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The evolution, structure, biology and pathophysiology of complement

John D. Lambris, Kenneth B.M. Reid and John E. Volanakis

Complement is a multicomponent, complex, highly evolved system that not only protects against invading pathogens but also contributes to the regulation of other host defence systems, specifically adaptive immunity. Aberrant activation or deficiencies of the system are associated with disease, thus, there is a need for effective pharmacological control of the activation process and/or its products. There has been significant progress in these and related areas of research over the past few years.

Complement evolution and diversity

Complement activities have been detected in the most ancient group of vertebrates (the jawless fish) as well as in some invertebrate species¹. The cloning of sea urchin C3 (Ref. 2) and factor B-like genes, and the purification from the plasma of solitary as-

A recent meeting discussed advances in complement research. New directions highlighted included elucidating the three-dimensional structure of complement proteins, understanding the evolution of the complement system, and developing pharmacologic inhibitors to control complement-mediated pathology.*

cidian *Halocynthia roretzi* of a mannose-binding lectin (MBL)-like molecule that shows C3-cleaving activity when complexed with MBL-associated serine protease (MASP) (H. Sekine, Fukushima) suggest that complement is a very ancient immune mechanism, at least 600–700 million years old. The appearance of complement would therefore pre-date the emergence of adaptive immunity. In virtually all species analysed to date, functionally active C3 exists as the product of a single gene. However, several fish, including trout¹, sea bream¹, medaka (M. Nonaka,

Tokyo) and carp (M. Nakao, Fukuoka), possess C3 in various isoforms that are the products of different genes. Trout and sea bream C3 isoforms have been shown to differ significantly in their binding efficiencies to various activating surfaces. This specificity appears to be associated with structural differences within the regions of C3 that determine specificity for various surfaces (M-R. Sarrias, Philadelphia, PA). The observed structural and functional diversity of C3 in fish might serve to augment the number of potential pathogens that C3 can recognize.

In mammals, factor B and C2 share extensive structural and functional homology and are thought to have originated by gene duplication from a common ancestral molecule. In trout (O.J. Sunyer, Philadelphia, PA) and nurse shark (S.L. Smith, Miami, FL), two factor B/C2 molecules have been identified. One of the trout B/C2 molecules plays a crucial role in the activation of both the alternative and the classical pathways of activation, and

might represent an ancestral molecule from which the mammalian factor B and C2 originated (Sunyer). Other molecules having overlapping complement activities have been isolated from the barred sand bass, in which the cofactor protein (SBP1) has been found to possess regulatory activities for both C4bp and factor H (C.M.H. Kemper, Hamburg).

Evidence was presented showing that the lectin pathway functions extensively in vertebrates and that its origin can be traced back to invertebrates. (Y. Endo, Fukushima).

Structure

A relatively new development is the use of crystallographic or nuclear magnetic resonance (NMR) methods to solve the three-dimensional structure of complement proteins, their domains or fragments. The crystal structure of C3d, the C3 activation fragment that is the ligand for CR2 revealed the molecule to comprise an α - α barrel displaying a convex and a concave surface at opposite ends (D. Isenman, Toronto). The thioester bond, through which C3d is attached to activating surfaces, is located on the convex surface, while an extended acidic pocket, possibly participating in CR2 binding is on the concave surface.

H. Jing (Birmingham, AL) presented the crystal structure of profactor D. This form of the enzyme only exists intracellularly, being converted to mature factor D before secretion into the circulation. Profactor D has many features in common with the zymogens of other serine proteases and its transition to mature factor D is associated with similar changes, despite the fact that factor D displays an inactive conformation of its catalytic centre. The crystal structure of the serine protease domain of factor B revealed that, despite a chymotrypsin-like structural fold, the domain has several distinct characteristics, including an apparently inactive conformation of the oxyanion hole and a unique disposition of the primary specificity pocket (S.V.L. Narayana, Birmingham, AL). Obviously, expression of proteolytic activity requires conformational changes of the active centre, which are probably induced by C3b. Finally, the structure of compstatin, a 13-residue cyclic peptide that binds to C3, inhibiting complement activation, was

shown to be characterized by a stable type I β -turn, which is critical for expression of inhibitory activity (A. Sahu, Philadelphia, PA).

Structural correlates of function

CCP modular proteins

Factor H, which is composed of 20 complement control protein (CCP) repeats, contains three binding sites for C3b that are located within CCPs 1–5, 6–10 and 16–20. A further three sites, located predominantly within the C-terminal half of factor H, bind to heparin, sialic acid or receptors on pathogens. A complex interplay, suggesting cooperation of the different binding sites helps explain the variable behaviour shown by factor H in control of activators of the alternative pathway (M. Pangburn *et al.*, Texas, Helsinki). Recombinant fragments of factor H were used in binding studies (T.S. Jokiranta *et al.*, Helsinki, Hamburg), which confirm and further define the locations of the three binding sites for C3b and show that they are directed towards different fragments of C3, i.e. CCPs 1–4, 12–14 and 19–20 of factor H bind C3b, C3c and C3d, respectively.

A study on membrane cofactor protein (MCP; CD46) provided insight into the role carbohydrate structures might play in glycoprotein function (M.K. Liszewski *et al.*, St Louis, MO). MCP, which inhibits complement activation in host cells and also acts as a receptor for measles virus, comprises four CCP repeats, an alternatively spliced serine/threonine/proline-enriched (STP) region, plus a transmembrane region and cytoplasmic tail. By expression of MCPs lacking the *N*-glycans known to be present on CCP repeats 1, 2 or 4, or with the heavily *O*-glycosylated STP region deleted, it was clearly established that the *N*-glycans of CCP-2 and CCP-4 were necessary for full MCP-mediated protection against cytolysis, whereas the *N*-glycan of CCP-1 was not required. The lack of the STP region influenced the activity but was not essential³.

Two sites on complement receptor 1 (CR1) were shown to be required for accelerating the decay of the classical and alternative pathway C5 convertases (M. Krych, St Louis, MO). The CR1 molecule is composed of 28 CCP repeats, which are evenly divided into four long homologous repeats (LHR-

A–D). Protein engineering has established that LHR-A needs to be linked to LHR-B or C for there to be efficient acceleration of C5 convertase decay. It was concluded that the probable roles of LHRs B or C in the regulation of the convertases was to bind C3b within the C3b–4b or C3b–3b dimers present within the classical or alternative pathway C5 convertases.

MBL/MASP

MBL and its two associated serine proteases (MASP-1 and MASP-2) are known to bring about complement activation by MBL binding to carbohydrate structures on the surfaces of a wide range of pathogenic microorganisms, thus providing a rapid innate defence mechanism. However, the precise mechanism of MBL–MASP-1/2 interaction, and the stoichiometry of complexes involving these proteins is still unclear. The interactions between these proteins is further complicated by the recent finding that a truncated 22 kDa portion of the 76 kDa MASP-2 protease is produced by alternative RNA processing (M. Takahashi, Fukushima). This 22 kDa N-terminal segment of MASP-2 lacks the serine protease domain and appears to associate with the intact MASP-1 protease.

There was general agreement with the report by M. Matsushita (Fukushima) that activated MASP-2 cleaves C4 and C2 but not C3, whereas activated MASP-1 can cleave C3 but not C4. Evidence for the control of both activated forms of MASP by C1-inhibitor was also presented. Thus, although there are striking similarities between the C1q–C1r₂–C1s₂ complex and the MBL–MASP-1–MASP-2 complex in terms of classical pathway activation via cleavage of C4, and control of activation via C1-inhibitor, the apparent direct activation of C3 by MASP-1 and the role of the non-proteolytic truncated 22 kDa form of MASP-2 require further investigation. Studies of a recombinant form of MASP-2, produced in a mammalian cell line (T. Vorup-Jensen, Aarhus), indicated that after self-activation this protease could cleave C4. In view of the difficulty in excluding MASP-1 from MASP-2 preparations, and vice versa, it seems likely that full understanding of the precise properties of each protease will require their

separate expression by recombinant techniques in proenzyme form.

Anaphylatoxins

Since the report of the cloning of the human C3a receptor, considerable advances have been made in understanding the structure-function relationships of the C3a and C5a anaphylatoxins and their receptors. The cDNA and genomic cloning of the mouse C3aR has shown that the entire coding sequence is, like other chemoattractant receptor genes, contained on a single exon and that the human and mouse C3aR genes are localized to syntenic chromosomal bands 12q13.2-3 and 6F1, respectively (T.J. Hollmann, Houston, TX). Thus, unexpectedly, the mouse C3aR gene is outside the gene cluster of chemotactic receptor genes found on chromosome 17. A mouse model of C3aR deficiency has now been developed by homologous recombination, and this will allow full analysis of the roles of C3aR and comparison with data from C3-knockout mice.

C3aR was reported to be upregulated in microglial cells and astrocytes in several human neurodegenerative disorders where there was inflammation of the brain, as seen in Alzheimer's, and other similar diseases (P. Gasque, Cardiff). The C3aR, as detected by immunostaining, was seen only in inflamed brain and not in normal brain sections, which is similar to previous reports of C5aR expression. A. Erdei (Göd, Hungary) examined the inhibitory effect of C3a on the secretory response of the mucosal-type mast cell-line RBL-2H3, caused by triggering of its FcεR1 receptor by anti-IgE. By use of a crosslinking reagent, an association between C3a and the β-chain of FcεR1 demonstrated and use of synthetic peptides indicated that the inhibitory effect was mediated by a sequence within the C-terminal 21 amino acids of C3a.

The possibility that C5a-C5aR interaction could inhibit the concomitant internalization of C3aR via its interaction with C3a was investigated (B. Settmacher *et al.*, Hanover). It was found that the normally rapid and complete disappearance of C3aR from the surface of granulocytes when triggered by C3a could be decreased by 50% when C5a was also added to costimulate the C5aR. However, there was no effect on C3aR internal-

ization when FMLP (*N*-formyl-methionyl-leucyl-phenylalanine) was added. It is not yet known if this inhibitory effect is due to competition from both C3aR and C5aR being internalized by the same route or whether there is a direct interaction involving, for example, a specific receptor kinase that is set in motion by triggering the C5a receptor. Transmigration studies to determine the effect of C3a and C5a on eosinophil adhesion and transendothelial migration demonstrated that C3a is an eosinophil-specific chemoattractant and that both anaphylatoxins trigger the use of the same integrins in adhesion and migration, i.e. α_Lβ₂ (CD11a/CD18), α_Mβ₂ (CD11b/CD18), or α₄β₁ (CD49d/CD29), depending upon the cell types used (R.G. DiScipio, La Jolla, CA).

The wide range of proinflammatory effects, other than leukocyte chemotaxis, that can be mediated by C5a were shown to include the enhanced generation of cytokines by alveolar macrophages and increased expression of vascular adhesion molecules on endothelial cells [directly, in the case of the enhancement of P-selectin expression or indirectly, via tumour necrosis factor α (TNF-α) production in the case of intercellular adhesion molecule 1 (ICAM-1) expression] (P.A. Ward, Ann Arbor, MI). In addition, C5aR mRNA was shown to be expressed by undifferentiated neuroblastoma cells in culture and C5a was found to protect these cells from cytotoxicity induced by amyloid β peptide (N.R. Cooper, La Jolla, CA). Furthermore, neuronal expression of C5aR was clearly demonstrated in the cortex, hippocampus and cerebellum of normal mouse and human brains. These findings are at variance with previous studies regarding the expression level and location of C5aR in normal and infected mouse, and human brain tissue and might reflect the use of a more sensitive detection procedure in current studies. However, it is clear that C5aR might play an important role in neuronal homeostasis.

Membrane attack complex

Activation of cellular functions

Many of the presentations in the session on the membrane attack complex (MAC) illustrated the growing number of biological effects that appear to be mediated by treatment

of nucleated cells with transient, sublytic doses of C5b-9. Z. Fishelson (Tel Aviv) reported how the activation of a kinase cascade takes place within K562 cells treated with sublytic (5-20%) doses of complement and provided evidence that this cascade system was essential for the generation of protection to subsequent lytic attack by complement. The sublytic doses of C5b-9 are considered to induce activation of protein kinase C (PKC), which promotes activation of mitogen-activated protein kinase (MAPK) kinase and then ERK. Two reports described the induction of the proliferation of cultured cells by treatment with sublytic doses of C5b-9. In the first case, involving the proliferation of human aortic smooth muscle cells, F. Niculescu (Baltimore, MD) showed that activation of phosphoinositide 3-kinase (PI 3-kinase) and ERK1, through activation of the G_i protein, was the major signal transduction pathway induced by C5b-9. In the second case, involving cultured Schwann cells, S. Dashiell (Baltimore, MD) found that in addition to induction of proliferation there was a reduction in the number of apoptotic cells and that the signal transduction mediated by the C5b-9 was again via G_i protein and ERK kinase.

Several genes have been identified whose expression is up- or downregulated during complement activation on rat oligodendrocytes. These 'response genes to complement' have been designated as RGC-1 to -32, with RGC-1 being identical to heat shock protein 105, RGC-2 being poly (ADP-ribose) polymerase and RGC-10 being interferon-inducible protein 10 (IP-10). The characterization of both rat and human RGC-32 (T. Badea, Baltimore, MD) by molecular cloning, tissue localization and mRNA expression showed that it was a novel protein of 137 amino acids, had a wide tissue distribution, was expressed in the cytoplasm and co-immunoprecipitated with cdc2. Its expression was upregulated in oligodendrocytes by C5b-9 assembly on the cells and it was suggested that RGC-32 plays a role in complement-induced cell-cycle activation.

Control of the MAC

CD59 is a GPI-anchored glycoprotein that controls the cytolysis of host cells by homologous complement through its binding to C8

and C9. In addition to its control of C5b-9 formation, CD59 might associate with CR3 on the same cells and influence CR3 function (R. Cramer, Trieste). For example, crosslinking of CD59, on polymorphonuclear leukocytes (PMNs), enhanced the CR3-mediated binding of the PMNs to endothelial cells and also co-capping experiments were consistent with there being an association between CD59 and CR3. Another study (C.W. van den Berg, Cardiff) examined the influence of the type of membrane attachment used to anchor CD59 to the cell surface on the effects mediated by CD59 crosslinking examined. By protein engineering, a transmembrane (TM) form of CD59 was constructed by replacing the C-terminal GPI-signal sequence by the TM and cytoplasmic tail of MCPcyt2. Both the GPI and TM forms of CD59 were shown to protect against MAC. Crosslinking of both GPI-anchored CD59 and TM-CD59 induced the same pattern of rapid tyrosine phosphorylation of several molecules. Although this indicated that the mode of anchorage was not important in the phosphorylation events, the interpretation of the results is complicated by the fact that the cytoplasmic region of the MCPcyt2 anchor has a signalling role and thus TM-CD59 constructs containing non-signalling anchors need to be examined. A single chain anti-human C5 (SG1.1 scFv) has been used successfully to inhibit the formation of C5b-9 on hypoxic/reoxygenated HUVECs (C.D. Collard, Boston, MA). This treatment, which attenuated the NF- κ B translocation and vascular cell adhesion molecule 1 (VCAM-1) expression on the hypoxic/reoxygenated HUVECs, might therefore be a useful therapeutic tool in a number of diseases. In a study of the mechanism by which proteins such as CD59 are anchored to cell surfaces via GPI, it was shown that the transfer of the GPI anchor could be divided into two steps: (1) recognition of the GPI attachment signals by GAA1; followed by (2) their presentation to, and proteolytic removal by, GP18 (K. Ohishi, Osaka).

Regulation of adaptive immunity

The critical role complement activation products play in the regulation of antibody responses is well established. The effect is

mediated mainly by C3 cleavage fragments reacting with complement receptors CR1 and CR2 on B cells and follicular dendritic cells. Previous studies using CR1/CR2-deficient mice demonstrated that impaired antibody responses are associated with defective germinal centre (GC) formation. Initial development of GC proceeds normally in CR1/CR2-deficient mice, but there is an inability to maintain these structures beyond ten days following immunization (R.G. Kelly, Denver CO). These findings are in agreement with a recent report suggesting that signalling via CR1/CR2 is necessary for survival of GC B cells⁴.

Although an intact classical pathway is necessary for normal antibody responses, patients with genetic deficiencies of components of this pathway have a pronounced susceptibility to autoimmunity, especially SLE and SLE-like syndromes. An initial explanation for this paradox was provided by two reports on the crucial role of complement activation products for development of tolerance to self-antigens. A.P. Prodeus (Boston, MA) presented data indicating that in the absence of C4 or CR1/CR2, self-reacting B cells responsive to antigen and displaying normal lifespans accumulate in the spleen and lymph nodes. By contrast, in normal or C3-deficient mice, such cells do not respond to antigen and have substantially reduced lifespans. Using a similar experimental model, C3 was found to be necessary for negative selection of self-reactive B cells (H. Noorchashm, Philadelphia, PA). The reasons for the discrepancy between the two sets of data are not evident. The widely held view that signalling initiated by CR2 is transduced through CD19 was challenged by data indicating that CR2 activation results in PI 3-kinase activation through a pathway distinct from the one triggered by CD19 (R. Frade, Paris).

Complement-pathogen interactions

Activation of complement in the presence or absence of antibodies leads to pathogen 'neutralization'. To circumvent this outcome, pathogens have not only developed mechanisms to control complement activation but also turned interactions with complement to their own advantage. The mechanisms de-

veloped by various pathogens to evade complement attack include: (1) structural and functional mimicry of human complement regulatory proteins; (2) use of complement receptors for cellular entry; and (3) use of human complement regulatory proteins.

The best known example of a structural homologue of the CCP module is a vaccinia virus CCP, VCP, which has been shown to inhibit both classical and alternative pathway-mediated lysis of erythrocytes. The concentration of VCP required for inhibition, however, is higher than that required for inhibition by factor H or CR1 (Sahu). In contrast to factor H and CR1, which display cofactor activity in factor I-mediated cleavage of the α' -chain of C3b at three different sites, rVCP primarily displays cofactor activity for the first site. It therefore appears that the interaction of VCP with C3 differs from those of factor H and CR1, although the single cleavage by factor I is sufficient to render C3b nonfunctional.

Proteins with structural homology to CCPs have been found in *Herpesvirus saimiri* (HVS) and the recently discovered Kaposi's sarcoma-associated herpesvirus (HHV-8). The herpes simplex virus (HSV) protein encoded by ORF15 is similar to CD59 and, when expressed in insect cells using the baculovirus vector, can protect cells against lysis by human complement (J.C. Bramley, Cambridge, UK). Another important complement-regulating viral protein is the glycoprotein C (gC) of HSV-1. gC-1 can destabilize C3 convertase by inhibiting the binding of properdin and C5 to C3b. Both the C3-binding and C5- and properdin-blocking domains are required for its inhibitory effect (H.M. Friedman, Philadelphia, PA).

Other mechanisms used by several pathogens to circumvent complement involve the binding and absorption of complement regulatory proteins H and C4bp onto their surface. The bacterial factors involved in these interactions include the M proteins (hypervariable region) (E. Johnsson, Lund); and other, as yet uncharacterized, bacterial factors of *Streptococci pyogenis* (D. Perez-Caballero, Madrid); the FHA protein of *Bordetella pertussis* (K. Berggard, Lund); and the gonococcal porin and sialylated lactosamine lipooligosaccharide of *Neisseria gonorrhoeae* (S. Ram, Boston, MA).

Pathophysiology

The involvement of complement in the pathogenesis of neuritic plaques (NP), the histologic hallmark of Alzheimer's disease, has been inferred from a number of previous studies. The recently developed transgenic mouse model of Alzheimer's has been used to demonstrate the strong association of C3 with NP in aged mice with the disease (N.R. Cooper, La Jolla, CA).

A novel pathway for complement participation in the pathogenesis of the proliferative vascular lesions seen in diabetes mellitus was suggested (J.A. Halperin, Boston, MA). The data indicate that glycation of CD59, as it could occur in diabetes, abrogates its inhibitory activity, thus resulting in increased formation of MAC complexes on endothelial cells. In turn, these complexes function as transient channels allowing the release of growth factors, which can induce abnormal vascular proliferation.

Genetic deficiency of C1q is almost always associated with systemic lupus erythematosus (SLE). A novel hypothesis about mechanisms underlying this association is based on data on the interaction of C1q with surface blebs of apoptotic cells (J.S. Navratil, Pittsburg, PA). The study demonstrated binding of C1q through its globular heads to the surface of such structures. It was proposed that the interaction leads to clearance of the blebs and of the potentially immunogenic autoantigens they contain.

An elegant study using gene targeting demonstrated the importance of complement regulatory proteins for fetomaternal tolerance (H. Molina, St Louis, MO). Homozygous deficiency in *Crry*, a murine C3 regulatory protein, resulted in fetal death with no live *Crry*^{-/-} mice obtained out of 262 live births from heterozygote matings. Breeding *Crry*^{-/-} mice to *C3*^{-/-} mice partially protected the animals from the lethal phenotype, suggesting that complement activation at the fetomaternal interface is responsible for fetal death of *Crry*^{-/-} mice.

Therapeutic intervention

Although complement is an important line of defence against pathogens, its unregulated activation might lead to host tissue damage. Indeed, complement has been implicated in the

pathogenesis of several diseases including autoimmune diseases, adult respiratory distress syndrome, stroke, heart attack, burn injuries, and complications of cardiopulmonary bypass (CPB) and xenotransplantation. To date, there are no inhibitors of complement activation available in the clinic. However, several candidates are now being developed and are in pre-clinical or clinical trials.

Several approaches have been taken to block complement activation at various stages of the cascade. One approach is to block complement activation at the C5 level. Both a single-chain antibody inhibitor CPB (S.A. Rollins, New Haven, CT) and an RNA haptamer (G. Biesecker, Boulder) are now being tested *in vivo* as potential therapeutic agents for clinical use. The single-chain humanized antibody inhibitor of human C5 was administered to CPB patients and was shown to be a potent inhibitor of complement and leukocyte activation *in vivo*; it was suggested that intervention at the C5 level reduces inflammation and myocardial tissue damage in CPB (Rollins).

A second approach to inhibiting complement activation is to use regulatory molecules to block complement activation at the C3 level. Both CR1 and decay-accelerating factor (DAF)-MCP chimeras have been used successfully *in vivo* in several disease models, and CR1 is now being tested in CPB (Phase II clinical trials). Both these C3-based inhibitors are large in size and efforts are under way to design smaller inhibitors. One such substance that inhibits complement activation by both the classical and alternative pathways was discovered by screening a random peptide library⁵. This disulphide-bonded cyclic peptide, compstatin, inhibits only primate complement (Sahu). The molecule actively inhibited complement and cellular activation in whole blood in two models of extracorporeal circulation (B. Nillson, Uppsala) and attenuated hyperacute xenograft rejection in a porcine-to-human *ex vivo* xenotransplantation model (T.E. Mollnes, Bodo). Other approaches to block early steps of complement activation include the generation of fusion molecules containing the C-terminal globular head region of the β -chain of C1q and the trimerizing α -helical, coiled-coil neck region of human lung surfactant protein D (U. Kishore, Oxford).

Concluding remarks

Complement remains an active field of basic and clinical investigation. Progress in understanding the structure of complement proteins, and particularly the topology and chemical nature of active centers and binding sites, is paralleled by fast accumulating information on function and participation in the pathogenesis of disease. Application of modern methodologies has allowed the development of inhibitors, which promise to lead to the long sought goal of pharmacological control of complement activation.

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