique, the Bonn researchers were able to track down the previously unexplained structure of coagulation factor XIII, namely a native heterotetrameric complex derived from human blood plasma at a high resolution of around 0.24 nanometers. Two catalytic FXIII-A and two protective FXIII-B subunits form a complex with a "crown-like" arrangement. The B subunits stabilize the A subunits in the bloodstream and mediate their calcium-dependent activation to catalyze fibrin cross-linking. "The structure provides us with detailed information about the interaction interfaces of the factor XIII

subunits, as they interact strongly in plasma," says first author Dr. Sneha Singh, postdoctoral researcher of the University of Bonn at the IHT of the UKB: "The clarification of the biophysical structure of a native coagulation complex in high resolution is unique, as it uses the protein directly from human plasma."

Opportunity for new therapies for coagulation disorders

"The structure we have deciphered is the basis for explaining how even heterozygous variants lead to the manifestation of FXIII deficiency, which is otherwise a rare, autosomal coagulation defect, i.e. inherited independently of gender," says Prof. Oldenburg. The study also provides a practical example of how the new structural information can be used. For example, four new mutations were found in a gene that codes for the factor XIII-A subunit in patients with severe factor XIII deficiency. "Understanding the structure of the factor XIII plasma complex is not only important for the identification of mutations, but also opens up new avenues for therapeutic development and could change the treatment of bleeding disorders associated with factor XIII in the future," says Prof. Oldenburg.

Funding and participating institutions: In addition to the three IHT researchers, Prof. Dr. Matthias Geyer and PD Dr. Gregor Hagelüken from the Institute of Structural Biology at the UKB, both members of the Cluster of Excellence ImmunoSensation2 and the Transdisciplinary Research Area “Life & Health” at the University of Bonn, as well as Dr. Deniz Urgular from Thermo Fisher Scientific in Eindhoven, Netherlands, were involved in the study. They utilized the state-of-the-art Next-Generation Sequencing (NGS) facility at the IHT and the extensive experience in cryo-EM for the genome analyses, which is an exceptional combination for the characterization of genes and structures in translational medicine.

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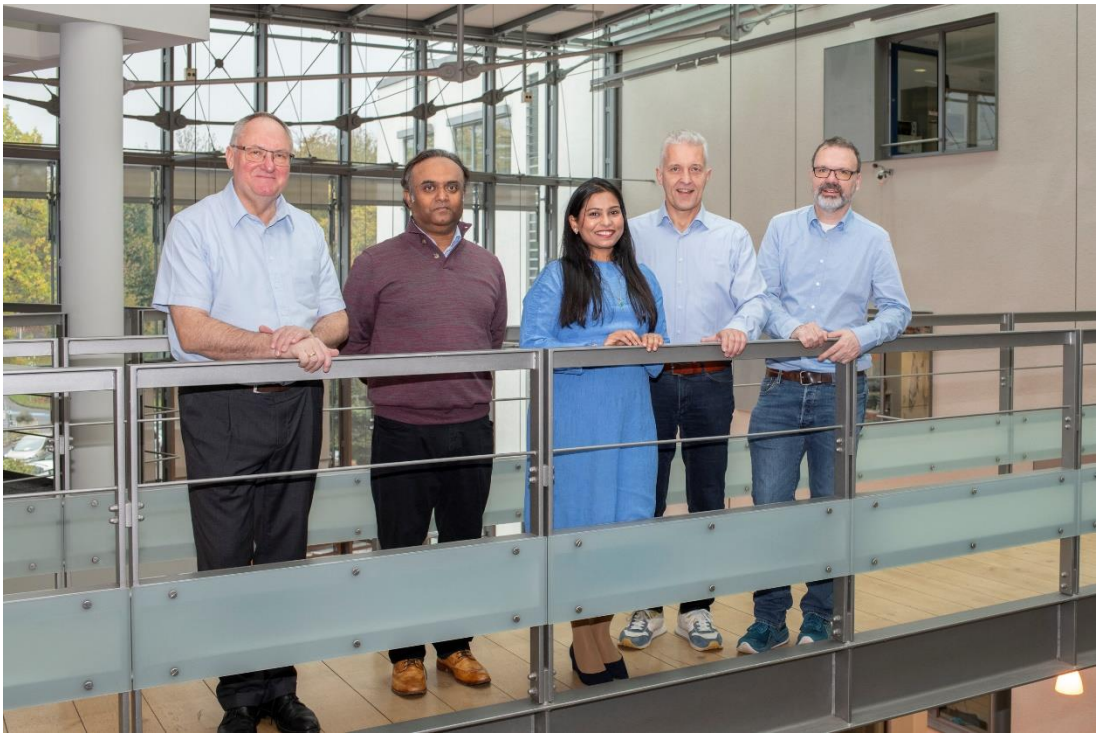

Caption: Bonn researchers decipher the structure of coagulation factor XIII using cryo-electron microscopy: (from left) Prof. Dr. Johannes Oldenburg, PD Dr. Arijit Biswas, Dr. Sneha Singh, Prof. Dr. Matthias Geyer and PD Dr. Gregor Hagelüken.

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

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".