Lutheran

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The Lutheran blood group system consists of 19 antigens: four pairs of antithetical antigens—Lu[a]/Lu[b], Lu6/Lu9, Lu8/Lu14, and Au[a]/Au[b]—and 11 antigens of very high frequency. These antigens are located on four of the five immunoglobulin-like domains of both isoforms of the Lutheran glycoprotein. The *LU* gene is on chromosome 19 and comprises 15 exons. The two glycoprotein isoforms differ in the length of their cytoplasmic tails as a result of alternative splicing of intron 13. Lu_{null} phenotype arises from homozygosity for inactivating mutations in the *LU* gene. The dominantly inherited Lu_{mod} phenotype, In(Lu), results from heterozygosity for inactivating mutations in *KLF1*, the gene for the erythroid transcription binding factor EKLF. Clinically, antibodies of the Lutheran system are relatively benign. When hemolytic, they generally cause only mild, delayed hemolytic transfusion reactions or hemolytic disease of the fetus and newborn that can be treated by phototherapy. The Lutheran glycoproteins, which are members of the immunoglobulin superfamily of adhesion molecules and receptors, bind isoforms of laminin with α5 chains, components of the extracellular matrix abundant in vascular endothelia. The primary function of the Lutheran glycoproteins on RBCs could involve the transfer of maturing RBCs from the bone marrow to the peripheral circulation. They could also be involved in vascular occlusion and thrombotic events as complications of sickle cell disease and polycythemia vera, respectively.

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History

Lutheran was the fifth blood group system to be discovered, after ABO, MN (but before S), P, and Rh. Anti-Lu[a], the first Lutheran antibody, was identified in 1945 in a serum that also contained the first examples of anti-C[w] and anti-Levay (which became anti-Kp[c]), plus anti-c and anti-N.[1,2] It was another 10 years before the antibody to the antithetical antigen, Lu[b], was identified.[3] Lutheran is now a complex system comprising four pairs of antithetical antigens plus 11 antigens of very high frequency (Table 1). In 1951 the first demonstration of linkage between human autosomal genes was between the Lutheran blood group gene and the gene originally believed to govern the Lewis blood group, but which turned out to be the ABO secretor gene.[4]

Lu_{null} phenotype, Lu(a–b–), with complete absence of Lutheran antigens and a recessive mode of inheritance, was found in an English woman in 1960[5]; its molecular background was resolved 47 years later.[6] A phenotype called Lu(a–b–), but often subsequently referred to as In(Lu) phenotype, was discovered in 1961 by Dr. Mary (Polly) Crawford, MD, in herself and in three generations of her family.[7] This phenotype, in which Lutheran antigens are barely detectable and there is also weakened expression of some other blood group antigens outside of the Lutheran system, has a dominant mode of inheritance. The molecular basis of In(Lu), heterozygosity for inactivating mutations in a gene for an erythroid transcription factor, was identified in 2008.[8]

Immunochemical analyses revealed that the Lutheran antigens were located on two isoforms of a glycoprotein.[9,10] Cloning and sequencing of the Lutheran gene in 1995,[11] and subsequent disclosure of its organization,[12,13] demonstrated

Table 1. Antigens of the Lutheran system

Antigen				Molecular basis of antigen-negative phenotype		
No	Name	Frequency	Antithetical	Nucleotides	Exon	Amino acids
LU1	Lu[a]	Polymorphic	Lu[b]	230A>G	3	His77Arg
LU2	Lu[b]	High	Lu[a]	230G>A	3	Arg77His
LU3	Lu3	High		Various		
LU4	Lu4	High		1. 524G>A 2. 524G>T	5 5	1. Arg175Gln 2. Arg175Leu
LU5	Lu5	High		326G>A	3	Arg109His
LU6	Lu6	High	Lu9	824C>T	7	Ser275Phe
LU7	Lu7	High		Not known		
LU8	Lu8	High	Lu14	611T>A	6	Met204Lys
LU9	Lu9	Low	Lu6	824T>C	7	Phe275Ser
LU11	Lu11	High		Not known		
LU12	Lu12	High		1. 99-104del 2. 419G>A	2 3	1. delArg34+Leu35 2. Arg140Gln
LU13	Lu13	High		1340C>T, 1742A>T	11, 13	Ser447Leu, Gln581Leu
LU14	Lu14	Low	Lu8	611A>T	6	Lys204Met
LU16	Lu16	High		679C>T	6	Arg227Cys
LU17	Lu17	High		340G>A	3	Glu114Lys
LU18	Au[a]	Polymorphic	Au[b]	1615A>G	12	Thr529Ala
LU19	Au[b]	Polymorphic	Au[a]	1615G>A	12	Ala529Thr
LU20	Lu20	High		905C>T	7	Th302Met
LU21	Lu21	High		282C>G	3	Asp94Glu

Obsolete: LU10, previously Singleton; LU15, AnWj (now 901009).

that the Lutheran (Lu) glycoproteins are members of the immunoglobulin superfamily of receptors and adhesion molecules and differ from each other in the length of their cytoplasmic tails as a result of alternative splicing. Elucidation of the molecular bases of the Lutheran polymorphisms and variants soon followed.[12–14]

Clinically Lutheran is not very important, but it is a very interesting system from genetic and functional perspectives.

The Lutheran Gene (*LU*) and the Lutheran Glycoproteins (CD239)

LU is located on the long arm of chromosome 19, at 19q13.2, as part of the linkage group that includes the genes for the H (*FUT1*), secretor (*FUT2*), and Lewis (*FUT3*) glycosyltransferases and for the LW blood group (*ICAM4*).[15,16] Lutheran cDNA was cloned from a human placental cDNA library by using an amino acid sequence derived from Lu-glycoproteins purified by immunoaffinity chromatography with a monoclonal antibody, BRIC 221.[11]

Immunoblotting of RBC membranes with monoclonal anti-Lu^b or with alloanti-Lu^a, -Lu^b, -Lu3, -Lu4, -Lu6, -Lu8, -Lu12, -Au^a, or -Au^b revealed components of apparent molecular weights of 85 and 78 kDa.[9,10,17] Immunoprecipitation experiments with a rabbit antiserum prepared to an amino acid sequence of the cytoplasmic domain showed that the 78-kDa structure lacks part of the cytoplasmic domain present in the 85-kDa isoform.[11]

The Lu-glycoproteins belong to the immunoglobulin superfamily (IgSF),[11] a large collection of glycoproteins that contain repeating extracellular domains with sequence homology to immunoglobulin variable (V) or constant (C1, C2, or I) domains. IgSF glycoproteins mostly function as receptors and adhesion molecules and may be involved in signal transduction.[18] The extracellular domain of the Lu-glycoproteins is organized into two V and three C2 IgSF domains,[11] with a distinctive bend and flexible junction between domains 2 and 3 (Fig. 1).[19,20] There are five potential *N*-glycosylation sites, one in the third domain and the other four in the fourth domain.

The *LU* gene is organized into 15 exons: exon 1 encodes the signal peptide; exons 2 through 12, the five IgSF domains; exon 13, the transmembrane domain and the cytoplasmic domain common to both isoforms; and exons 14 and 15, the C-terminal 40 amino acids of the 85-kDa isoform.[12,13] *LU* transcripts of 2.5 kb and 4.0 kb encode the 85-kDa and 78-kDa Lu-glycoprotein isoforms, respectively.[21] The two transcripts differ as a result of alternative splicing of intron 13: in the 2.5-kb transcript intron 13 has been removed by splicing and exons 14 and 15 encode the *C*-terminal 40 amino acids of the larger isoform; in the 4.0-kb transcript intron 13 is retained and contains a translation-stop codon, so the unspliced intron 13 and exons 14 and 15 are not translated and the protein product has a cytoplasmic domain consisting only of the 19 amino acids encoded by exon 13.[21] The 78-kDa transcript had previously been identified as an epithelial cancer antigen, and is often referred to by its earlier name, B-CAM,[22] or as Lu(v13).[21]

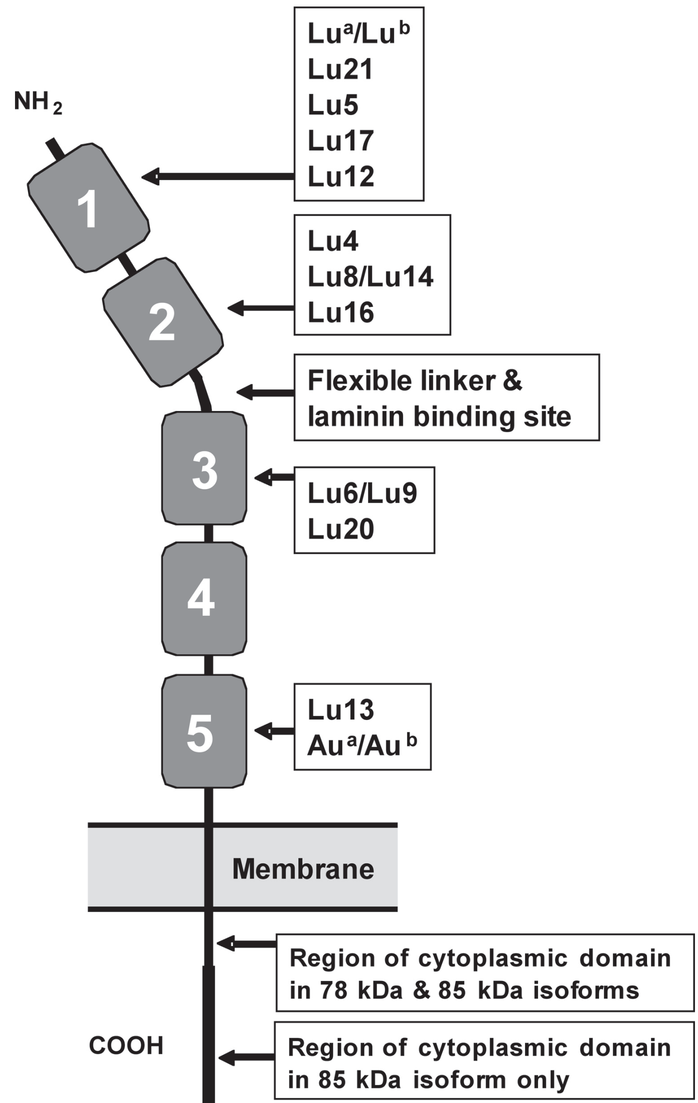

Fig. 1 Model of the Lu-glycoproteins showing the five IgSF domains, the location of the Lutheran antigens, and the cytoplasmic domains in the two isoforms.

The Lutheran Antigens

Lu^a (LU1) and Lu^b (LU2)

Lu^a and Lu^b are inherited as codominant allelic characters.[15] Lu^a is widely distributed among Europeans, Africans, and North Americans, with a frequency of around 6 to 8 percent, but it is very rare in or absent from all other indigenous populations studied.[23] In Caucasian populations the incidence of Lu(b–) is about one in a thousand. Typical frequencies were obtained from tests with anti-Lu^a and -Lu^b on about 1500 white Canadians: Lu^a 6.9 percent; Lu^b 99.9 percent; Lu(a–b+) 93.1 percent; Lu(a+b+) 6.8 percent;

Lu(a+b–) 0.1 percent; *Lu*^{a} allele 3.5 percent; *Lu*^{b} allele 96.5 percent.[24,25] All of 1102 Chinese genotyped were homozygous for *Lu*^{b}.[26]

The Lutheran antigens are very variable in strength, but the antigenic strength usually remains roughly constant within families. There is also heterogeneity of Lutheran antigen strength among individual RBCs within a person, which accounts for the characteristic mixed field agglutination patterns often seen with Lutheran antisera, especially anti-Lu^{a}. Occasionally adsorption and elution tests are required to detect weak Lu^{b} on Lu(a+b+) cells. RBCs from cord samples and from infants in the first year of life have markedly weakened expression of Lu^{a} and Lu^{b} compared with those from adults.[15]

Lu^{a}/Lu^{b} results from a single nucleotide polymorphism (SNP) in exon 3 of *LU*, encoding an amino acid substitution in the first IgSF domain of the Lu-glycoproteins: *Lu*^{a} A230, His77; *Lu*^{b} G230, Arg 77 (Table 1).[12,13] This SNP is associated with an *Aci*I restriction-site polymorphism.[13]

Lu6 (LU6) and Lu9 (LU9)

Lu6 and Lu9, Lutheran antigens of high and low frequency, respectively, have an antithetical relationship and represent an SNP and *Cfo*I restriction polymorphism in *LU* encoding an amino acid substitution in the third IgSF domain (Table 1).[14] The original anti-Lu9 was found, together with anti-Lu^{a}, in the serum of a white woman.[27] RBCs of her husband were Lu(a+b+) and Lu:9. Study of his family showed that Lu9 expression was controlled by the LU locus, although it did not represent an allele of *Lu*^{a} and *Lu*^{b}. The only other example of anti-Lu9 was found in a multiply transfused woman and tests on 200 RBC samples unearthed only one Lu:9 sample (0.5%).[28] Tests with the original anti-Lu9 suggested a higher frequency of 1.7 percent,[27] but that serum also contained anti-HLA-B7 (-Bg^{a}).[29]

RBCs of the original Lu:–6 propositus and those of her two Lu:–6 siblings were strongly Lu:9, suggesting homozygosity.[30] All other Lu:–6 individuals (who are not Lu$_{null}$) have also been Lu:9.

Lu8 (LU8) and Lu14 (LU14)

Lu8 and Lu14, Lutheran antigens of high and low frequency, respectively, have an antithetical relationship and represent an SNP and *FatI* and *Nla* restriction polymorphisms in *LU*, encoding an amino acid substitution in the second IgSF domain (Table 1).[14] The original anti-Lu8 was reported as an antibody to a high-frequency antigen absent from Lu$_{null}$ cells.[31] An antibody in the serum of a multiply transfused dialysis patient, which reacted with RBCs of 2.4 percent of random white donors, reacted strongly with three examples of Lu:–8 and was numbered anti-Lu14.[32]

Au^{a} (LU18) and Au^{b} (LU19): the Auberger Antigens

The first anti-Au^{a} was identified in 1961 in the serum of a multiply transfused woman.[33] The antibody to the antithetical antigen, Au^{b}, was not found until 1989. For many years the Auberger antigens were considered to be independent of Lutheran, despite being absent from In(Lu) RBCs, mainly because of results on one family, which showed recombination between *Au*^{a} and *Lu*^{a}.[34] After the demonstration that Au^{a} and Au^{b} are located on the Lu-glycoproteins,[17] the family was retested for Au^{a} and tested for Au^{b}; errors in the original testing were discovered and the family then supported linkage between Auberger and Lutheran.[35] Family studies confirmed that Auberger and Lutheran antigens are controlled by the same gene.[36] Au^{a} has an incidence of between 80 percent and 90 percent in European populations.[33,37] Au^{b} has an incidence of about 50 percent in a European population and 68 percent in an African American population.[38] Genotyping in Chinese predicted antigen frequencies for Au^{a} and Au^{b} of 98 percent and 24 percent, respectively.[26]

Au^{a} and *Au*^{b} represent an SNP in exon 12 encoding an amino acid substitution in the fifth IgSF domain.[12]

Other Lutheran Antigens

Lu3, Lu4, Lu5, Lu7, Lu11, Lu12, Lu13, Lu16, Lu17, Lu20, and Lu21 are antigens of very high incidence.[15,39] All are absent from Lu$_{null}$ RBCs and absent from, or extremely weakly expressed on, In(Lu) cells. All except Lu11 have been shown to be located on the Lu-glycoproteins by immunoblotting, monoclonal antibody-specific immobilization of erythrocyte antigens assay, or flow cytometry with K562 cells transfected with *LU* cDNA,[10,12,39,40] or their absence has been associated with a mutation in the *LU* gene (Table 1).[6,14,39] Lu11 has not been shown to be inherited[29] and the evidence that Lu11 belongs to the Lutheran system is limited, so Lu11 should be referred to as a para-Lutheran antigen.

Absence of most of these high-frequency antigens is associated with a single nucleotide change in *LU*, encoding an amino acid substitution, but there are some exceptions (Table 1). Lu3 is defined by antibodies produced by immunized individuals with Lu$_{null}$ phenotype and is described later. Homozygosity for two different mutations within the same codon has been responsible for the rare phenotype in the only two known unrelated Lu:–4 individuals: 524G>A encoding Arg175Gln and 524G>T encoding Arg175Leu.[14,41] Lu:–12 also had two different molecular backgrounds in two individuals: (1) a six-nucleotide deletion in exon 2 encoding a deletion of Arg34 and Leu35; (2) 419G>A in exon 3 encoding Arg140Gln.[14] Although the mutations are in different exons, when mapped to a three-dimensional schematic presentation of the Lu-glycoprotein the amino acid changes appeared to be located in close spatial proximity because of the protein folding.[14] It is likely that the mutations altered the same epitope on the Lu-glycoprotein, affecting binding of the anti-Lu12. Lu:–12 was associated with weak expression of Lu^{b} in the original family and in an Lu:–12 individual found by screening 1050 Canadian donors with anti-Lu12.[42] Lu12 and Lu^{b} are both located on the first IgSF domain, so

the Lu^b weakening may result from conformational changes caused by the amino acid changes arising from the Lu:–12 mutations.

Recombinant Lutheran Antigens

Lutheran antigens have been used as models for the application of recombinant proteins in antibody identification.[12,43,44] Recombinant proteins containing all or some of the IgSF domains of the Lutheran protein have been expressed in eukaryotic or prokaryotic cells. The purified protein was then used in agglutination inhibition tests, attached to polystyrene plates for detection by an ELISA procedure, or coupled to superparamagnetic particles for detection in a particle gel immunoassay.[43–45] Alloanti-Lu^a or -Lu^b, as specified by the cDNA transfected, was detected with high sensitivity and specificity.

Lu_{null} and Lu_{mod} Phenotypes

Lu_{null}

The only true Lu_{null} phenotype is extremely rare and has a recessive mode of inheritance. No antigens of the Lutheran system can be detected on the RBCs, and individuals with the Lu_{null} phenotype may make an antibody, anti-Lu3, which reacts with all RBCs apart from those with the Lu_{null} phenotype. Lu_{null} RBCs have normal expression of those antigens, such as AnWj, that are expressed weakly on In(Lu) RBCs.

The molecular background of Lu_{null} has been identified in five individuals. All are either homozygous or doubly heterozygous for inactivating mutations in the LU gene.

1. English woman.[5] Heterozygosity for a nonsense mutation 691C>T in exon 6, encoding Arg231STOP, and for a deletion of exons 3 and 4.[6]
2. Japanese blood donor. Homozygosity for a nonsense mutation 711C>A in exon 6 encoding Cys237STOP.[6]
3. German woman of Czech origin. Homozygosity for a nonsense mutation 361C>T in exon 3 encoding Arg121STOP.[6]
4. Japanese blood donor. Homozygosity for a 27-kb deletion encompassing exons 3 to 15 of *LU*.[46]
5. Pregnant Dutch Caucasian woman. Homozygosity for a dinucleotide deletion, 123GG, in exon 2, converting 42Glu-Val-Met to 42Gly-Arg-STOP.[47]

In(Lu)

In(Lu) was the name given for a rare, dominant suppressor of the Lutheran antigens and has subsequently also been used to describe the phenotype. RBCs of most individuals with an *In(Lu)* gene appear to be Lu(a–b–) and Lu_{null} by agglutination tests, but will bind selected Lutheran antibodies, as determined by adsorption and elution tests. Adsorption and elution tests with anti-Lu^a and -Lu^b permitted the determination of the Lutheran genotype in some In(Lu) members of families, which demonstrated that the *In(Lu)* suppressor gene is not inherited at the *LU* locus.[48] No Lutheran system antibody has been detected in the serum of any person with an *In(Lu)* gene, presumably because of the weak expression of Lutheran system antigens on their RBCs.

A large survey of about 250,000 London blood donors with anti-Lu^b and -Lu^a revealed 79 Lu(a–b–) donors, an incidence of about 0.03 percent.[49] Most of these were probably *In(Lu)*. A similar incidence was found by screening African Americans in Detroit.[50] Screening of US donors in Houston and Portland with monoclonal anti-CD44 or with anti-AnWj, which would be more specific for In(Lu), gave frequencies of 0.02 percent and 0.12 percent, respectively.[51,52]

The term In(Lu) is not really appropriate as the In(Lu) phenotype is also characterized by weakened expression of RBC antigens belonging to other blood group systems:

- P1, although the effect is less obvious than that of the Lutheran antigens[49,53];
- i antigen as judged by selected anti-i[49,53];
- CD44, and consequently the high-frequency In^b (IN2), INFI (IN3), and INJA (IN4) antigens located on CD44, although these determinants are still easily detected on In(Lu) RBCs[54,55];
- AnWj, an antigen of very high incidence, which may be associated with the CD44 glycoprotein, is not expressed, or at least is expressed only very weakly[56];
- Kn^a, McC^a, Sl^a, and Yk^a of the Knops system (CD35),[57] Cs^a,[57] and MER2 (CD151),[15] although the effect is slight and family studies are required.

Individuals with an *In(Lu)* gene are generally healthy with no obvious anemia or reticulocytosis, although a degree of acanthocytosis has been associated with *In(Lu)*.[58]

Singleton et al.[8] demonstrated that In(Lu) resulted from heterozygosity for mutations in *KLF1*, in the presence of a normal *KLF1* allele. *KLF1* encodes the erythroid transcription factor erythroid Kruppel-like factor (EKLF), which is essential for terminal differentiation of erythroid cells. The following mutations were detected: two nonsense, two frameshift, four encoding single amino acid substitutions, and one single nucleotide change in the promoter region.

Lu_{mod} of the X-linked Type

In another type of Lu_{mod}, found in just one large Australian family, the mode of inheritance showed the characteristics of resulting from a recessive X-borne inhibitor gene.[59] All the Lu_{mod} members were males, and although the Lu_{mod} phenotype occurred in successive generations, there was no example of transmission of the phenotype from parent to child. The regulator locus is called *XS; XS1* is the common allele and *XS2* the rare inhibitor allele. The Lu_{mod} RBCs were Lu(a–b–) and lacked the other Lutheran antigens, yet anti-Lu^b could be adsorbed and eluted from the RBCs. The RBCs were AnWj+, appeared to have slightly enhanced i antigen, and had weak P1 antigens, although this may have been attributable to the presence of a weak *P1* gene in the family.

Lutheran Antibodies and Their Clinical Significance

If Lutheran antibodies are implicated in hemolytic transfusion reactions, they are almost always mild and delayed,[15] although there could be exceptions.[60] Lutheran antibodies have not been reported to have caused hemolytic disease of the fetus and newborn severe enough to require any treatment beyond phototherapy.[15] Lu^a antibodies may be naturally occurring or immune and are often IgM, but may also be IgG and IgA. They are usually reactive by direct agglutination of Lu(a+) RBCs, but often also react by an indirect antiglobulin test (IAT). Antibodies to Lu^b and other Lutheran antigens are most often IgG, predominantly IgG1, although IgM or IgA may be present. Most anti-Lu^b RBCs react best by IAT, but some are directly agglutinating with a temperature optimum of 20°C.

Monoclonal anti-Lu^b has been produced from mice immunized with Lu(b+) RBCs,[9] and a single-chain variable fragment (scFv) with Lu^a specificity has been produced by phage display and recombinant DNA technology.[61]

Lutheran antibodies react with papain-treated RBCs, but not with trypsin- or α-chymotrypsin-treated RBCs. RBCs treated with 6 percent 2-aminoethylisothiouronium bromide (AET) or with 200 mM dithiothreitol (DTT) do not usually react with Lutheran antibodies. This should be expected considering that Lutheran antigens are located in disulfide-bonded IgSF domains and sulfhydryl reducing agents, such as AET and DTT, break disulfide bonds, unfolding the protein.

Functional Aspects of the Lutheran Glycoproteins

In addition to RBCs, the Lu-glycoproteins are present on vascular endothelial cells and epithelial cells of multiple tissues.[11,21] The Lu-glycoproteins bind laminin, a component of the extracellular matrix (ECM) abundant in basement membranes and also present in vascular endothelia. The 15 known types of laminin are composed of different isoforms of three protein chains (α, β, γ). Lu-glycoproteins bind specifically and with high affinity to the two isoforms of laminin that contain α5 chains (511 and 521).[62,63] The laminin binding site is formed by Asp312 and a surrounding group of negatively charged residues in the region of the flexible linker between IgSF domains 2 and 3 of the Lu-glycoproteins (Fig. 1).[19]

During in vitro erythropoiesis, the Lu-glycoproteins appear on the erythroid cells at about the orthochromatic erythroblast stage.[64,65] This late appearance correlates with binding of the cells to laminin.[66] The presence of laminin 511/521 on the subendothelium basement membrane of bone marrow sinusoids has led to speculation that the Lu-glycoproteins are involved in facilitating movement of maturing erythroid cells from the erythroblastic islands of the bone marrow, across the sinusoidal endothelium, to the peripheral circulation.[62,64] The Lu-glycoproteins may also play a role in the migration of erythroid progenitors from the fetal liver to the bone marrow.[11] No obvious pathologic process, however, is associated with the Lu_{null} or Lu_{mod} phenotypes.[15]

The IgSF glycoproteins expressing Lutheran and LW blood group activity are overexpressed on SS RBCs in sickle cell disease. Enhanced binding of the Lu-glycoproteins to laminin 511/521 on the endothelia of inflamed or damaged blood vessels could contribute to blockage of the vessels and the painful episodes of vaso-occlusion often suffered by sickle cell patients.[67] Although laminin 511 and 521 are usually considered unique ligands of the Lu-glycoproteins, the integrin α4β1 (VLA-4) on SS reticulocytes may also bind Lu-glycoproteins on endothelial cells, contributing to the vaso-occlusion.[68] Phosphorylation of Lu-glycoprotein serines 596, 598, and 621 in RBCs, stimulated by the physiologic stress mediator epinephrine, could induce conformational changes to the external domains of these proteins, modulating their attraction to their corresponding ligands on endothelial cells.[67,69]

Polycythemia vera (PV) is a chronic myeloproliferative disease in which clonal proliferation of multipotent hemopoietic cells results in an increase in the RBC mass. It is usually associated with a somatic mutation in the gene for JAK2 tyrosine kinase and is often complicated by thrombotic events. The Lu-glycoproteins are phosphorylated in PV, but not in normal cells under the same conditions. Expression in an erythroid cell line of recombinant JAK2 containing the PV mutation potentiated Lu-glycoprotein phosphorylation. As phosphorylation of the Lu-glycoproteins increases RBC adhesion, this led to the proposal that increased RBC adhesiveness may be a factor promoting thrombosis in PV.[70]

Both Lu-glycoprotein isoforms interact directly with spectrin of the cytoskeleton, through Arg-Lys at positions 573 and 574 of their cytoplasmic tails.[71] This interaction with spectrin appears to modulate the adhesive activity of the Lu-glycoproteins as disruption of the interaction resulted in weakened linkage to the cytoskeleton and enhanced adhesion of RBCs to laminin.[72] An et al.[72] speculate that phosphorylation of the cytoplasmic tail of the Lu-glycoproteins weakens its interaction with spectrin, enabling the freely floating transmembrane molecules to cluster and generate a larger adhesive force.

It is becoming clear that the Lutheran blood group, which is of minor clinical importance in transfusion medicine, may play a much more substantial role in the pathology of sickle cell disease or PV.

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Manuscripts

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