How do we and pathogens avoid being killed by the innate complement system?

Seppo Meri, University of Helsinki, Finland

Complement uses many recognition molecules, like antibodies, CRP and certain lectins for its activation via the classical or the lectin pathway. In contrast, the alternative pathway (AP) becomes activated by default unless it is specifically prevented. Thus, it is vital that our cell surfaces and blood plasma contain multiple inhibitors. The AP can deposit large amounts of C3b molecules covalently on activating structures via an amplification system. In the AP the discrimination between self and non-self is performed by factor H, which has binding sites for polyanions (sialic acids, glycosaminoglycans, phospholipids). This robust recognition of 'self' protects our own viable cells and tissues, while activating structures are opsonized for phagocytosis or killed. Mutations in factor H predispose to severe diseases. In atypical hemolytic uremic syndrome (aHUS), they promote complement attack against blood cells and vascular endothelial cells and lead, for example, to kidney and brain damage. Other serious complement-mediated diseases are PNH and C3 glomerulopathy. Dysregulation of complement with consequent chronic inflammation and tissue damage also occurs in age-related macular degeneration (AMD), Alzheimer's disease and atherosclerosis. Pathogens have multiple mechanisms to escape complement killing, some of them stolen from us. Most importantly, they exploit factor H for their protection. In fact, the ability to bind factor H by specific microbial proteins discriminates most pathogens from nonpathogens. Dysregulation of complement thus plays critical roles in rare and common human diseases, as well as in microbial pathogenicity.