Review

The FORS awakens: review of a blood group system reborn

A.K. Hult and M.L. Olsson

The presence of the FORS1 antigen on red blood cells was discovered relatively recently, and in 2012, the International Society of Blood Transfusion (ISBT) acknowledged FORS as blood group system number 031. This rare antigen is carried by a glycosphingolipid and formed by elongation of the P antigen. Most people have naturally occurring anti-FORS1 in their plasma. The clinical significance of these antibodies is unknown in the transfusion setting, but they can hemolyze FORS1+ erythrocytes in the presence of complement in vitro. First believed to be part of the ABO system, it was later shown that the gene encoding the glycosyltransferase giving rise to FORS1 expression is *GBGT1*. This gene had previously been deemed nonfunctional in humans, but a mutation, so far only detected in FORS1+ individuals, restores the enzymatic activity. Tissue distribution of the antigen in FORS1+ individuals has not been studied in detail, although the gene is expressed in several cell types. The antigen itself is known to be a receptor for various pathogens and toxins and has been detected in different forms of cancer, but the implications thereof are not fully understood. ***Immunohematology* 2017;33:64–72.**

Key Words: FORS, FORS1, low-prevalence antigen, Forssman, A_{pae}

The first blood group system was discovered in 1900 by Landsteiner,[1,2] and its antigens were later characterized as glycans.[3,4] Since then, ABO has been joined by six other systems that are also of carbohydrate nature: P1PK, H, Lewis, I, GLOB, and FORS (www.isbt-web.org). The defining antigens in these blood group systems are all determined by immunodominant sugar moieties of glycoproteins and/or glycosphingolipids. The function of these structures is unknown, but it has been suggested that they are a part of our innate immune defense.[5] Carbohydrate expression is relatively well conserved in mammals, but the variation seen both within and between species may reflect evolutionary developments to differentiate the individual species-specific susceptibility to various pathogens.[6] Another common principle for these blood group systems is that naturally occurring antibodies are formed against the carbohydrate antigens that are lacking. These antibodies have the potential to neutralize pathogens expressing the corresponding glycan epitopes.[7,8] In modern medicine, however, they mainly constitute a significant transfusion and transplantation barrier and can also cause fetomaternal incompatibility. This review will summarize the current knowledge on the newest of our carbohydrate blood group systems, FORS, acknowledged by the International Society of Blood Transfusion (ISBT) in 2012. For obvious reasons, the body of knowledge is still limited, especially when it comes to the clinical significance of this system.

Forssman: Historical Aspects

The first mention of what was later designated the Forssman (Fs) antigen was reported in 1907 by Frouin.[9] This heterophilic antigen was re-identified in 1911 by John Forssman (1868–1947), professor of microbiology, pathology, and general medicine at Lund University, Lund, Sweden (Fig. 1). He immunized rabbits with tissue from guinea pig or horse, and these rabbits produced an antibody that was shown to hemolyze red blood cells (RBCs) from sheep in the presence of complement. Tissue from other species (e.g., cow or rat) did not induce the same immune response.[10] In honor of his detailed description of these experiments, the antigen recognized by these antisera was named after Dr. Forssman.

Fig. 1 Dr. John Forssman, professor of pathology, microbiology, and general medicine at Lund University, Lund, Sweden. (Image source: The South Swedish Society for the History of Medicine.)

By using the antibodies towards this (then structurally undefined) antigen, different animal species were categorized to be either Fs+ or Fs–.[11] Humans were defined as an Fs– species, although there are reports claiming the presence of this structure in human tissue from malignant tumors[12–17] and even a few publications on its presence in normal tissue.[12,18]

The Fs antigen is a carbohydrate moiety present in various tissues, including RBCs, depending on species. The structure of the antigen was resolved some 60 years after Dr. Forssman's experiments and identified to be GalNAcα1-3GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-Cer by Siddiqui and Hakomori.[19] A few years later, the structure was confirmed by mass spectrometry.[20]

Over the years, the naturally occurring antibodies towards Fs present in the vast majority of people have been associated with different autoimmune diseases such as rheumatoid arthritis,[21] Guillain-Barré syndrome,[22] and Graves' disease.[23] The significance of these findings is still unclear. In recent years, anti-Fs has been reported to play a role in the xenotransplantation setting.[24–26]

Nomenclature

In light of recent developments, a motion was made to make FORS the 31st blood group system, and this proposal was accepted by the ISBT Working Party for Red Cell Immunogenetics and Blood Group Terminology at its meeting in 2012.[27] FORS1 (031001) is so far the only antigen of the FORS blood group system. The correct nomenclature is shown in Table 1.

Table 1. Summary and nomenclature of the FORS blood group system

System name	FORS (ISBT no. 031)
System symbol	FORS
Antigen name	FORS1 (ISBT no. 031001)
Carrier molecule	Forssman glycosphingolipid
Synthesized by	Forssman synthase
Gene name	*GBGT1*

ISBT = International Society of Blood Transfusion.

Transition from ABO to FORS

The history of the human FORS1 antigen on RBCs originates back to 1987 when Dr. Robert Stamps and co-workers reported what appeared to be a peculiar weak A subgroup that they termed A_{pae}. This phenotype was present in healthy individuals from three different unrelated English families.[28] The "p" in A_{pae} stands for the reaction observed with *Helix pomatia,* and "ae" identifies its ability to adsorb and elute some polyclonal anti-A reagents. For a long time, the antigen underlying this phenotype was considered to be one of the many A_{weak} variants within the ABO blood group system (ISBT no. 001) and, as stated in a textbook ("Had the authors chosen to call A_{pae} a form of A_x it is doubtful that many would have argued"), it was considered very similar to one of the less uncommon ABO subgroup phenotypes, A_x.[29]

Genomic typing of *ABO* was performed in our laboratory on samples from two unrelated individuals displaying the A_{pae} phenotype. The purpose was to characterize the underlying *A* allele that caused the hypothesized weak expression of A. The surprising result was that both individuals were homozygous for the common deletion, c.261delG, in the most frequent *O* alleles (*ABO*O.01.01/*O.01.01* and *ABO*O.01.01/*O.01.02*) and should clearly phenotype as group O. Based on this result and in collaboration with Professor Steve Henry in Auckland, New Zealand, and scientists at the University of Gothenburg in Sweden, we subsequently came up with the hypothesis that the A_{pae} phenotype must be due to an A-like but ABO-independent antigen. In 2013, we published the biochemical and genetic characterization of the new blood group.[30] We showed that the gene that gives rise to the A_{pae} phenotype was indeed not *ABO* but *GBGT1* (globoside α-*N*-acetylgalactosaminyltransferase, EC 2.4.1.88), the Forssman gene. Based on the data from that report, which included extensive serologic testing, structural analysis of the glycolipid antigen, and transfection studies, all the data were in place to promote A_{pae} to become the new blood group system FORS. The phenotype name A_{pae} was deemed obsolete, and the antigen was accordingly named FORS1.

Biochemistry

FORS1 is a glycosphingolipid that is part of the globo-series synthesis pathway. This pathway also harbors other carbohydrate blood group antigens such as P^k, P, NOR, LKE, and the globo version (type 4) of H, A, and B. Depending on the sugar moiety added to lactosylceramide, different glycosphingolipid pathways are created. The globo-series is initiated by addition of a galactose (Gal) in the α1–4 position to lactosylceramide, and this structure constitutes the P^k antigen (also known as globotriaosylceramide, Gb3, or CD77). Adding an *N*-acetyl-D-galactosamine (GalNAc) in a ß1–3 position to the P^k structure will result in the P antigen (globoside, Gb4), and this structure is the precursor for the enzyme that makes FORS1, the Fs synthase (Fig. 2). It has been suggested that the Fs antigen may also occur as the glycan portion of glycoproteins, but this has not yet been corroborated in humans.[16,31]

The Fs synthase has a topology that matches well with the structure of a single-pass type II transmembrane glycosyltransferase. In analogy with the blood group A transferase, 3-α-*N*-acetylgalactosaminyltransferase (GTA), the Fs synthase transfers a terminal GalNAc in α1–3 linkage.

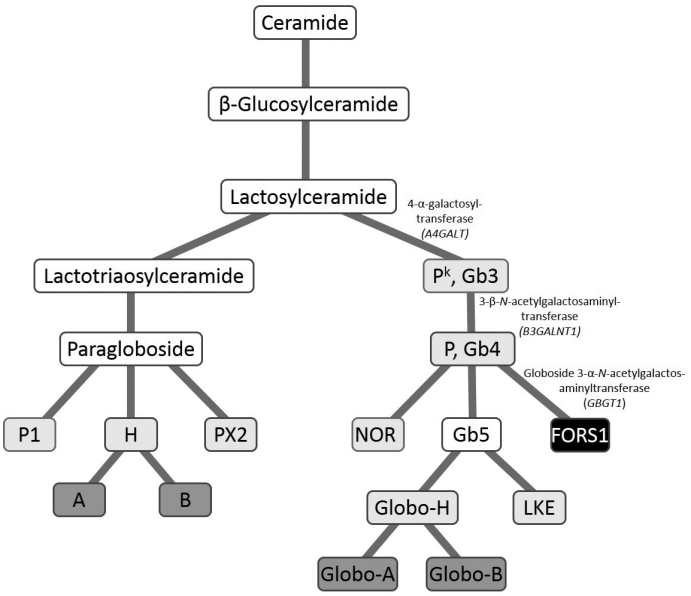

Fig. 2 Synthetic pathway for the glycosphingolipid constituting the FORS1 blood group antigen (black box) as well as schematic representation of other related structures (white and gray boxes) of the globo-series (right) and neolacto-series (left). ABO antigens are shown in dark gray; other blood group antigens are shown in light gray. For the globo-series pathway resulting in the FORS1 antigen, the responsible genes are given in parentheses under the implicated enzymes.

Instead of the H antigen, however, the required precursor for Fs synthase is the P antigen (globoside, Gb4), as mentioned earlier (Fig. 3).

Based on sequence similarities, glycosyltransferases have been categorized into families in the Carbohydrate-Active EnZymes (CAZy) database.[32] The Fs synthase is encoded by the *GBGT1* gene and belongs to the GlycosylTransferase 6 (GT6) family alongside, for example, ABO (Table 2).

Until the discovery of FORS1+ individuals, GTA and 3-α-galactosyltransferase (GTB)—responsible for blood group

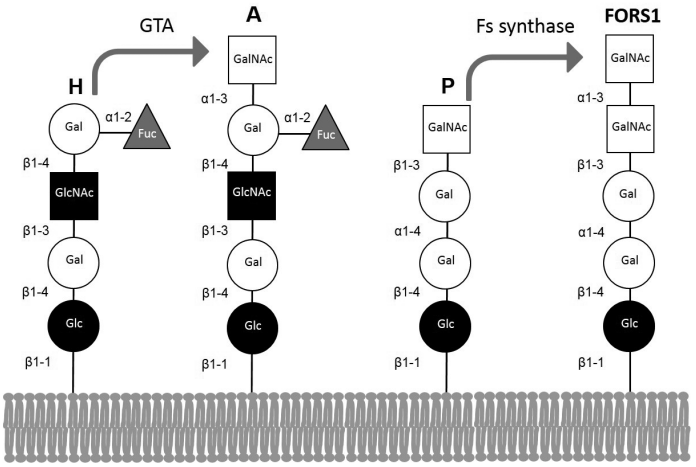

Fig. 3 The FORS1 antigen and its precursor, the P blood group antigen (also known as globoside, Gb4), are shown schematically in comparison with blood group A antigen synthesis by A glycosyltransferase (GTA), where the H antigen is the required precursor.

A and B expression,[33] respectively—were considered to be the only functional glycosyltransferases in the human GT6 family. The other members (Table 2) had been deemed nonfunctional.[30,34–37] The number of GT6 genes varies from species to species, and even within phylogenetic groups, the type and number of genes can vary significantly.[39]

Genetic and Molecular Basis

The sequence homology between the members of the GT6 family indicates that these genes were derived from the same ancestral gene where gene duplications have occurred with subsequent divergence. The expansion and deletions of GT6 genes during vertebrate evolution suggests that this multigene family follows a birth-and-death evolution type.[39,40]

Table 2. Details about the most investigated members of the human GlycosylTransferase 6 (GT6) gene family

EC no.	Glycosyltransferase	Donor	Acceptor	Gene	Chromosome location	Transcribed	Translated	Produced antigen	Reference
2.4.1.37	3-α-galactosyltransferase	UDP-Gal	H antigen	*ABO*	9q34	Yes	Yes	B	33
2.4.1.40	3-α-*N*-acetylgalactosaminyl-transferase	UDP-GalNAc	H antigen	*ABO*	9q34	Yes	Yes	A	33
2.4.1.87	3-α-galactosyltransferase	UDP-Gal	Galβ1-4GlcNAc-R	*GGTA1*	9q33	Yes	No	α-Gal epitope	34 35
2.4.1.87	3-α-galactosyltransferase	UDP-Gal	Galβ1-4Glcβ1-Cer	*A3GALT2*	1p35	Yes	No	iGB3	36
2.4.1.88	globoside 3-α-*N*-acetylgalactosaminyl-transferase	UDP-GalNAc	Globoside/P antigen/Gb4	*GBGT1*	9q34	Yes	No/Yes	Forssman	30 37 38

EC no. = enzyme commission number.

The cDNA corresponding to the canine Fs synthase was cloned in 1996 by Haslam and Baenziger.[41] A 347–amino acid (aa) open reading frame (ORF) was predicted, and as previously mentioned, the overall structure matches well with a type II transmembrane glycosyltransferase. The canine Fs synthase construct was tested in a transfection experiment where it was shown to result in expression of the Fs antigen in the COS-1 cell line.

The human *GBGT1* equivalent was cloned in 1999 by Xu et al.[37] It is situated on chromosome 9 (9q34) in close proximity to the *ABO* gene and consists of seven exons spanning over ~11 kb (Fig. 4). The human aa sequence showed a 45 percent homology to GTA and GTB.[33,36] The ORF (1041 nucleotides [nts]) encodes a 347-aa-long protein with a molecular weight of ~40 kDa. In that study, the authors also showed by transfection studies that the human Fs synthase did not possess the ability to synthesize Fs glycolipid, as the canine version did. This finding corroborated the known expression of Fs in dogs and its absence in humans. Chimeric constructs, namely, combinations of canine and human sequences, showed that the human catalytic site was inactive, but no precise reason as to why was proposed. RNA expression in a variety of tissues was measured, and transcripts were detected in all tissues examined but did not appear to give rise to Fs antigen expression. The authors hypothesized that, given the high expression of RNA, this human Fs synthase might have acquired an altered enzyme specificity. Others have argued that the high homology with canine Fs synthase and the presence of transcripts suggest that the human ability to synthesize Fs was lost quite recently in an evolutionary perspective.[42]

Svensson et al.[30] reported the first verified and structurally confirmed expression of the Fs antigen on human RBCs. In addition to extensive serological and biochemical verification of the antigen, it was shown that individuals with the A_{pae} phenotype had a single nucleotide polymorphism (SNP) in the ORF of the *GBGT1* gene. The mutation c.887G>A gave rise to an aa change, p.Arg296Gln, and we hypothesized that this was the key residue for the gain of function for the Fs synthase in these individuals. This idea was supported by genetic analysis of available members in the family pedigrees and also confirmed by transfection of Fs– cell lines that became Fs+ when 887A but not 887G Fs synthase-encoding constructs were introduced.[30] The same finding, but from a different angle, was simultaneously corroborated in a study by Yamamoto et al.,[38] in which they showed aa position 296 to be essential for Fs antigen expression. This was hypothesized by comparing aa sequences of Fs– and Fs+ species, thereby identifying candidate aa positions in the enzyme conserved in Fs+ species and differing from Fs– species. This approach revealed three positions for further testing: c.536C>T (p.Ile179Thr), c.688G>A (p.Gly230Ser), and c.887A>G (p.Gln296Arg). Each of these substitutions was evaluated by introducing them into a mouse Fs construct (an Fs+ species) for subsequent expression in the COS-1 cell line. Two positions were shown to be crucial for Fs antigen expression, when changing nts c.688 and c.887 to the murine equivalent in a human construct, the Fs synthase activity was completely restored to allow synthesis of Fs antigen in the COS-1 cell line. The conclusion drawn was that p.Ser230Gly and p.Gln296Arg constitute the cause of Fs negativity in humans, although the study by Svensson et al.[30] showed that p.Arg296Gln suffices for RBC expression of Fs activity.

The prevalence of c.887G>A is very low, less than 1 percent in the populations tested, but c.887G>A has been detected on two distinct alleles in different families. In addition to the investigated pedigrees from Stamps et al.,[28] the mutation has also been found in a database search in the NHLBI-ESP (National Heart, Lung, and Blood Institute–Exome Sequencing Project),[43] although the phenotype has not been confirmed there. A mutation, c.363C>A, that gives rise to an early stop codon in exon 7 truncates the Fs synthase prematurely and is predicted to cause lack of the enzymatic site. This null allele is fairly common and shows a prevalence of greater than 4 percent according to the Erythrogene database (www.erythrogene.com), an open Web resource that summarizes the allelic variation in all blood group genes in the 2504 individuals (from 26 different populations around the globe) included in the 1000 Genomes Project.[44] Multiple other *GBGT1* variants were observed in this database but, for most, their prevalence is very low. Among the 68 *GBGT1* alleles noted in Erythrogene so far, only 4 have an allele frequency greater than 1 percent, and 32 were found only once and may need

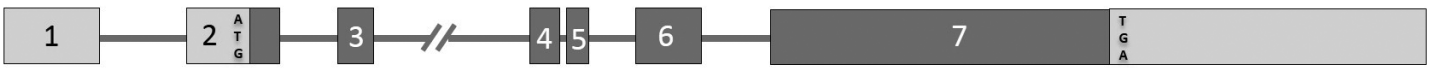

Fig. 4 Genomic organization of the *GBGT1* gene. The seven exons are represented by numbered rectangles drawn to scale (introns, represented by a gray line, are not). Black vertical lines in exons 2 and 7 indicate the start and stop codons, respectively, and the open reading frame is shown in dark gray.

confirmation. In fact, the two alleles that give rise to FORS1 were not found at all in the 1000 Genomes samples but are included only in the ISBT reference lists (www.isbt-web.org).

Antigens and Antibodies in the System

Antigens

Because FORS1+ is very rare, its real prevalence is unknown, but so far only three families with the A_{pae} phenotype (now referred to as FORS1+) have been reported. In addition, a single individual with the same genetic variant has been noted, but no phenotypic data were available. So far, the antigen has only been detected in individuals of European extraction. The Fs glycosphingolipid structure is normally not expressed on any type of human tissue and is widely regarded as a structure only found in certain animal species. Because screening for FORS1 is not a standard procedure, it is unlikely to detect this rare phenotype on a routine basis. Nevertheless, if detection of c.887G>A were to be integrated on commercially available genotyping platforms in the future, screening could easily become part of daily practice. A possible reason to do this would be to rid blood banks of donated RBC units expressing FORS1. This may become an issue of debate if the naturally occurring antibodies against FORS1 (discussed in the next section) found in the plasma of most people were found to be clinically significant—that is, hemolytic in vivo.

In the original report by Stamps et al.,[28] the A_{pae} phenotype was detected by a cross-reaction of a polyclonal anti-A, but because polyclonal ABO reagents are scarce today and standard ABO phenotyping is now performed with monoclonal reagents, detecting this rare phenotype by ABO typing is unlikely. In a study by Barr et al.,[45] the authors tested 19 monoclonal anti-A reagents against kodecytes, RBCs uploaded with a FORS1 pentasaccharide Function-Spacer-Lipid (FSL) construct,[46] and did not notice any of the cross-reactivity seen with polyclonal reagents.

Antibodies

In analogy with ABO, most humans have naturally occurring antibodies to the FORS1 antigen they lack. These antibodies are believed to be formed in response to microbial surface glycan structures in the commensal gut flora, because some of the latter are very similar to carbohydrate blood group antigens. Their presence may be a microbial strategy to evade the immune defense in the host in accordance with the molecular mimicry concept.[47] The human anti-Fs are mainly of IgM type, but there may also be a component of IgG.[48,49] Svensson et al.[30] reported crossmatch reactivity with FORS1+ RBCs to be about 6 percent by the indirect antiglobulin test, and approximately 23 percent caused direct agglutination. Great variation in antibody strength was seen among the almost 300 samples of random blood donor plasmas tested.

In a recent screening study, which included 800 blood donors, it was shown that all plasma samples but one had antibodies against sheep RBCs, which are known to express very high levels of the Forssman antigen. These donor plasma samples also reacted with kodecytes.[50] The possible influence of other human anti-sheep xenoantibodies as reported by Strokan et al.[49] and potential cross-reactions of the polyclonal anti-A present in human plasma were not discussed in that report.

The clinical relevance of anti-FORS1 in a transfusion setting remains unclear, but it has been shown that human ABO-compatible plasma has the ability to hemolyze FORS1+ RBCs in the presence of complement. This finding is further emphasized when RBCs have been papainized.[30] From a transfusion point of view, FORS1+ units should only be transfused following a negative crossmatch until we know more (i.e., electronic crossmatch using type-and-screen should not be used).[30] The electronic crossmatch is currently used in many parts of the world; thus, a FORS1+ unit may be 4+ incompatible and still be transfused. Because of the low prevalence of this phenotype, it is still questionable whether genetic screening to exclude FORS1+ donors is worthwhile.

Tissue Distribution

The heterophilic Fs antigen has been recognized in several species, both mammals and others. Because it is expressed in some species, but not in others, the presence or absence of the Fs antigen has classified species as Fs+ or Fs–.[11] Sheep, dog, cat, and mouse are examples of Fs+ animals, whereas pigeon, rabbit, cow, and rat do not express the Fs antigen. The level of antigen seen on RBCs varies; some are high expressers, like sheep RBCs, with lower expression seen on RBCs from dogs and cats. There is also heterogeneity with respect to what cell types carry the antigen; in many species, Fs antigen expression is not found on RBCs but is restricted to other tissue. Purification of the Fs glycolipid from different species has been performed from kidney tissue and intestinal mucosa, among others.[20,31] Humans and apes have been considered Fs–, but there are some reports of Fs glycolipid expression in normal human non-hematopoietic tissue.[12,16,18] Because the Fs synthase has been deemed nonfunctional in the majority of humans, the mechanism underlying this expression remains unknown.

Although the expression of Fs antigen on human RBCs was unequivocally shown by Svensson et al.,[30] the presence of the antigen in non-erythroid tissue in these individuals was not investigated. It has been shown that the *GBGT1* gene is transcribed in different human tissues,[37] but this finding is not expected to give rise to any Fs antigen expression in FORS1– individuals. It is tantalizing, therefore, to speculate that an individual expressing the antigen on RBCs may express the antigen in other tissues as well, since other antigens in the globo-series like P and P^k are expressed, for example, in the urinary tract. The mRNA levels as measured in blood did not show any significant difference between FORS1+ individuals and FORS1– controls, but the c.887G>A-activated version of the *GBGT1* gene is able to give rise to significant levels of FORS1 on RBCs. This finding begs the question in these FORS1+ individuals: Is the Fs glycosphingolipid expressed in all the various tissues where the gene is transcribed? Post-transcriptional and epigenetic factors may of course influence this, and so does the availability of acceptor substrate for the translated enzyme. Another major question that remains to be answered is how is this gene regulated.

Disease Associations

Infections

The first type of structures that many pathogens encounter in the host are glycans on cell surfaces and in mucus. There are numerous examples of bacteria, viruses, and parasites that invade/impact the host cells via these carbohydrate structures, some of them being blood group antigens. For example, *Helicobacter pylori,* known to cause gastritis, uses the Le^b antigen,[51] and the norovirus that causes gastroenteritis is dependent on the ABO secretor status of the host.[52,53] In the most virulent species of the malaria parasite, *Plasmodium falciparum,* it has been shown that the parasite-rosetting ligands PfEMP1 and RIFINs bind to RBC surface structures including CR1 and A antigens, respectively. For instance, when infected RBCs form rosettes with uninfected RBCs in a group A individual, the rosettes are bigger and not as easily disrupted as the ones formed in group O individuals. In fact, the latter interaction may be the reason why blood group O protects against severe outcomes from cerebral malaria.[54–57] Currently, however, there is no human disease that shows a clear association with the FORS1+ phenotype, possibly because such individuals have only recently been identified.

The expression of different carbohydrate structures may determine host tropism to microorganisms and, as with many other antigens, the Fs structure can act as an involuntary receptor for microbes. Xu et al.[37] used a canine *GBGT1* construct for transfection experiments and expressed the Fs antigen in either a human or a primate cell line. Following transfection, canine uropathogenic *Escherichia coli* were able to bind the Fs-expressing cells but not the wild-type mock-transfected cells.[37]

P-fimbriated *E. coli* strains may express papG or prsG adhesins, which recognize blood group structures. Whereas papG prefers the Galα4Gal motif in glycolipids like P1 and P^k antigens, the prsG adhesion binds to the Fs-terminating structure GalNAcα3GalNAc.[58] It has also been shown that prsG+ *E. coli* can agglutinate RBCs from FORS1+ individuals and from sheep but not control RBCs from healthy blood donors, independent of ABO group.[30] The clinical consequence of this is not clear but proposes a potential for trans-species infections to occur if the Fs antigen is present on urinary tract epithelium, as many of the related glycolipids are.

Expressing the Fs antigen can also protect the host in some scenarios. The susceptibility to Shiga toxin (Stx) 1 is lowered because the preferred binding site (the P antigen, Gb4) is converted into the Fs antigen.[42] On the other hand, Stx2e isolates from pigs and humans showed a clear interaction with the Fs glycosphingolipid in another study, whereas Stx1 and Stx2 did not.[59]

Cancer

The complex role of glycosylation in cancer is widely acknowledged but not fully understood. Glycosylation alterations such as over- and underexpression and aberrant expression is associated with oncogenic transformation.[60] The COSMIC (Catalogue of Somatic Mutations in Cancer) database[61] lists 66 mutations found in the *GBGT1* gene in relation to various forms of malignancies. There are a number of reports of the Fs antigen being expressed in different forms of cancer and malignant tumor tissue,[12–17] but the mechanism behind this expression is still to be elucidated. Interestingly, Hakomori et al.[12] reported that when the Fs glycolipid was detected in malignant tissue, the surrounding normal tissue typed Fs–; conversely, when present in normal tissue, the Fs glycolipid was not detectable in tumor tissue. The authors also suggested that the incompatible A-like antigen seen in some tumors in non-A individuals may instead be the Fs antigen.[12]

The mechanisms behind this enigmatic expression of the Fs antigen are yet to be resolved, and there are many aspects to take into consideration. In an interesting study from 2017, Yamamoto et al.[62] showed that other glycosyltransferases can be pushed to synthesize the Fs antigen in the laboratory setting based on artificial (not naturally occurring) recombinant

glycosyltransferases. In a situation like cancer, where genetic events are not as closely surveilled and corrected, mechanisms like this may interact with other factors that need to be further examined, such as aberrations in splicing, post-translational modification of the protein, various epigenetic factors, and so forth. As an example of this, Jacob et al.[63] showed that *GBGT1* expression in ovarian cancer cells could be epigenetically downregulated through hypermethylation of the promoter, and this finding was also correlated to protein, Fs synthase, expression.

Summary

The FORS blood group system is young in the context of transfusion medicine. Nevertheless, its single antigen, FORS1, and its corresponding antibody specificity have played a role in medicine for more than a century. The presence and significance of FORS1 in non-erythroid human tissue is still under debate, both in health and disease. The rare FORS1+ RBC phenotype is important to bear in mind when running into unexpected results with lectins and in ABO discrepancies, especially because most people have naturally occurring anti-FORS1 in their plasma. Solving the biochemical and genetic basis underlying human FORS1 expression has added valuable information to our knowledge base about carbohydrate blood group antigens.

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Annika K. Hult, PhD, Postdoctoral Scientist (corresponding author), Clinical Immunology and Transfusion Medicine, Division of Laboratory Medicine, Office of Medical Services, Region Skåne, Klinikgatan 21, SE-221 85 Lund, Sweden, Annika.Hult@med.lu.se; and Martin L. Olsson, MD, PhD, Professor of Transfusion Medicine, Deputy Head of Department, Division of Hematology and Transfusion Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden, and Medical Director, Nordic Reference Laboratory for Genomic Blood Group Typing, Clinical Immunology and Transfusion Medicine, Division of Laboratory Medicine, Office of Medical Services, Region Skåne, Sweden.