Complement Regulatory Proteins

Secondary article

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Complement regulatory proteins are plasma and cell membrane molecules that regulate complement activation and protect host cells against complement damage. Certain diseases, such as hereditary angio-oedema, membranoproliferative glomerulonephritis and paroxysmal nocturnal haemoglobinuria, are caused by complement regulator deficiency.

Introduction

The complement system is a major antimicrobial defence system in the human body. During inflammation, complement activation products attract and activate leucocytes against their targets: bacteria, fungi and parasites. Target cells can become opsonized by complement components C3b and C4b either following deposition of antibodies (the classical pathway, CP), a carbohydrate-binding protein, mannose-binding lectin (MBL) (lectin pathway) or directly via the alternative pathway (AP). Lysis of the target is caused by the membrane attack complex of complement (MAC). The complement system also has a role in maintaining homeostasis of the host, for example by removing macromolecular aggregates and senescent endogenous cells.

Because of its strong potential for generating inflammation and causing tissue destruction, the complement system has to be kept strictly under control. Cells of the host need special protection against the products of complement lysis. Out of the 30 different glycoproteins belonging to the human complement system, 20 act in plasma and 10 are regulators or receptors on cell membranes. These molecules regulate complement activation at different steps of the complement cascade, participate in the clearance of complement-coated particles and/or protect host cells from damage. A general outline of the activation and regulation of the complement system pathways is presented in **Figure 1**. The importance of complement regulators becomes apparent in cases where their deficiency results in disease. Examples of these diseases are indicated in **Figure 1**.

The Major Complement Regulatory Proteins

Fluid-phase regulators

Because of its tendency for rapid activation and its ability to amplify its own activation, the complement system needs to be well controlled in the fluid phase. The relatively short half-life and continuous decay-dissociation of the bimolecular complement enzyme complexes naturally restrict complement activation. To fully prevent self-depletion and excessive production of phlogistic substances, a set of fluid-phase regulators is required. These include C1 inhibitor (C1 INH), C4b-binding protein (C4bp), factor H, clusterin (apo-J) and S protein (vitronectin).

C1 inhibitor

C1 inhibitor (C1 INH) is a single-chain, 105-kDa plasma glycoprotein with 478 amino acid residues. Carbohydrate side-chains constitute up to a third of the weight, making C1 INH one of the most highly glycosylated plasma proteins. C1 INH is synthesized mainly in the liver, but also by monocytes and skin fibroblasts. The synthesis is stimulated by interferon γ, interleukin 1 (IL-1) and IL-6. The gene encoding C1 INH is located in chromosome 11 and consists of eight exons and seven introns. The gene contains an unusually high number of *Alu* repeats. These repeats predispose the gene region to rearrangements by homologous recombination, which may lead to unequal crossing-over and deletions and insertions in the C1 INH gene.

C1 INH belongs to the family of serine protease inhibitors (serpins). The serpins (e.g. antithrombin III, α_1-antitrypsin and α_2-macroglobulin) share structural and functional properties. The target specificity is determined by the structure of the serpin's reactive centre which binds to the target protease. Although the serpin is cleaved by the protease, it remains tightly bound, thereby rendering the protease inactive.

In the complement system, C1 INH inhibits the C1r and C1s serine proteases and prevents the autoactivation of the C1qrs complex. In circulation, C1 INH is bound reversibly to C1s and C1r. When C1q is activated, C1r and C1s cleave C1 INH and remain bound, as described above. C1 INH is also a biologically significant inhibitor of kallikrein and coagulation factor XII. In addition, C1 INH has been

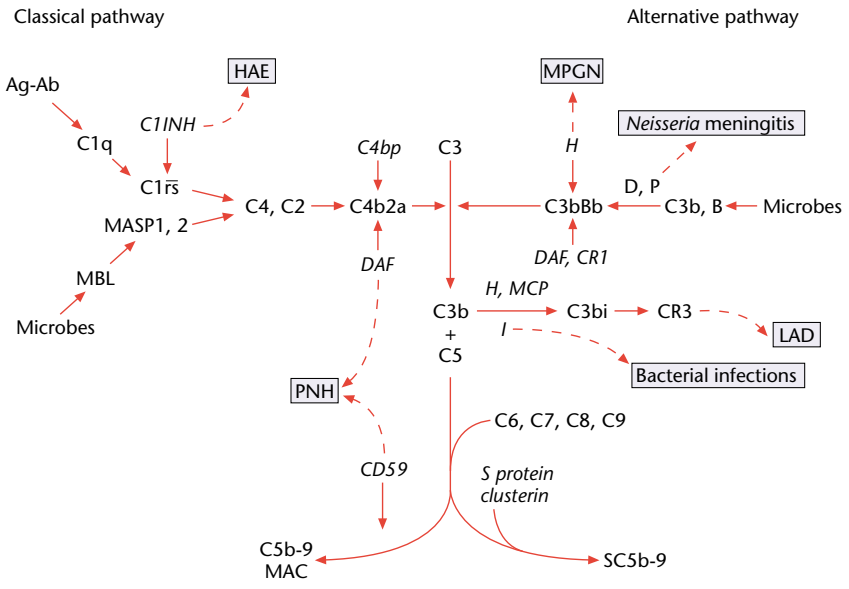

Figure 1 An overview of complement activation, regulation and diseases caused by deficiencies of complement regulator proteins. The C1r and C1s are serine esterases that are inhibited by the plasma protein C1 inhibitor (C1 INH). C1 INH also inhibits analogous MBL-associated serine proteases (MASP-1 and MASP-2). Activity of the classical pathway C3/C5 convertase, C4b2a, is inhibited by the plasma factor C4b-binding protein (C4bp). The activity of the alternative pathway C3/C5 convertase, C3bBb, can be enhanced by the only known physiological positive complement regulator, properdin (P). The self-amplifying process of the AP is inhibited by multiple regulator molecules described in **Figure 2**. The five terminal plasma glycoproteins (C5, C6, C7, C8 and C9) bind sequentially to each other to generate the cytolytic membrane attack complex (MAC). Soluble regulators S protein and clusterin keep forming terminal C complexes in the fluid phase. On human cell membranes the main inhibitor of MAC is CD59 (protectin). Consequences of major complement regulator deficiencies are indicated by broken arrows. HAE, hereditary angio-oedema; PNH, paroxysmal nocturnal haemoglobinuria; MPGN, membranoproliferative glomerulonephritis; LAD, leucocyte adhesion deficiency.

shown to inhibit plasmin and coagulation factor XIa, but these functions are of less importance. Recent studies indicate that C1 INH can also inhibit the MBL-associated serine proteases MASP-1 and MASP-2.

C4b-binding protein

C4b-binding protein (C4bp) is a multichain inhibitor of the classical pathway C3 convertase C4b2a. It is the largest physiological complement inhibitor, consisting of seven identical α chains and one β chain linked together by disulfide bridges and noncovalent forces. The polypeptide chains are arranged in an octopus-like structure where one of the legs (β chain) is shorter than the others. A basic structural unit in C4bp and many other complement regulators is the so-called short consensus repeat unit (SCR). One SCR unit is composed of approximately 60 amino acids linked together with two disulfide bridges. Each α chain (75 kDa) of C4bp contains eight globular SCR units. The β chain (45 kDa) contains three SCRs.

In the complement system, C4bp acts as a decay-accelerating factor for C4b2a and as a cofactor for cleavage of C4b by the plasma protease factor I (C4b/C3b inactivator) (**Figure 2**). A decay-accelerating activity means that C4bp irreversibly displaces C2a from C4b2a. The cofactor activity of C4bp leads to inactivation of C4b to C4c and C4d.

Factor H

An analogue of C4bp in the alternative pathway is factor H ($\beta 1_H$-globulin). It is a fluid-phase inhibitor of the AP C3 convertase enzyme C3bBb. As such, factor H is a key regulator since in its absence the AP will deplete itself almost completely. Factor H is composed of 20 tandemly arranged SCR units. The factor H gene is close to the genes for other complement regulators containing SCR units. Collectively, the genes of complement regulators constitute the regulators of complement activation (RCA) gene cluster on the long arm of chromosome 1.

The principal functional domain and one binding site on factor H for C3b has been located to the N-terminal SCRs 1–5. In addition, two other sites for C3b have been detected in the central and the C-terminal (SCR 19–20) parts of H. Upon binding to C3b factor H competes with factor B for binding to C3b. Factor H also displaces Bb from the C3bBb convertase (decay-accelerating activity). The third mechanism whereby factor H inhibits the AP C3

convertase is to act as a cofactor for factor I in the cleavage of C3b to iC3b. Together, these activities efficiently keep the AP under control. Fluid-phase C3b molecules are rapidly inactivated. On surfaces, factor H appears to be capable of discriminating between activator- and non-activator-bound C3b molecules. 'Activators' include microbes and other foreign substances that are in particulate form. 'Nonactivators' include host cells and other structures that carry polyanionic substances, like sialic acid or glycosaminoglycans, on their surfaces. The high affinity of factor H for nonactivator-bound C3b seems to be due to a joint recognition of both C3b and surface structures. At least two binding sites for polyanionic substances exist on factor H.

Various microbes have capsules (group B streptococcus, *Escherichia coli* capsule type K1 and group B meningococcus) or lipo-oligosaccharides (*Neisseria gonorrhoeae*) rich in sialic acid. Sialic acid appears to help bacteria in escaping AP activation, opsonization by C3b and phagocytosis. Group A streptococcus has M protein on its surface. Direct binding of factor H to the N-terminal hypervariable region of M protein also seems to block AP activation and prevent phagocytosis of group A streptococcus.

In addition to factor H, human plasma has proteins that have antigenic similarity to complement factor H. Factor H-like protein (FHL-1) is an alternatively spliced product of the *fH* gene that contains the seven most N-terminal SCR fragments of factor H. As such, it is equipped with most of the regulatory activity of H. The other factor H-related proteins (FHR-1–4) in human plasma are encoded by separate genes. The products of these genes have either four or five SCR units. The FHR proteins bind to C3b but have only a weak C regulatory activity.

Clusterin and S protein/vitronectin

Clusterin is a multifunctional plasma protein which consists of two disulfide-linked chains (α and β) that are both products of one gene. Clusterin is a 70–80-kDa amphiphilic molecule. It has a tendency to aggregate cells, including Sertoli cells and erythrocytes. It binds to the terminal complement complexes and prevents their insertion into cell membranes. The resulting complexes are soluble and unable to induce complement lysis.

S protein is initially synthesized as a single-chain glycoprotein. One major allelic form of S protein readily undergoes proteolytic cleavage to yield a two-chain form. In plasma S protein appears as a characteristic mixture of 65- and 75-kDa forms. The major site of S protein synthesis is liver but it is also produced by platelets and macrophages. In addition to plasma and other body fluids S protein can be found in the connective tissue where it probably has an important function in cell–matrix interactions. Like clusterin, S protein binds to the nascent C5b-7, C5b-8 and C5b-9 complexes and prevents their incorporation into cell membranes.

Membrane regulators of complement

Membrane regulators of complement include four well-characterized molecules (**Figure 2**). Three of the regulators, C3b receptor (CR1, CD35), membrane cofactor protein (MCP, CD46) and decay-accelerating factor (DAF, CD55) act as inhibitors of the C3/C5 convertases whereas protectin (CD59) is an inhibitor of MAC. An additional inhibitor of the MAC, homologous restriction factor (HRF) or C8-binding protein (C8bp), has been described in the literature but to date this molecule has not been cloned and therefore remains less well defined. The main function of the membrane regulators is to protect human cells against autologous complement attack.

Complement receptor type 1 (CR1, CD35)

C3b/C4b receptor (CR1) is a long membrane glycoprotein which exists in two major allelic forms of 190 and 220 kDa. The molecule is present on erythrocytes, some T lymphocytes, B lymphocytes, neutrophils, monocytes and eosinophils. It is also expressed on follicular dendritic cells,

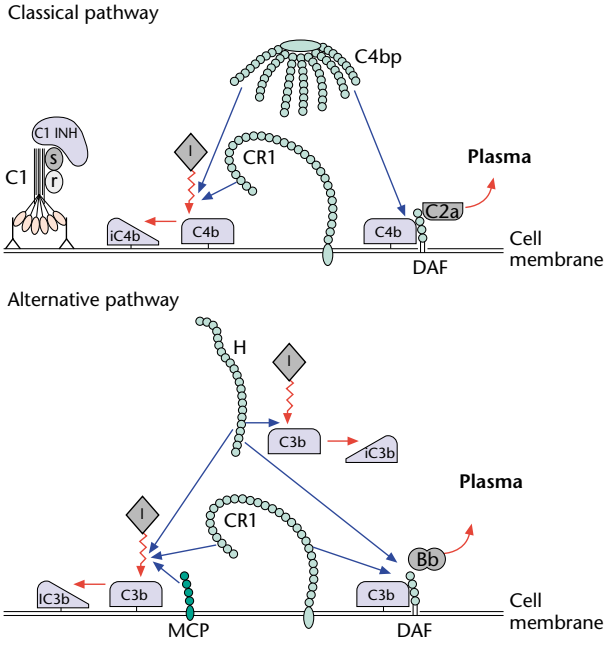

Figure 2 Regulators of the classical (CP) and alternative (AP) pathways of complement. Membrane regulators include decay accelerating factor (DAF; CD55), complement receptor type 1 (CR1; CD35) and membrane cofactor protein (MCP; CD46). Soluble regulators include C1-inhibitor (C1 INH), C4b-binding protein (C4bp), factor I (I) and factor H (H).

peripheral nerve fibres and glomerular podocytes. Notably, CR1 is absent from platelets.

CR1 contains 30 SCR units arranged tandemly in a thread which can extend up to 90 nm from the cell surface. CR1 has three binding sites for C4b and/or C3b. Multiple binding sites probably allow multivalent interactions with immune complexes containing many C3b and C4b molecules. CR1 has decay-accelerating activity towards the C3/C5 convertases of both the classical and the alternative pathway. It also acts as a cofactor for factor I-mediated cleavage of C3b and C4b and also for the cleavage of iC3b to C3c and C3dg. On erythrocytes, CR1 serves as the carrier of C3b-bearing immune complexes. Erythrocytes carry immune complexes to spleen or liver for further processing. In both the spleen and liver the immune complexes are taken up by the macrophage iC3b receptor CR3 (CD11b/CD18).

Membrane cofactor protein (MCP, CD46)

MCP is a 51–68 kDa integral membrane glycoprotein. It is present on all circulating cells, except erythrocytes, and on nearly all other cell types examined so far including haematopoietic, epithelial and endothelial cells. MCP was known earlier as a trophoblast/leucocyte common antigen (TLX). It has an overall structure very similar to DAF, containing four SCRs with three glycosylation sites. There are two differently glycosylated forms of MCP (58–68 kDa and 51–59 kDa). Altogether, four different isoforms are expressed by individual cells. The expression level of the various isoforms may vary between different tissues and cell types. No deficiencies of MCP have been described yet.

MCP binds to C3b and acts as a cofactor for factor I in mediating cleavage of C3b. MCP has also weak cofactor activity for the cleavage of C4b. The binding site of MCP for C3b is located within the third and fourth SCRs most adjacent to the cell membrane. The C-terminus of the protein contains 70 amino acids rich in serine, threonine and proline residues (STP-rich region). The STP-rich and heavily glycosylated C-terminal region probably directs the protein away from the cell membrane and protects it from proteolysis.

Very importantly, MCP has been identified as the cellular receptor for the measles virus. Monoclonal antibodies against MCP have been shown to prevent infection of human cells with the measles virus.

Decay-accelerating factor (DAF, CD55)

DAF is a 70-kDa glycoprotein that is present on the membranes of peripheral blood cells, vascular endothelial cells, placenta and many types of epithelial cells. The extracellular N-terminal part of DAF contains four SCRs and an STP-region. Anchoring of DAF to phospholipids on the cell membrane occurs through a glycosylphosphatidylinositol (GPI) moiety. Soluble forms of DAF without the anchor phospholipid have been found in many body fluids including plasma, tears, saliva, urine, synovial and cerebrospinal fluids. If DAF is detached from the cell membranes with an intact GPI-phospholipid tail it can readily reincorporate into new cell membranes. Some release of DAF may occur *in vivo*.

DAF binds to and dissociates both the classical (C4b2a) and the alternative (C3bBb) pathway C3/C5 convertase enzymes. Since DAF has a higher affinity for C4b and C3b when they are in complex with their respective catalytic subunits it can recycle from C4b and C3b sites to active C3 convertase enzymes. In contrast with CR1, DAF acts intrinsically, i.e. it decays C3 convertases on the same cell where it is located.

Compared with MCP and CD59 the expression level of DAF is relatively low but it can be upregulated by various stimuli. On epithelial cells of the urinary tract, DAF acts as a ligand for the Dr adhesin of certain *E. coli* strains that cause urinary tract infections. In addition, DAF has been shown to act as a receptor for certain types of echo- and coxsackie B-viruses. Some pathogens, like human immunodeficiency virus (HIV) and *Schistosoma mansoni* worms, have been found to 'hijack' GPI-anchored DAF into their cell membranes in a functionally active form.

Recent studies have shown that the expression level of DAF is increased in many types of malignant tumours. In general, the expression of DAF prevents opsonization, release of complement anaphylatoxins and complement lysis, thereby suppressing inflammatory reactions and tissue destruction. The fact that the complement system acts as the main immune effector mechanism in the hyperacute rejection of xenogeneic organ transplants has resulted in the development of pigs that are transgenic for human DAF. Organs (mainly heart and liver) from these animals have been shown to have a prolonged survival in primate hosts.

Protectin (CD59)

The human CD59 antigen is an 18–25-kDa (in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)) glycoprotein that inhibits complement lysis. Because of its independent isolation in different laboratories CD59 has been given various names: p18, membrane attack complex inhibiting factor (MACIF), homologous restriction factor 20 (HRF20) membrane inhibitor of reactive lysis (MIRL) and protectin. CD59 is very widely expressed in human cells and tissues. It is present on all circulating blood cells, endothelial cells, in most epithelial cells and spermatozoa. In normal human heart CD59 is expressed on myocytes but appears to become lost from infarcted myocardium. The expression of CD59 is strong on most types of malignant cells.

Like DAF, CD59 has a GPI anchor. Enzymatic cleavage of the polypeptide from the anchor phospholipid by phospholipase C (PIPLC) or direct release from cell membranes generate soluble forms of CD59. The phos-

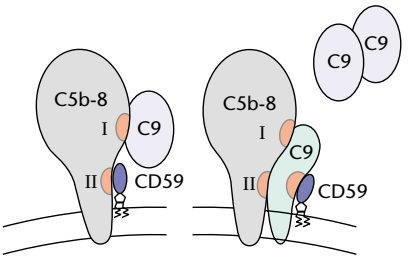

Figure 3 Inhibition of the membrane attack complex of complement by protectin (CD59). By binding to the C56-8 complex at the C8α chain and C9b sites, CD59 inhibits C9 incorporation and polymerization in the MAC.

pholipid-containing and free forms can be found in human urine, saliva, tears, breast milk, blood plasma, amniotic fluid and seminal plasma in various ratios. In SDS-PAGE gels CD59 appears as a smear of 18–25 kDa. The gene for CD59 is located on chromosome 11p13 and has four exons. The 77 amino acids of protectin constitute together a distinct domain with five internal disulfide bridges.

Protectin inhibits the final steps of MAC assembly on cell membranes. By binding to the C5b-8 complex, protectin limits C9 input and prevents formation of the polymeric C9 complex (**Figure 3**). The binding sites of erythrocyte protectin on C8 and C9 have been localized to the C8 α chain and the C9b fragment. Like DAF, CD59 can readily incorporate into cell membranes. Binding of CD59 has been shown to occur to HIV, *Schistosoma mansoni* and *E. coli* outer cell membranes.

Diseases Caused by Deficiencies of Complement Regulatory Proteins

Hereditary angio-oedema

An inherited deficiency of C1 INH causes hereditary angio-oedema (HAE). HAE is inherited in an autosomal dominant fashion and is divided in two biochemically distinct types. Type I (approximately 85% of patients) is characterized by low antigenic levels of C1 INH in plasma. It is caused by major structural changes in the C1 INH gene, e.g. deletions, insertions or mutations preventing the production of C1 INH messenger RNA (mRNA). Type II HAE is caused by point mutations at or near the gene region encoding the reactive centre residues of the C1 INH protein (Circolo and Strunk, 1997). The patients have normal or even elevated plasma levels of antigenic C1 INH but the protein is functionally defective. In addition to the hereditary form, C1 INH deficiency occurs in an acquired form (acquired angio-oedema, AAE) which is usually associated with lymphoproliferative disorders.

Clinically, all forms of HAE and AAE are identical. The disease is characterized by recurrent attacks of oedema of the skin and mucosa. The extremities and face are common sites of swelling. The oedema is typically painless, nonitching and nonpitting. Gastrointestinal oedema can cause colicky abdominal pain and has led to unnecessary surgery. Laryngeal oedema can be life-threatening. The swelling episodes are self-limiting and usually subside within 12–72 hours. The attacks are triggered by, for example, physical trauma, dental procedures, stress or hormonal factors or no triggering factor can be identified. The severity and frequency of attacks may vary from one patient to another.

The actual mediator of the oedema attacks in HAE is not known for certain. C1 INH is physiologically significant in the regulation of the complement, kallikrein and plasmin systems. Bradykinin is the most probable mediator of the symptoms but other factors, e.g. C2b, can have an influence.

HAE can be diagnosed by measuring the plasma level and biochemical activity of C1 INH. A typical feature of HAE is a low level of C1 INH in plasma. Lack of C1 INH lowers the threshold for CP complement activation. As a result, C2 and C4 are consumed during HAE attacks. In contrast, the C3 level remains normal. In AAE, C1q is characteristically low, which distinguishes AAE from the hereditary form.

Surprisingly, although HAE patients are heterozygous for the mutated gene, the plasma levels of C1 INH and the biochemical activity are below the expected 50% value. This can possibly be explained by *trans*-inhibition of the synthesis or secretion of the normal form by the mutated form.

Acute HAE attacks can be treated with C1 INH concentrates, fresh frozen plasma or with antifibrinolytic agents. In long-term prophylactic treatment, attenuated androgens like danazol have proven most effective. In short-term prevention, e.g. before surgical procedures, danazol, C1 INH concentrates or antifibrinolytic drugs have been used.

Factor H deficiency and membranoproliferative glomerulonephritis type II

Recent evidence from studies on humans and experimental animals indicates that the dysfunction or deficiency of factor H can lead to membranoproliferative glomerulonephritis (MPGN) type II (Høgåsen *et al*., 1998). In this disease complement components can be found in glomerular basement membranes (GBMs) which have become thickened because of electron-dense intramembranous deposits. MPGN commonly begins in early adolescence and presents with haematuria, proteinuria or nephrotic syndrome. Microscopically, MPGN is characterized by

glomerular capillary wall thickening and mesangial cell proliferation with increased amounts of mesangial extracellular matrix.

The discovery of Norwegian piglets deficient in factor H was a major breakthrough in fevunderstanding the pathogenesis of MPGN II. The affected piglets invariably developed glomerular changes typical for MPGN II and died of renal failure at a median age of 37 days. Infusion on normal plasma or purified factor H increased plasma H levels and significantly prolonged the median survival time.

Human factor H deficiency is rare and appears to cause less severe consequences than in pigs. Some members of families with hereditary H deficiency have MPGN II, a few have haemolytic uraemic syndrome, others have miscellaneous autoimmune disorders or are healthy.

In addition to H deficiency other mechanisms can lead to alternative pathway hypercatabolism and MPGN II. An immunoglobulin G (IgG) antibody called C3 nephritic factor (C3Nef) binds to the C3bBb convertase and prevents its intrinsic or factor H-mediated decay. Also, a monoclonal immunoglobulin light chain dimer has been shown to bind to factor H, prevent its function and cause MPGN II. The net effect in all these cases is that the alternative complement pathway undergoes enhanced turnover and becomes consumed. In addition to MPGN II, patients with alternative pathway dysfunction may present with symptoms of partial lipodystrophy.

The fact that GBMs become the target for complement attack in factor H deficiency is probably due to the lack of complement membrane regulators on these structures. Complement components have free access to the GBM through fenestrations in the glomerular endothelium. While under normal circumstances complement activation is controlled by an interaction between the anionic components of the GBM and factor H, an absolute or relative lack of factor H leads to alternative pathway activation at this site. As a consequence, complement activation may result in subsequent intraglomerular inflammation and mesangial cell proliferation.

Paroxysmal nocturnal haemoglobinuria

Deficiency of complement regulators CD59 and DAF leads to a disease called paroxysmal nocturnal haemoglobinuria (PNH). PNH is a rare haemolytic disorder characterized by intravascular haemolysis, haemoglobinuria and a tendency to vascular thrombosis. The frequency of PNH is approximately 1–10 per one million. The course of PNH varies, the median survival time from diagnosis is 10–15 years but spontaneous recoveries are known to occur.

The basic pathogenetic mechanism of PNH is now relatively well understood. The erythrocytes and leucocytes of PNH patients lack several GPI-anchored proteins. The GPI anchor is synthesized separately by the cell and attached to the protein polypeptides posttranslationally. Several enzymes are needed for the synthesis of the GPI anchor. In PNH, a block of GPI anchor synthesis occurs at an early step, during the transfer of an *N*-acetylglucosamine moiety to the phosphatidylinositol acceptor (Rosse, 1997). The gene (*PIG-A* for phosphatidylinositol glycan complementation class A) coding for the enzyme needed for this step has been cloned and mapped to the X chromosome (Xp22.1).

In PNH the mutation in the X-chromosomal *PIG-A* gene occurs in a haematopoietic stem cell. Thus, all daughter cells of this stem cell are incapable of synthesizing the GPI anchor and proteins attached to the cell membrane by GPI anchoring are not expressed. The affected cells have been shown to be of clonal origin. However, in many patients, two or more defective clones arise. Thus the *PIG-A* gene appears to be unduly susceptible to mutations or the circumstances in the bone marrow favour the mutation. Also, the defective clone tends to dominate over normal cells. The reason for this dominance is yet unknown and remains as the main unresolved question in PNH.

Two complement regulatory proteins, DAF (CD55) and protectin (CD59), are GPI anchored. In PNH these regulators are totally or partially missing from the leucocytes, platelets and erythrocytes deriving from the faulty stem cell. Most of the symptoms of PNH can be traced to the deficiency of CD59 since an isolated deficiency of DAF (the *Inab* phenotype) causes no symptoms. A single case of an inherited homozygous deficiency of CD59 has been described in the literature; this patient suffered from a severe form of PNH.

The deficiency of protectin renders the erythrocytes susceptible to lysis by autologous complement. The haemolytic symptoms often aggravate during infections, i.e. when complement activation is enhanced. The lack of protectin from platelets allows the assembly of terminal complement complex C5b-9 on the platelet surface. This may lead to the release of granule contents and shedding of vesicles from the surface and increased prothrombin activity. Subsequently, excessive thrombin generation may result in the development of venous thromboses, another manifestation of PNH.

PNH is diagnosed by demonstrating cells totally or partially deficient in GPI-anchored proteins. This is usually done by measuring CD59 expression on erythrocytes or leucocytes by fluorescence-activated cell sorter (FACS) analysis. Normally, CD59 is expressed on all cells. In PNH, a proportion of cells may lack CD59 totally (PNH III cells) or partially (PNH II cells). In general, the proportion of CD59-deficient cells in PNH can vary between 5 and 95%. In severe anaemia PNH has been treated by blood transfusions and bone marrow transplantation. Anticoagulation therapy is often indicated to prevent thromboses. Some patients may benefit from immunosuppressive chemotherapy.

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