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Introduction to the complement system

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Complement is the essential effector mechanism in humoral immunity to infection. Combination of antibody with antigen causes cross-linking, leading to precipitation of soluble antigens and agglutination of particular antigens, but no more. Unless complement is also present, agglutinated microorganisms can, in appropriate media *in vitro* grow out and form as lethal a culture as if not reacted with antibody. That this is also true *in vivo* is apparent from experience with patients with inherited deficiencies in complement components. The pattern is complex because of the presence of two pathways of activation, but in the rare cases of deficiency of the third component, C3†, which is central to both pathways, the individuals are susceptible to repeated bacterial infections similar to aggammaglobulinaemics who are unable to synthesize antibodies. Both antibodies and complement are essential for effective humoral immunity. Whether complement has any direct or indirect role in cellular immunity is still unclear, though the presence of cell surface receptors on a variety of cells for bound complement components has led to the suggestion that it has a role in the immune response as well as being the major effector mechanism of humoral immunity.

There is some molecular evidence that the complement system may have had an unusual evolutionary history as five components have unique structural features not found to date in other proteins. These are C1q with its half collagen, half globular structure to be discussed by Dr Reid, C2 and factor B (Dr Gagnon and Dr Campbell) which appear to be unique forms of serine proteases and C3 and C4 (Dr Fey and Dr Carroll) which have an intrachain thioester bond found only on one other protein so far, the serum protease inhibitor α_2 M.

Complement is a complex system with two pathways of activation in which a series of proteolytic zymogens are converted to active proteases and lead to the formation of a lytic complex able to lyse bacterial and animal cells. In the classical pathway, initiation of activation depends on the binding of the first component C1 to antibodies after their interaction with antigens. C1 contains three proteins: C1q which binds to the Fc part of the antibody and the $C1r_2$–$C1s_2$ tetramer complexed with the C1q. Professor Colomb and Professor Fothergill will discuss these initial steps leading to the activation of C1r–C1s. It is $\overline{C1s}$ which activates C4 and C2, $\overline{C4}$ forms a covalent bond with antibody or antigen through a reactive acyl group from the thioester bond and $\overline{C2}$ interacts weakly with the bound $\overline{C4}$. The $\overline{C42}$ complex is a protease (C3 convertase) which will split a bond in C3, the activated $\overline{C3}$ then binding covalently, as $\overline{C4}$, to antibody or antigen. $\overline{C3}$ bound adjacent to $\overline{C42}$ forms the complex protease $\overline{C423}$ which is a C5 convertase and will hydrolyse a bond in C5. In both C3 and C5 convertases the active proteolytic site is in the $\overline{C2}$ component of the complex. Activation of C5 leads to the assembly of a lytic complex of late components C5, C6, C7, C8 and C9. The early stages

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† The nomenclature of the complement components is that recommended by the World Health Organization (1968, 1981). Activated components have a bar above, e.g. $\overline{C1}$. Fragments of components released during activation or inactivation are followed by small letter, e.g. C4a, C4b and C4d.

24-2

of activation all occur bound on to the antibody antigen complex but the lytic complex can lyse adjacent cells which have not interacted with antibody. Dr Bhakdi will discuss aspects of this lytic mechanism.

In the alternative pathway, high molecular mass polysaccharides such as are found on yeast and bacterial cell walls can initiate activation as well as antibody–antigen aggregates. The first reactions are still not entirely clear but factor B, when associated with activated $\overline{\text{C3}}$, is hydrolysed by factor D to give $\overline{\text{C3}}\overline{\text{B}}$, a C3 convertase. Factor D is present in blood as the active enzyme so that the presence of $\overline{\text{C3}}$ usually bound to the activator enables activation of the
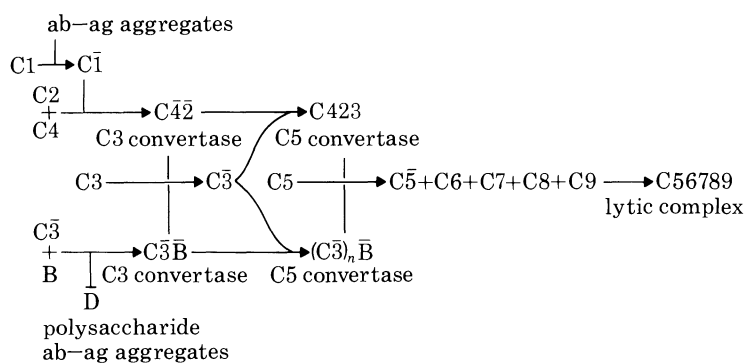

FIGURE 1. There are two pathways of activation of complement. The classical pathway (above) is activated primarily by antibody–antigen aggregates when the first component C1, a complex of three proteins, C1q, C1r and C1s, binds to the Fc portion of the aggregated antibody. This leads to conversion of C1r and C1s into proteases and $\overline{\text{C1s}}$ catalyses the activation of C4 and C2. $\overline{\text{C4}}$ forms a covalent bond with antibody and antigen and C2 associates with it non-covalently. $\overline{\text{C4}\,\overline{2}}$ catalyses the breakage of a peptide bond in C3 and $\overline{\text{C3}}$ binds covalently to antibody, the $\overline{\text{C4}\,\overline{2}\,\overline{3}}$ complex catalyses activation of C5. $\overline{\text{C5}}$ initiates formation of the complex $\overline{\text{C5}\,\overline{6}\,\overline{7}\,\overline{8}\,\overline{9}}$ which can lyse adjacent cells.

The alternative pathway (below) is activated by antibody–antigen complexes but also by other substances such as high molecular mass polysaccharides found in bacterial and yeast cell walls. Activated $\overline{\text{C3}}$ binds covalently to aggregates or polysaccharides and when factor B associates with it, it is split by factor $\overline{\text{D}}$ and forms $\overline{\text{C3}}\overline{\text{B}}$ which is a C3 convertase and activates C3. Binding of more $\overline{\text{C3}}$ molecules gives a $\overline{\text{C5}}$ convertase which initiates formation of the same lytic complex as in the classical pathway.

For simplicity, the control proteins, which inhibit or inactivate different components of the system, have been omitted.

alternative pathway to commence. Addition of one or more activated C3 molecules to the C3B complex changes the specificity to a C5 convertase as in the classical pathway and activated $\overline{\text{C5}}$ initiates the assembly of the same lytic complex as in the classical pathway. Thus there are two distinct pathways of activation each with complex proteases of similar specificity but different composition, the C3 convertases $\overline{\text{C4}\,\overline{2}}$ and $\overline{\text{C3}}\overline{\text{B}}$ and C5 convertase C423 and $\text{C3}_n\text{B}$. The components C2 and factor B are very similar in structure and function and are coded by adjacent genes as Dr Campbell will describe. C3 and C4 are also similar in structure but are coded by genes on different chromosomes.

It was shown by Lachmann & Thompson (1970) that activation of complement could lead to the lysis of adjacent cells by the lytic complex even though these cells were not themselves concerned in the activation. *In vivo*, damage to the animal's own tissues might occur during complement activation by the lytic complex or the several active proteases that are formed and it is not surprising to find that activation is limited by inactivators or inhibitors at several different stages. C1 inhibitor, for example, displaces and inhibits C1r and C1s from the C1

complex. Factor I, with appropriate protein coenzymes, inactivates $C\bar{3}$ and $C\bar{4}$. Another protease of carboxypeptidase B specificity removes a C-terminal arginine from the peptides C3a and C5a released during activation of C3 and C5 and which have chemotactic and anaphylactic acitivity. The lytic complex is inactivated by reaction with another serum protein.

Polymorphism of complement components has been recognized by antigenic differences but mainly by differences in charge, and interest in their genetics increased when it was recognized that *C2*, *C4* and *Factor B* genes were within the HLA complex in man. C4 and a haemolytically inactive homologue Slp were found in mice to be coded by genes in H2 and more recently the *Factor B* gene was also shown to be in the same position. In man, the complement genes lie between HLA-D and HLA-B and in mice between H2-I and H2-D. This is an area of particular interest because of the important role that products of this region play in the immune response. It is of medical importance because susceptibility to some rather common diseases of autoimmune character is associated with particular haplotypes in this section of the MHC. Because of linkage disequilibrium it is not yet clear which products or combination of products are responsible for this susceptibility. The different *C4* alleles may vary five to ten fold in their haemolytic activity *in vitro* and it is possible that if this is also true *in vivo*, the risk of tissue damage in autoimmunity will vary with the *C4* allele that is present (Porter 1983). The organization and other aspects of the molecular genetics of these complement proteins will be discussed by several speakers. C3 though related in structure an function to C4 is coded by a gene on chromosome 19 in man. Dr Fey will describe work on the *C3* gene and Dr Reid some aspects of C1q genetics.

Many important aspects of the complement system have been omitted from this discussion meeting, but it is hoped that together the papers will give some assessment of the biochemical and genetic aspects of the system.

Recent reviews of different aspects of the complement system will be found in Porter (1984), Reid & Porter (1981) and Müller-Eberhard (1983).

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