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Chapter

The Duffy Blood Group System

Fatima A. Aldarweesh

Abstract

The Duffy group system includes six known antigens that reside on a glycoprotein which acts as a receptor for chemokines. It is also a receptor for some malaria species. There are significant racial variations in expression of Duffy antigens. Approximately 68% of Blacks lack both Fy^a and Fy^b antigens. Individuals with this unique phenotype are resistant to two malaria species. Antibodies formed against the Duffy antigens are of IgG subclass and are clinically significant as they can be implicated in acute and delayed hemolytic transfusion reactions as well as hemolytic disease of fetus and newborn. Patients who form anti-Fya or anti-Fy^b must receive antigen negative blood units in the future.

Keywords: Duffy, RBC antigens, FYA, FYB, DARC, hemolysis, fetus, HDFN

1. Introduction

The Duffy blood group system, ISBT number 008/symbol (FY), was published for the first time in 1950 when anti-Fya was identified in a suspected hemolytic transfusion reaction in a 43-year-old patient with hemophilia who received 3 packed red blood cell (PRBC) units for treatment of spontaneous bleeding and who developed jaundice 1 day after transfusion [1, 2]. Approximately, 1 year later, anti-Fyb was discovered in a postpartum blood sample from a patient who gave birth to her third child [3].

Chromosome 1 has both FY and RH gene loci. The FY locus is located on the long arm at position 1q22-q23 where it consists of two exons distributed over 1.5 kbp of gDNA, whereas RH resides on the short arm. The Duffy system is N-glycosylated multi-pass transmembrane glycoprotein (**Figure 1**) [4] also known as the atypical chemokine receptor 1 (ACKR1, CD234). The protein is composed of 336 amino acids. There are two possible Duffy mRNAs which are translated from the Duffy antigen gene, a less abundant α form (338 amino acids) and a major β form (336 amino acids) which differ by 2 amino acids in the N-terminus. Approximately 6000–13,000 copies of the Duffy protein are found on the surface of RBCs [5].

The Duffy blood group includes six known antigens that differ by amino acid sequence. The Duffy antigen prevalence varies between racial groups.

ACKR1 (previously known as DARC) is a receptor for a variety of chemokines, including interleukin-8, monocyte chemotactic protein-1, and melanoma growth stimulatory activity. Also, this glycoprotein is a receptor for *Plasmodium vivax* and *Plasmodium knowlesi*; thus red cells with Fy(a-b-) phenotype are resistant to invasion by these malarial species. Antibodies formed against the Duffy antigens show a dosage effect and are a cause of both hemolytic transfusion reactions and hemolytic disease of fetus and newborn. The Duffy protein is also found on the endothelial cells of capillary and postcapillary venules, the epithelial cells of kidney collecting ducts, lung alveoli, and Purkinje cells of cerebellum [6].

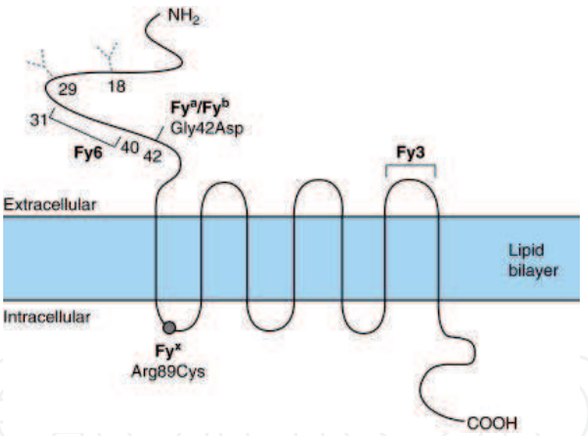

Figure 1.
The predicted seven-transmembrane domain structure of the Duffy protein. The amino acid change responsible for Fya/Fyb polymorphism, the mutation responsible for Fyx, and the glycosylation sites and the regions where Fy3 (and Fy6) map are indicated (reproduced with permission).

2. Duffy antigens

There are six known antigens with four main phenotypes; Fy(a+b+), Fy(a−b+), Fy(a+b−), and Fy(a−b−) (**Table 1**) [5]. The most common antigens are, two polymorphic and antithetical, Fya (FY1) and Fyb (FY2) which differ by one amino acid at position 42 on the extracellular domain, with glycine resulting in Fya expression and aspartic acid resulting in Fyb expression [5, 7]. They are sensitive to destruction when RBCs are treated with proteolytic enzymes such as papain or ficin, whereas, there is no RBCs destruction with trypsin treatment [8].

Fya antigen has a prevalence of 66% in Caucasians, 10% in Blacks, and 99% in Asians. It has been identified on fetal RBCs as early as 6 weeks gestation and reaches adult levels in approximately 12 weeks after birth. Fyb has a prevalence of 83% in Caucasians, 23% in Blacks, and 18.5% in Asians. It is expressed on cord blood cells. Fy3 antigen is expressed in 100% of Caucasians, 32% of Blacks, and 99.9% of Asians. It is also expressed on cord cells and demonstrates increased expression after birth. Fy5 antigen is expressed on 32% of Blacks and 99.9% of Caucasians and Asians. It is not expressed on Rh null RBCs. Fy6 is expressed in 100% of most populations and 32% of Blacks. The Fy(a–b–) phenotype is the major phenotype in approximately 70% Blacks, but is very rarely found in other populations. This phenotype is characterized by the

Red cell phenotype	Prevalence (%)		Allele
	Caucasians	Blacks	
Fy (a+b−)	17	9	FY*01/FY*01 or FY*A/FY*A
Fy (a−b+)	34	22	FY*02/FY*02 or FY*B/FY*B
Fy (a+b+)	49	1	FY*A/FY*B
Fy (a−b−)	Rare	68	FY*/N.01–05, FY*/N.01–02‡
Fy^3	100	32	
Fy^5	99.9	32	
Fy^6	100	32	

‡Nomenclature pending approval by the ISBT working party on terminology for red cell surface antigens.

Table 1.
Duffy blood group system phenotypes and prevalence. Reproduced with permission and modification.

absence of the Fyb antigen on RBCs and its presence on non-erythroid cells. Duffy mRNA is not detected in the bone marrow of Fy(a–b–) individuals; however, it is detected in other tissues including the colon, lung, and spleen. This unique phenotype is caused by a single amino acid substitution at position 46 in the Duffy (Fyb) gene. This mutation impairs the promotor activity in erythroid cells by disrupting the binding site for GATA1 erythroid transcription factor. Furthermore, some individuals with this phenotype do not make anti-Fyb. This is believed to be due to a mutation in the, erythroid promoter, GATA-1 binding motif. Interestingly, the same Fy(a–b–) phenotype rarely found in Caucasians is characterized by absence of Duffy antigens expression in both erythroid and non-erythroid tissues due to possibly presence of mutations which prevent formation of Duffy protein. These individuals can form anti-Fy3. The have high prevalence antigens; Fy3, Fy5, and Fy6 are conformational epitopes as opposed to specific sequence epitopes with Fy5 hypothesized to be a combined conformational epitope of Duffy and Rh protein. [9–12].

3. Duffy antibodies

Anti-Fya and -Fyb are clinically significant RBC alloantibodies which can cause immediate and delayed hemolytic transfusion reactions (HTRs) as well as hemolytic disease of the fetus and newborn (HDFN). They often result from previous exposure such as after transfusion or pregnancy. They are not usually naturally occurring. The Duffy antibodies are predominantly of the IgG subclass whereas the IgM form is rare.

The mechanism of extravascular hemolysis (EH) in both HDFN and HTR is similar. In HDFN, the mother lacks a certain red cell antigen which the fetus is positive for, thus the mother is allo-immunized (i.e., made a new antibody) during the first pregnancy. If she gets exposed to the same antigen in subsequent pregnancy (ies), the fetus (es) is/are at risk of HDFN. Similarly, if a patient lacks a certain red cell antigen but receives red cell transfusion with a unit that has such antigen, the patient is at risk for allo-immunziation after the transfusion and HTR in subsequent transfusion (s). EH is typically induced by IgG red cell antibodies. EH consists of consumption of antibody and/or C3b-bound red cells by phagocytes in the reticuloendothelial system (RES) causing a delayed hemolytic transfusion reaction (DHTR). DHTRs can be clinically significant leading to morbidity and possibly mortality. To avoid DHTR, patients with known clinically significant antibodies, receive red cell units that lack antigen (s) to their the cognate antibody (ies). The Duffy antibodies are usually associated with a moderate DHTR and mild HDFN [13].

Anti-Fya is identified more than anti-Fy3, anti-Fy5, or anti-Fyb. Fya is 20 times more immunogenic than Fyb. Some of anti-Fya can bind and activate complements [14]. Anti-Fy3 is also clinically significant antibody which can cause mild HDFN and HTRs. Serologically, it can react with enzyme treated Fy(a+) or Fy(b+) RBCs, but fails to react with Fy(a−b−) RBCs [15]. Anti-Fy4 shows lack of consistent test results. It was found to be reactive with Fy(a−b−), some Fy(a+b−), some Fy(a−b+) RBCs but shows no reaction with Fy(a+b+) RBCs [16]. Anti-Fy5 reacts with enzyme treated Fy(a+) or Fy(b+) RBCs with no reaction with Fy(a−b−) RBCs or Rh null RBCS. It has been reported in sickle cell patients with delayed HTRs in the presence of other clinically significant alloantibodies [17]. A human anti-Fy6 has not been identified [18].

4. The Duffy glycoprotein as a receptor for chemokines

The Duffy glycoprotein can bind to a variety of chemokines and is known commonly as the Duffy antigen receptor for chemokines (DARC) or more recently

atypical chemokine receptor 1 (ACKR1). Chemokines are proteins secreted by immune cells as a mean to communicate signals to guide their interactions. The exact function of DARC is not fully clear. One postulated function is that DARC permits erythrocyte to act a chemokine scavenger to limit leukocyte activation. The importance of this function in inflammatory diseases is not well established [6, 19].

5. Duffy and malaria

The Duffy glycoprotein plays an important role in malaria transmission by acting as the erythroid receptor for *Plasmodium vivax* through binding to the Fy6 epitope (previously known as *P. vivax* Duffy-binding protein (PvDbp)) and for Plasmodium knowlesi. Individuals with Fy(a−b−) phenotype were resistant to parasitic invasion in a study performed on 11 volunteers, whereas those who contracted malaria were Fy(a+) or Fy(b+). Fy6 is present on all erythroid cells with an Fy(a+) or Fy(b+) phenotype. Thus it is absent on red cells with Fy(a−b−) phenotype. In west Africa, individuals with Fy(a−b−) phenotype are found in greater frequency than in areas where *P. vivax* is absent. The protective effect of Fy(a−b−) phenotype does not extend to *P. falciparum* which can infect red cells of all Duffy phenotype [20].

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Conflict of interest

The author declares no conflict of interest.

Author details

Fatima A. Aldarweesh
Department of Pathology, Biological Sciences Division, Blood Bank and Transfusion Service, The University of Chicago, Chicago, IL, USA

*Address all correspondence to: faldarweesh@uchicago.edu

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