Complement System

Zaahira Gani, Cambridge, UK

Complement was discovered by Jules Bordet as a heat-labile component of normal plasma that causes the **opsonisation** and **killing of bacteria**. The complement system refers to a series of >20 proteins, circulating in the blood and tissue fluids. Most of the proteins are normally inactive, but in response to the recognition of molecular components of microorganisms they become sequentially activated in an enzyme cascade – the activation of one protein enzymatically cleaves and activates the next protein in the cascade. Complement can be activated via three different pathways (**Figure 1**), which can each cause the activation of **C3**, cleaving it into a large fragment, **C3b**, that acts as an **opsonin**, and a small fragment **C3a** (anaphylatoxin) that promotes inflammation. Activated C3 can trigger the **lytic pathway**, which can damage the plasma membranes of cells and some bacteria. C5a, produced by this process, attracts **macrophages** and **neutrophils** and also activates **mast cells**.

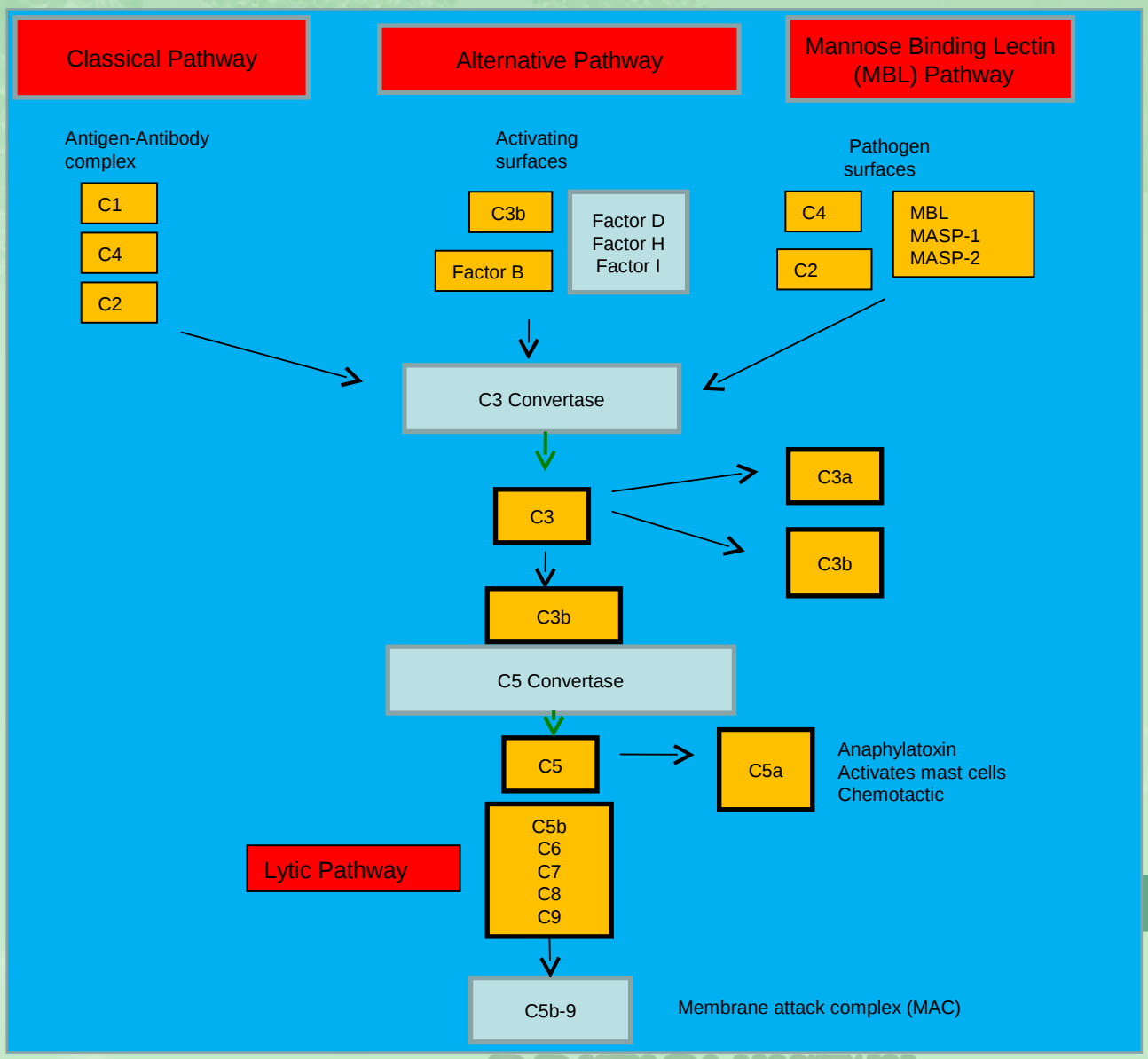

Figure 1. Complement pathways

Complement System
cont.

Classical Pathway

This pathway involves complement components **C1**, **C2** and **C4**. The pathway is triggered by **antibody-antigen complexes** binding to **C1**, which itself has three subcomponents **C1q**, **C1r** and **C1s**. The pathway forms a C3 convertase, **C4b2a**, which splits C3 into two fragments; the large fragment, **C3b**, can covalently attach to the surface of microbial pathogens and **opsonise** them; the small fragment, **C3a**, activates **mast cells**, causing the release of vasoactive mediators such as histamine.

Alternative Pathway

This pathway involves various factors, **B, D, H** & **I**, which interact with each other, and with C3b, to form a C3 convertase, **C3bBb**, that can activate more C3, hence the pathway is sometimes called 'the amplification loop'. Activation of the loop is promoted in the presence of bacterial and fungal cell walls, but is inhibited by molecules on the surface of normal mammalian cells.

Mannose-binding Lectin Pathway

This pathway is activated by the binding of **mannose-binding lectin** (**MBL**) to mannose residues on the pathogen surface. This in turn activates the MBL-associated serine proteases, **MASP-1** and **MASP-2**, which activate **C4** and **C2**, to form the C3 convertase, **C4b2a**.

Lytic Pathway

This pathway is initiated by the splitting of **C5**, and attachment of **C5b** to a target. **C6, C7, C8** and **C9** unite with C5b, and this **membrane-attack complex** (**MAC**), when inserted into the outer membrane of some bacteria, can contribute to their death by lysis. Red cells which have antibody bound to the cell surface can also activate the classical and lytic pathways, and become susceptible to lysis.

Role of Complement in Disease

The complement system plays a critical role in inflammation and defence against some bacterial infections. Complement may also be activated during reactions against incompatible blood transfusions, and during the damaging immune responses that accompany autoimmune disease. Deficiencies of individual complement components or inhibitors of the system can lead to a variety of diseases (**Table 1**), which gives some indication of their role in protection against disease.

Table 1. Diseases associated with complement deficiencies

Complement Deficiency	Disease
C3 and Factor B	Severe bacterial infections
C3b-INA, C6 and C8	Severe Neisseria infections
Deficiencies of early C components C1, C4, C2.	Systemic lupus erythematosus (SLE), glomerulonephritis and polymyositis
C1-inhibitor	Hereditary angioedema