Immune reactions identified that may cause antibody development in hemophilia A cases

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In hemophilia A cases, the body either partially or completely lacks the blood coagulation factor VIII (FVIII), or the factor is formed incorrectly. Patients usually receive FVIII that comes from donor blood

or is produced using genetic engineering. However, about one third of those treated for severe hemophilia A develop antibodies (inhibitors) against FVIII. Researchers at the Paul-Ehrlich-Institut have found that complement proteins from the immune system strongly influence the reactions of T cells (immune cells) to FVIII and can be involved in inhibitor formation. *Haematologica* reported on the results of their work in its online edition on February 2, 2023.

Hemophilia A is the most common form of hemophilia (blood disease). Patients experience spontaneous or prolonged bleeding due to the partial or complete lack of FVIII, or the loss of function of the FVIII that they have. The disease occurs almost exclusively in boys and men (hemophilia incidence is about 1:5,000 in male newborns). Treatment with replacement therapy usually consists of regular injections of the missing coagulation factor VIII, thus enabling normal hemostasis. FVIII proteins used in replacement therapy are either obtained from donor plasma or produced with genetic engineering (recombinant). Alternatively, emicizumab, a monoclonal antibody replacing the function of factor VIII, can be injected.

Complication: Formation of antibodies against coagulation factor VIII

The most serious complication in hemophilia A treatment is the development of antibodies against factor VIII (also called inhibitors), which occur in about 35% of patients with severe hemophilia A, especially in the early phase of their treatment. The risk of this complication is higher in hemophilia A patients who are completely deficient in endogenous FVIII than in patients with mild or moderate hemophilia A, in whom FVIII is still functional to a certain extent. However, it is still possible for patients with minor FVIII variations to develop inhibitors and, conversely, for patients with severe hemophilia A

not to develop inhibitors. Other factors such as immunogenetic properties or the intensity and circumstances surrounding an FVIII treatment also seem to have an effect on the risk level.

It has not yet been fully clarified as to which immunological processes eventually lead to the development of inhibitors against FVIII products. It is suspected that immunological danger signals promote inhibitor formation. Danger signals are molecules or messenger substances that communicate to the body when there is a critical situation. These signals include molecules that typically occur on the surface of bacteria (lipopolysaccharides, LPS) or certain proteins or messengers that the body releases during surgery. Avoiding FVIII treatment at vulnerable times, such as during acute infectious diseases—associated with the increased presence of immunological danger signals—has been observed to reduce the risk of inhibitor formation.

Focus on complement components

The research group led by Professor Zoe Waibler, head of the product testing of the Immunological Drugs Section and deputy head of the Immunology Division at the Paul-Ehrlich-Institut, had already shown in previous studies that plasma-derived FVIII proteins, but not recombinant FVIII proteins, can activate immune cells (dendritic cells) in the presence of such immunological danger signals, which can then mediate the formation of specific T cells.

In the current study, the research group investigated whether components of the blood plasma, which are naturally contained in both plasma-derived FVIII products and in human plasma, are able to influence T-cell reactions. The researchers found that the addition of plasma to recombinant FVIII and lipopolysaccharide-stimulated immune cells, called dendritic cells, induces the maturation of FVIII-specific T cells. Lipopolysaccharides are located on the surface of bacteria and are

perceived by the immune system as a danger signal. In further experiments, the research group demonstrated that the complement proteins C3a and, to a lesser extent, C5a are crucial to these LPS-mediated T-cell reactions.

The research suggests that complement proteins strongly influence T-cell responses to FVIII. This could explain why administration of FVIII could contribute to the development of inhibitors in certain situations, such as infections.

"The formation of antibodies against coagulation factor VIII, usually referred to as inhibitors, is a serious complication arising from replacement therapy in hemophilia A patients. We have now found that complement proteins, which belong to the innate immune system, play an important role in the formation of these inhibitors in conjunction with danger signals. Molecules that function to indicate the presence of an infection to the body are an example of such danger signals. The knowledge gained in this study could help with the development of approaches to reduce the risk of inhibitor formation during treatment of hemophilia A patients," says Waibler.

More information: Eva Ringler et al, Complement protein C3a enhances adaptive immune responses towards FVIII products, *Haematologica* (2023). DOI: 10.3324/haematol.2022.281762

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