A DESIGNED MINI-FACTOR H TO INHIBIT ANTI-FACTOR H AUTOANTIBODIES

Józsi, Mihály
Mario Hebecker[1], María Alba-Domínguez[2], Lubka T. Roumenina[3], Stefanie Reuter[1], Satu Hyvärinen[4], Marie-Agnès Dragon-Durey[3,5], T. Sakari Jokiranta[4], Pilar Sánchez-Corral[2], and Mihály Józsi[1,6]
[1]Junior Research Group for Cellular Immunobiology, Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany; [2]Research Unit, Hospital Universitario La Paz – IdiPAZ, and CIBER de Enfermedades Raras, Madrid, Spain; [3]Cordeliers Research Center, INSERM; Université Pierre et Marie Curie; Université Paris Descartes, Sorbonne Paris Cité, France; [4]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Finland; [5]Hopital Europeen Georges-Pompidou, Service d'Immunologie Biologique, APHP, Paris, France; [6]MTA-ELTE "Lendület" Complement Research Group, Department of Immunology, Eötvös Loránd University, Budapest, Hungary

Introduction. Autoantibodies to complement factor H (FH) are associated with the kidney diseases atypical hemolytic uremic syndrome and C3 glomerulopathies. Restoring FH function could be a treatment option for such diseases. Therefore, we designed a minimized human FH (mini-FH) construct that directly combines the two major functional regions of FH, namely the N-terminal complement regulatory domains and the C-terminal surface recognition domains. The aim of this study was the comprehensive functional characterization of mini-FH.
Materials and methods. Recombinant mini-FH was expressed in insect cells. Interaction with C3b and C3d was analyzed by surface plasmon resonance. Binding to pentraxins, malondialdehyde epitopes and extracellular matrix was analyzed by ELISA. Cofactor activity of bound mini-FH was measured by analyzing C3b cleavage with Western blot. Cell protective activity was analyzed by flow cytometry using HUVEC. Sheep erythrocytes were used to measure complement-mediated cell lysis. Plasma samples of patients were collected after informed consent.
Results. Mini-FH bound to C3b and had complement regulatory functions similar to those of full-length FH. Mini-FH bound to C3d with higher affinity compared to FH. Mini-FH also bound to the FH-ligands pentraxin 3, C-reactive protein and malondialdehyde epitopes. Mini-FH was functionally active when bound to pentraxins, extracellular matrix and endothelial cells *in vitro* and inhibited C3 deposition on the cells. Disease-associated autoantibodies recognized mini-FH. Furthermore, mini-FH efficiently inhibited complement-mediated lysis of host-like cells in patients' plasma caused by anti-FH autoantibodies that bind to the N- or the C-terminal domains of FH. Notably, mini-FH was more efficient inhibitor in the cellular assays than FH.
Conclusion. These data suggest that mini-FH, in addition to blocking anti-FH autoantibodies, could be potentially used as a complement inhibitor targeting host surfaces and to replace dysfunctional FH.