19 Cromer Blood Group System

19.1 Introduction

Cromer system antigens are located on the complement regulatory glycoprotein decay-accelerating factor (DAF or CD55), which is attached to the red cell membrane by a glycosylphosphatidylinositol (GPI) anchor. The system includes 18 antigens: 15 of very high frequency; three of low frequency (Table 19.1). All are absent from red cells of the Cromer-null phenotype, the Inab phenotype, an inherited DAF deficiency. Cells lacking the Cromer system antigen Dr^a express the other high frequency Cromer antigens weakly. Complement-sensitive red cells from patients with paroxysmal nocturnal haemoglobinuria (PNH) are deficient in DAF and other GPI-linked proteins and do not express Cromer-system antigens.

CD55, the Cromer gene, is part of the regulator of complement activation cluster on chromosome 1q32, which contains several genes encoding related glycoproteins.

19.2 Decay-accelerating factor (DAF) and the Cromer system

19.2.1 DAF (CD55)

DAF is an intrinsic membrane glycoprotein of red cells, granulocytes, platelets, and lymphocytes, and is widely distributed throughout the body (reviewed in [1,2]). It is also present in soluble form in body fluids including plasma and urine. DAF functions to regulate complement activity (Section 19.5).

DAF is part of a family of glycoproteins anchored to cell membranes by means of the glycophospholipid GPI (reviews in [3,4]). The typical structure of a GPI anchor is shown in Figure 19.1. Other GPI-linked membrane glycoproteins on red cells are acetylcholinesterase (Yt blood group, Chapter 11), ART4 (Dombrock, Chapter 14), CD108 (JMH, Chapter 24), the Emm blood group antigen (Chapter 30), the complement regulatory glycoprotein CD59 (Section 19.5), CD58 (LFA-3), C8-binding protein, and the prion protein, PrP^C. GPI-anchored glycoproteins appear to be preferentially located in lipid rafts, membrane microdomains that float freely in the bilayer and are rich in glycosphingolipids and cholesterol [4,5]. The complement-sensitive red cell population (PNHIII) from patients with the rare, acquired, haemolytic disease paroxysmal nocturnal haemoglobinuria (PNH) are deficient in GPI-linked proteins [6,7] (Section 19.5).

Oligonucleotide probes based on the N-terminal amino acid sequence of DAF were used to isolate cDNA from libraries derived from HeLa epithelial cell line and HL-60 promyelocytic leukaemia cell line [8,9]. The cDNA sequence predicted a 347 amino acid protein preceded by a 34 amino acid N-terminal leader peptide sequence. The DAF polypeptide has four regions of marked homology of about 60 amino acid residues each called complement control protein repeats (CCPs) or short consensus repeats (SCRs). Each CCP domain consists of five β sheets, contains four cysteine residues, and is maintained in a folded conformation by two disulphide bonds [10] (see Figure 20.2). A single *N*-glycan is located between the first two CCPs [11,12]. The rigid stalk linking the four CCP domains to the GPI-anchor of the 70 kDa red cell

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Table 19.1 Antigens of the Cromer system.

Antigen				Molecular basis*		
No.	Name	Frequency	Antithetical antigen	Nucleotides	Exon	Amino acids†
CROM1	Cr^a	High		679G (C)	6	Ala227 (Pro)
CROM2	Tc^a	High	CROM3, CROM4	155G (T or C)	2	Arg52 (Leu or Pro)
CROM3	Tc^b	Low	CROM2, CROM4	155G>T	2	Arg52Leu
CROM4	Tc^c	Low	CROM2, CROM3	155G>C	2	Arg52Pro
CROM5	Dr^a	High		596C (T)	5	Ser199 (Leu)
CROM6	Es^a	High		239T (A)	2	Ile80 (Asn)
CROM7	IFC	High		(Various)		
CROM8	WES^a	Low	CROM9	245T>G	2	Leu82Arg
CROM9	WES^b	High	CROM8	245T (G)	2	Leu82 (Arg)
CROM10	UMC	High		749C (T)	6	Thr250 (Met)
CROM11	GUTI	High		719G (T)	6	Arg240 (His)
CROM12	SERF	High		647C (T)	5	Pro216 (Lys)
CROM13	ZENA	High		725T (G)	6	His242 (Gln)
CROM14	CROV	High		466G (A)	3	Gln156 (Lys)
CROM15	CRAM	High		740A (G)	6	Gln247 (Arg)
CROM16	CROZ	High		389G (A)	3	Arg130 (His)
CROM17	CRUE	High		639G (A)	5	Leu217 (Trp)
CROM18	CRAG	High		173A (G)	2	Asp58 (Gly)

*Molecular basis of antigen-negative phenotype in parentheses.
†Historically, amino acids were numbered from the first residue of the mature protein, now Asp35.

membrane form of DAF consists of a highly charged, 68 amino acid serine/threonine-rich domain, with 19 predicted *O*-glycosylation sites, and a hydrophobic stretch of 24 amino acids [12] (Figure 19.2).

CD55 (encoding DAF) spans about 40 kb and is organised into 11 exons [13] (Table 19.2). *CD55* belongs to the regulator of complement activation (RCA) cluster of genes, localised to chromosome 1q32, which also contains the genes encoding complement receptor type 1 (CR1, Knops antigen, Chapter 20), CR2, and C4-binding protein [14–17].

19.2.2 Cromer system antigens are located on DAF

In 1987 Spring *et al.* [18] showed that two murine monoclonal antibodies, which are considered Cromer-related because they did not react with Inab phenotype cells and reacted only very weakly with Dr(a–) cells, stained on immunoblots a red cell membrane sialoglycoprotein of apparent MW 70 kDa. This structure was subsequently shown to be DAF [19]. Further confirmation that DAF is the Cromer antigen came from immunoblotting with human alloanti-Cr^a and other Cromer system antibodies [18], monoclonal antibody-specific immobilisation of erythrocyte antigens (MAIEA) assays [20,21], tests with recombinant DAF constructs [20–24], and association of mutations in the *CD55* gene with variant Cromer phenotypes (Table 19.1). Red cells of the Cromer-null (Inab) phenotype had only minimal activity with murine monoclonal and rabbit anti-DAF [19,25,26]. PNHIII cells, which are deficient in DAF, did not react with antibodies to high frequency Cromer system antigens [19].

19.3 Inab, the Cromer-null phenotype, and anti-IFC (-CROM7)

The Inab phenotype, a Cromer-null phenotype in which the red cells lack all Cromer system antigens, is very rare. Nine unrelated Inab phenotype individuals have been reported (not including those shown to have a transient Inab phenotype): five Japanese [27–31], two of Moroccan

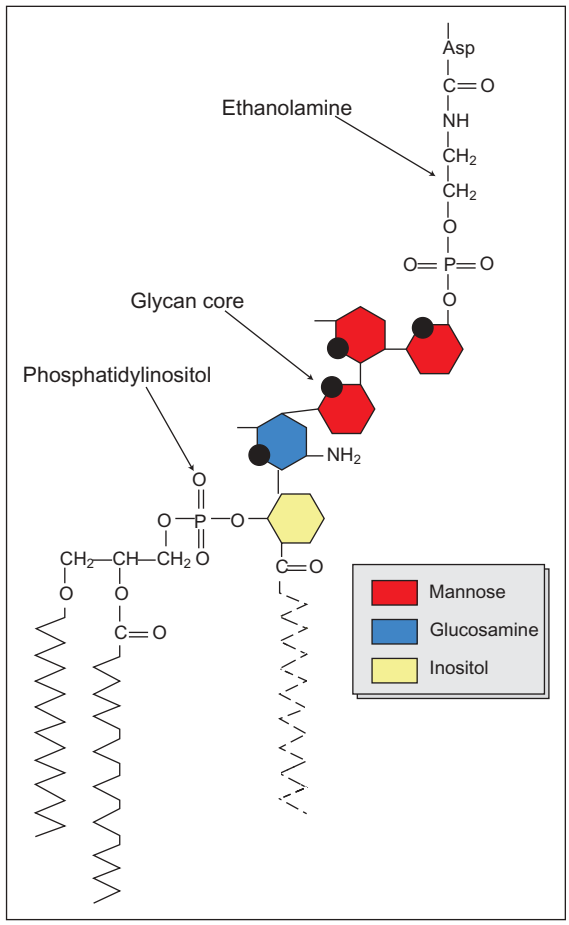

Figure 19.1 Structure of a glycosylphosphatidylinositol anchor. The protein is linked through ethanolamine to a glycan core, attached to phosphatidylinositol, which is embedded in the cell membrane. Three fatty acids are present in red cells. Redrawn from [3], with permission from Taylor & Francis Group.

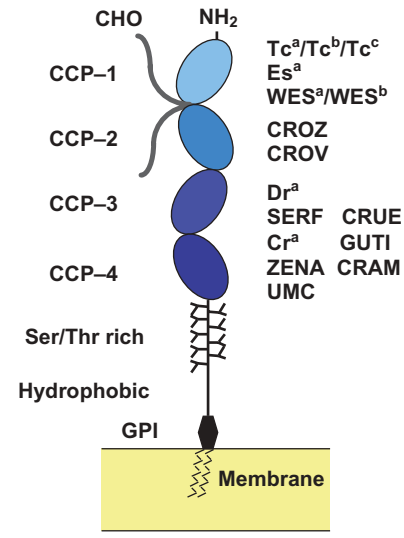

Figure 19.2 Diagrammatic representation of the DAF glycoprotein showing the four complement control protein repeats (CCPs), the *O*-glycosylated serine/threonine-rich region, the hydrophobic region, and the glycosylphosphatidylinositol (GPI) anchor inserted into the cell membrane. Also shown are the locations of the Cromer system antigens on the four CCPs.

descent [32,33], a Jewish American [34], and a white American woman of Italian descent, whose brother also had the Inab phenotype [35]. Homozygosity for four mutations in *CD55* has been reported to be responsible for the Inab phenotype.

1 A nonsense mutation, 261G>A (*CROM*01N.01*), in exon 2 of the original Inab phenotype propositus and in another Japanese propositus: Trp87stop [29,36].

2 A nonsense mutation, 508C>T (*CROM*01N.03*), in exon 4 of another Japanese propositus: Arg170stop [31].

3 A single nucleotide insert, 367A (*CROM*01N.04*) in exon 3, resulting in a reading frameshift and a premature stop codon at Glu128 [32].

4 A 1579C>A change 24 bp upstream of the 3′ end of exon 2 in two Japanese individuals, which creates a novel splice site (TGGT**C**AGA to TGgt**a**aga), giving rise to a 26 bp deletion in the mRNA, resulting a reading frameshift and a translation stop codon immediately downstream of the mutation (*CROM*01N.02*) [28,30].

Sera from eight of the Inab phenotype propositi contained anti-IFC, an antibody reacting with all red cells apart from those of the Inab phenotype [27,29–31, 33–35]. Haemagglutination-inhibition experiments with soluble-recombinant constructs representing different segments of DAF showed that anti-IFC comprises a mixture of antibodies to each of the four CCP domains [29].

There are three reports of patients with a transient Inab phenotype and anti-IFC. On later testing, the antibody had disappeared, or almost disappeared, and DAF expression and Cromer phenotype returned to normal in two patients, and became weakly expressed in the third. One had splenic infarctions [37], one chronic lymphatic leukaemia [38], and one gastrointestinal abnormalities [39]. In one patient, whilst the red cells had the Inab phenotype, lymphocytes, monocytes, granulocytes, and

Table 19.2 Organisation of the *CD55* gene.

Exon	Size (bp)	3′ intron size (kb)	Amino acids*	Region of DAF encoded	Antigens encoded
1		0.5	1–34	5′ untranslated; signal peptide	
2	186	2.3	34–96	CCP-1	$Tc^a/Tc^b/Tc^c$, CRAG, Es^a, WES^a/WES^b
3	192	0.9	96–160	CCP-2	CROZ, CROV
4	100	1.0	160–193	$CCP\text{-}3_A$	
5	86	4.3	193–222	$CCP\text{-}3_B$	Dr^a, SERF, CRUE
6	189	5.4	222–285	CCP-4	Cr^a, GUTI, ZENA, CRAM, UMC
7	126	0.6	285–327	$Ser/Thr\ rich_A$	
8	81	1.9	327–354	$Ser/Thr\ rich_B$	
9	21	1.2	354–361	$Ser/Thr\ rich_C$	
10	118	19.8	(361–400)	*Alu* (alternatively spliced)	
11	956		361–381	Hydrophobic; 3′ untranslated	

Table 19.3 Some population studies on high frequency Cromer antigens.

Antigen	Population	No. tested	No. negative	References
Cr^a	African Americans	>4000	0	[42]
	African Americans	8858	2	[43]
Tc^a	African Americans	950	1	[44]
	White Americans	5000	0	[44]
	Japanese	5000	0	[44]
Es^a	American donors	3400	0	[45]
UMC	Japanese	45 610	0	[46]
GUTI	American donors	>1000	0	[47]
SERF	Thai donors*	1041	1	[48]

*Tested by PCR-RFLP.

platelets expressed CD55, albeit at a lower level than cells of common phenotype [37].

Four of the nine propositi with non-transient Inab phenotype, plus an African American boy who probably had the Inab phenotype [29], had intestinal disorders including protein-losing enteropathy [27], Crohn's disease [34], blood capillary angioma of the small intestine [29], and a chronic progressive gastrointestinal disorder resulting from Budd-Chiari syndrome, a blockage of the hepatic vein [33]. One of the patients with transient Inab phenotype, an 18-month-old boy, had significant gastro-oesophageal reflux and milk and soy intolerance [39]. DAF is present on the epithelial surface of intestinal mucosa [40], but any suggestion of an association between DAF-deficiency and intestinal disease is offset by the absence of any such disorder in two of the Japanese propositi [28,31] and in an 86-year-old Inab phenotype woman and her 70-year-old brother [35]. Mice deficient in the major form of DAF, resulting from a *Daf1* knockout, are more susceptible than control mice to colitis induced by dextran sulphate sodium [41]. Any conclusive evidence for an association between DAF deficiency and inflammatory gastrointestinal disease in humans remains elusive.

19.4 Cromer system antigens and antibodies

19.4.1 Cr^a (CROM1)

In 1965 McCormick *et al.* [42] described an antibody in the serum of an African American antenatal patient, Mrs Cromer, which reacted with red cells of more than 4000 African American donors (Table 19.3), but not with her

own red cells or with those of two of her siblings. Stroup and McCreary [49] recognised a possible serological association between anti-Cr^a and the antibody now called anti-Tc^a. Many more examples have been found in people of African origin, and one in a Spanish American [50].

DAF cDNA deletion-mutants lacking the regions encoding each of the four CCPs were used to transfect Chinese hamster ovary cells [51]. Anti-Cr^a reacted on immunoblots with lysates from these transfected cells with the single exception of those transfected with the cDNA lacking the region encoding CCP-4. Sequencing of genomic DNA from three Cr(a–) individuals revealed a 679G>C change encoding an Ala227Pro in CCP-4 (*CROM*–01*) [22].

19.4.2 Tc^a (CROM2), Tc^b (CROM3), Tc^c (CROM4), and Tc^{a}Tc^b

Two antibodies of identical specificity, shown to be related to anti-Cr^a through common absence from Inab phenotype cells [27], were named anti-Tc^a when a third example was described [44]. One Tc(a–) individual was found as a result of testing red cells from 950 African American donors with anti-Tc^a (Table 19.3).

Anti-Tc^b reacted with red cells of about 6% of African Americans and family studies showed that *Tc^a* and *Tc^b* are alleles. From the results of testing 350 African American donors with anti-Tc^b the following gene and genotype frequencies were calculated: *Tc^a* 0.97, *Tc^b* 0.03; *Tc^a/Tc^a* 0.941, *Tc^a/Tc^b* 0.058, *Tc^b/Tc^b* 0.001 [52].

Red cells of a Tc(a–b–) white woman and her sister, neither of whom had the Inab phenotype, were found to have a low frequency antigen, which was subsequently named Tc^c [53]. Both parents and three of four other siblings were Tc(a+b–c+). Six months after the delivery of a Tc(a+) child, the serum of the Tc(a–b–c+) propositus contained an antibody that represents inseparable anti-Tc^{a}Tc^b; it reacted with neither her own cells nor with those of her Tc(a–b–c+) sister, but did react with Tc(a–b+c–) and Tc(a+b–c–) cells [53]. A second example of anti-Tc^{a}Tc^b has been found in a Tc(a–b–) white woman [54]. Another anti-Tc^c was identified in a Tc(a+c–) pregnant woman with a Tc(a+c+) husband [55].

Arg52Leu and Arg52Pro substitutions in CCP-1, are responsible for Tc^b and Tc^c expression, respectively (*CROM*01.03* and *CROM*01.04*) [22,56,57] (Table 19.1). The *Tc^b* mutation creates a *Stu*I restriction site and both *Tc^b* and *Tc^c* mutations destroy an *Rsa*I site.

19.4.3 Dr^a (CROM5)

Most reported examples of anti-Dr^a have been found in Jews of Uzbekistani origin [58–62], although other examples were found in a Russian woman [36,63] and a Japanese blood donor [29].

In addition to lacking Dr^a, Dr(a–) red cells have weak expression of all other high frequency Cromer system antigens as they have only 40% of normal expression of cell surface DAF [64]. Immunoblotting revealed no gross alteration in Dr(a–) DAF, but did confirm the quantitative difference [64,65].

Dr(a–) phenotype results from homozygosity for 596C>T in exon 5 of *CD55* encoding Ser199Leu within CCP-3 (*CROM*01.–05*) [36,64] (Table 19.1) This mutation results in the loss of a *Taq*I restriction site. Sequencing of cDNA derived from Dr(a–) individuals revealed two *DAF* transcripts: a minor one encoding full-length DAF containing the Ser165Leu substitution and a more abundant form having a 44 nucleotide deletion, which introduces a reading frameshift and the generation of a premature stop codon six codons downstream from the deletion. Any polypeptide produced by the major transcript would consist of an N-terminal leader sequence plus 165 amino acid residues, but lacking the remainder of the molecule, including the GPI anchor [36]. Only DAF encoded by the minor transcript is present at the cell surface, explaining the low levels of DAF and weak expression of the Cromer antigens. The C>T mutation responsible for the loss of Dr^a creates a cryptic splice site 44 nucleotides upstream of intron 4 so that 44 nucleotides of exon 3 are spliced-out of the majority of the mRNA molecules together with intron 4. Site-directed mutagenesis experiments confirmed that the 596C>T change, without the 44 nucleotide deletion, was responsible for loss of Dr^a antigen expression [64].

19.4.4 WES^a (CROM8) and WES^b (CROM 9)

WES^a was detected on the red cells of 61 of 10 982 (0.56%) Finns [66], two of 1610 (0.12%) white Americans [67], seven of 1460 (0.48%) African Americans [67], and five of 245 (2.04%) black North Londoners [68].

Only two examples of antibodies to the high frequency antigen WES^b are known, both found in the sera of black women with WES(a+) red cells [68,69]. The only other known *WES^a* homozygote was a Finnish woman with six WES(a+) and no WES(a–) children [68].

The WES^b/WES^a polymorphism results from Leu82Arg in CCP-1 of DAF [57] (Table 19.1). The *WES^a* allele (*CROM*01.08*) lacks an *Afl*II restriction site. In a MAIEA

assay, two murine monoclonal antibodies to epitopes on CCP-1 blocked binding of anti-Tc^a, whereas a third did not. The opposite result was obtained with the same monoclonal antibodies and anti-WES^b, suggesting that Tc^a and WES^b are on opposing faces of CCP-1 [21]. These results support the molecular model of Kuttner-Kondo *et al.* [10].

19.4.5 Other high frequency Cromer antigens

Eight other Cromer antigens have been described, all of very high frequency. Antigen-negative phenotypes all result from homozygosity for single nucleotide changes encoding amino acid substitutions in DAF [32,47,57,70, 71] (Table 19.1 and Figure 19.2). Some frequency studies are listed in Table 19.3.

19.4.5.1 Es^a (CROM6)

Three examples of anti-Es^a and three Es(a–) propositi are known: a woman of Mexican descent with two Es(a–) siblings [45], a Jewish woman of Tunisian origin with an Es(a–) brother [72], and an African American man [73]. Anti-WES^b reacts slightly less strongly with Es(a–) cells than with Es(a+) cells, whereas two examples of WES(a+b–) cells reacted only very weakly with anti-Es^a, requiring adsorption/elution tests for detection [68]. The close proximity between the amino acid substitutions associated with Es(a–) and that responsible for the WES^b/WES^a polymorphism (positions 80 and 82) explains the serological interaction between Es^a and WES^b.

19.4.5.2 UMC (CROM10)

The only known UMC– propositus is a Japanese blood donor detected during screening for donor antibodies in northern Japan [46]. One of her three siblings was also UMC–.

19.4.5.3 GUTI (CROM11)

Anti-GUTI was found in a previously transfused Chilean man, with a GUTI– sister [47]. Application of a *Mae*II PCR-RFLP assay revealed six heterozygotes for the GUTI mutation among 114 Chilean Mapuche Indians (allele frequency 2.6%).

19.4.5.4 SERF (CROM12)

Anti-SERF was identified in a pregnant Thai woman [70]. A *Bst*N1 PCR-RFLP assay revealed 21 heterozygotes and one homozygote for the SERF mutation among 1041 Thai donors (allele frequency 1.1%) [48].

19.4.5.5 ZENA (CROM13)

Anti-ZENA was identified in a Syrian Turkish antenatal patient [71]. A *Bsr*1 PCR-RFLP assay revealed no alleles with the ZENA mutation among 150 Israeli donors.

19.4.5.6 CROV (CROM14)

Anti-CROV was identified in a Croatian woman who had been pregnant three times [71]. A *Taq*1 PCR-RFLP assay revealed no alleles with the CROV mutation among 100 Croatians.

19.4.5.7 CRAM (CROM15)

Anti-CRAM was identified in a Somali woman in her third pregnancy [71]. CRAM– red cells, with an amino acid substitution at position 247, have weakened expression of GUTI (amino acid 240), but normal expression of the other antigens on CCP-4: ZENA (242), Cr^a (227), and UMC (250). GUTI– cells have weakened expression of CRAM.

19.4.5.8 CROZ (CROM16)

Anti-CROZ was identified in a 78-year-old Australian woman [32]. CROZ– is associated with Arg130His. Arg130 plays an important role in DAF functional activity: Arg130Ala and Arg130Leu substitutions synthesised by site-directed mutagenesis, abolished and significantly reduced C3 convertase activity, respectively [74].

19.4.5.9 CRUE (CROM17)

Anti-CRUE was found in a Thai woman heterozygous for two rare alleles with mutations in exon 5:

1 650T>G, Leu217Trp, presumably responsible for the CRUE– phenotype; and

2 639G>A, Trp213stop, an inactivating mutation that would be predicted to produce no DAF which would be present in the membrane [75].

19.4.5.10 CRAG (CROM18)

Anti-CRAG was found in a woman of Greek ancestry with Leu82Pro in CCP-1 [76]. She was transfused with three incompatible units of blood from random donors, with no adverse consequences.

19.4.6 Other serological characteristics of Cromer system antigens

Cromer system antigens are readily destroyed by treatment of the red cells with α-chymotrypsin, but not by trypsin, papain, ficin, or sialidase, and in this way are easily distinguished from virtually all other blood group antigens. Treatment of intact red cells with the disulphide

bond reducing agents AET and DTT results in only slight weakening of the Cromer antigens. This is surprising, considering that each CCP domain is maintained in its folded configuration by two disulphide bonds (Section 19.2.1).

Haemagglutination-inhibition has demonstrated that Cromer system antigens are present in serum and urine of individuals with the corresponding antigen on their red cells [35,44,46,59,66,68,77]. Anti-Cr^a can be readily removed from sera by adsorption with platelet concentrates [78,79].

19.4.7 Clinical significance of Cromer system antibodies

Cromer system antibodies are mostly IgG, though IgM anti-Cr^a is reported [80]. IgG1 generally predominates, but Cromer system antibodies of all four subclasses have been reported [60–62,66,73,80–83].

Cromer system antibodies are not usually considered clinically significant and there are many reports of successful transfusion of incompatible red cells to patients with anti-Cr^a and -Tc^a [50,84–86]. Anti-Cr^a [85] and -Tc^a [87], however, have been blamed for clinical transfusion reactions, with the anti-Tc^a destroying six units of Tc(a+) red cells, three of them within a day of transfusion. Conclusions from *in vivo* red cell survival studies and *in vitro* functional assays with Cromer system antibodies have varied, some suggesting that the antibodies are of no clinical importance [50,60,61,78,80,83–85,88,89] and others predicting reduced survival of transfused incompatible red cells [34,44,61,73,79,82,83,85,87,90–92]. Only 38% of radiolabelled IFC+ red cells survived 24 hours after injection into an Inab phenotype man with anti-IFC [34] and another example of anti-IFC removed all IFC+ cells within 15 minutes of injection [90]. Anti-Tc^a comprising IgG1, IgG2, and IgG4 gave results in the monocyte monolayer assay (MMA) suggestive of clinical significance; two years later the serum contained only IgG2 and IgG4, and the MMA and *in vivo* red cell survival tests suggested that incompatible transfusion would be well tolerated [83]. In most cases, least incompatible red cells may be selected for transfusion to patients with Cromer system antibodies, although, if possible, antigen-negative red cells should be selected for strong examples of the antibody. Transplantation of a Dr(a+) kidney into a Dr(a–) patient with IgG2 plus IgG4 anti-Dr^a was successful, with good graft function and no increase in titre of the antibody [60].

Despite the indications that Cromer system antibodies often have the potential to be haemolytic, these antibodies are never responsible for clinical signs of HDFN. DAF is present on placental trophoblast epithelial cells derived from the fetus [93]. It is common for strongly reactive Cromer antibodies (anti-Cr^a, -Dr^a, -WES^b, -CRAM) to become weakly reactive or undetectable in maternal plasma during the second and third trimesters of pregnancy, only to reappear shortly after parturition [42,61,69,71,78]. In one case anti-Cr^a could be eluted from the placenta [94]. It is likely, therefore, that maternal Cromer system antibodies become absorbed by the placenta, protecting the fetus from the antibodies.

19.4.8 Monoclonal antibodies

Numerous rodent monoclonal antibodies to DAF have been produced, defining epitopes on each of the four CCPs [13,24,51,95]. They generally behave like anti-IFC as they do not react with red cells of the Inab phenotype and react only very weakly with Dr(a–) cells. Human monoclonal anti-IFC was produced from lymphocytes of an individual with Inab phenotype [30].

19.5 Functional aspects DAF and CD59: GPI-linked complement-regulatory proteins

DAF protects cells from complement-mediated damage by inhibiting the amplification stage of complement activation. DAF inhibits association and accelerates dissociation of C4b2a and C3bBb, the C3 convertases of the classical and alternative pathways, respectively. Classical pathway C3 convertase regulatory function resides within CCP-2 and -3, whereas alternative pathway regulatory function resides within CCP-2, -3, and -4 [96]. DAF has a wide distribution in the body. It is present on granulocytes, monocytes, and lymphocytes [1], and on many epithelial cells, including placental trophoblast epithelium, where it plays a role in protecting the fetus from maternal complement-mediated attack [93].

CD59, also known as the membrane inhibitor of reactive lysis (MIRL), is a complement-regulatory glycoprotein of the Ly-6 superfamily. It inhibits complement-mediated haemolysis by binding to C8 and C9 and preventing assembly of the membrane-attack complex. CD59 is present on red cells, but does not have blood group activity. Like DAF, CD59 is attached to the red cell membrane by a GPI anchor. For reviews on CD59 see [3,97,98].

Paroxysmal nocturnal haemoglobinuria (PNH), a disease characterised by intravascular haemolysis, venous

thrombosis, and blood cytopenias, is caused by somatic mutations in *PIGA*, an X-linked gene that encodes a subunit of an enzyme essential for the biosynthesis of the GPI anchor. Over 100 different mutations, most of which are small insertions or deletions, have been identified, and occur within haemopoietic stem cells [6]. Somatic cells contain only one active X-chromosome, and consequently only one active *PIGA* gene. For the disease to manifest, the affected clone must expand at the expense of normal cells. Healthy people have low numbers of *PIGA* mutated cells, but in PNH an autoimmune process develops in which cytotoxic T cells of the patient target GPI-linked proteins on normal blood cells and selectively destroy the normal blood cell population, leaving the mutated clone, which lack GPI-linked proteins, to proliferate [7,99].

The affected red cells in PNH patients (PNHIII cells) are deficient in all GPI-linked proteins, including DAF and CD59, and can be lysed, *in vitro*, by acidified human serum, a process that involves the activation of the alternative complement pathway. Despite DAF deficiency, red cells of the Inab phenotype show no evidence of haemolysis and Inab phenotype is not associated with any symptoms of haematological disease [25,26,28,29]. Unlike PNH cells, Inab phenotype cells are not lysed by acidified serum or by cobra venom and they are only slightly more susceptible to lysis than normal cells in standard complement-mediated lysis tests, such as lysis in the presence of cold antibody or sucrose. Direct antiglobulin tests on Inab phenotype cells with antibodies to human complement components demonstrated that there is no accumulation of C3 fragments on Inab phenotype cells, as might have been expected in the absence of a C3 convertase inhibitor [25,26]. When CD59 has been inactivated by the addition of monoclonal anti-CD59, however, Inab phenotype red cells are haemolysed by acidified human serum [29,100]. DAF and CD59 share the role of protecting red cells from the activity of autologous complement. CD59 appears more effective than DAF in this respect: a patient with red cell CD59 deficiency resulting from homozygosity for single base deletion within the CD59 gene, but with normal levels of DAF and other GPI-linked glycoproteins, had a mild PNH-like haemolytic anaemia [101,102]. In a complement-mediated lysis sensitivity (CLS) test, the following scores (in CLS units) were obtained: DAF-deficient (Inab) red cells, 4.6; CD59-deficient red cells, 11.7; DAF- and CD59-deficient (PNHIII) red cells, 47.6 [103].

Decreased levels of CD55 and, possibly, CD59 may be a cause of anaemia in children infected with the malarial parasite, *Plasmodium falciparum* [104]

The first CCP domain of DAF, which is not involved in complement regulation, is a ligand for CD97, present on monocytes and granulocytes, and up-regulated on the activation of T and B cells [105]. The function of this interaction is not known.

19.6 DAF as a receptor for pathogenic microorganisms

Like globoside, the P antigen (Section 4.10.1), DAF is exploited as an attachment site on epithelial cells for strains of *Escherichia coli* associated with urinary tract infection, cystitis, and protracted diarrhoea [106]. Fimbriae from 075X-positive *E. coli* agglutinated red cells *in vitro*, with the exception of those with the Inab and Dr(a–) phenotypes [107]. The 075X and other fimbria-like adhesins that bind to Dr^a are referred to as Dr adhesins. *E. coli* and purified Dr adhesins bound Chinese hamster ovary (CHO) cells transfected with normal *DAF* cDNA, but not untransfected cells or cells transfected with *DAF* cDNA encoding the Ser199Leu substitution associated with the Dr(a–) phenotype [108]. In addition to Ser199, Ser189 and, to a lesser extent, Tyr194 and Leu196, are important in binding Dr adhesin, inferring that one loop in CCP-3 is involved in anchorage and subsequent internalisation of Dr-fimbriated *E. coli* by epithelial cells [109,110].

DAF is a ligand for many picornaviruses, including echoviruses and coxsackieviruses, which cause a range of symptoms including diarrhoea, aseptic meningitis, and severe respiratory disease in neonates [2,105]. Some echoviruses are capable of agglutinating red cells [111]. Each of the four CCP domains of DAF are exploited by different viruses [105].

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