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The Gerbich blood group system: old knowledge, new importance

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ABSTRACT

Antigens of the Gerbich blood group system are expressed on glycophorin C (GPC) and glycophorin D (GPD), minor sialoglycoproteins of human erythrocytes. GPC and GPD help maintain erythrocyte shape of and contributes to the stability of its membrane. There are six high-prevalence Gerbich antigens: Ge2, Ge3, Ge4, GEPL (GE10), GEAT (GE11), GETI (GE12) and five low-prevalence Gerbich antigens: Wb (GE5), Ls[a] (GE6), An[a] (GE7), Dh[a] (GE8), GEIS (GE9). Some Gerbich antigens (Ge4, Wb, Dh[a], GEAT) are expressed only on GPC, two (Ge2, An[a]) are expressed only on GPD, while others (Ge3, Ls[a], GEIS, GEPL, GETI) are expressed on both GPC and GPD. Antibodies recognizing GPC/GPD may arise naturally (so-called "naturally-occurring RBC antibodies") or as the result of alloimmunization, and some of them may be clinically relevant. Gerbich antibodies usually do not cause serious hemolytic transfusion reactions (HTR); autoantibodies of anti-Ge2- or anti-Ge3 specificity can cause autoimmune hemolytic anemia (AIHA).
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GPC and GPD are erythrocyte receptors for the *Plasmodium falciparum* EBA-140 merozoite ligand, which binds specifically to the N-terminal fragment of GPC (amino acid residues 36–63). Homologs of EBA merozoite ligands (including EBA-140) have been found in *P. reichenowi*, a chimpanzee parasite. Recent data suggest that GPD on chimpanzee erythrocytes is a receptor for the *P. reichenowi* EBA-140 ligand, while its human-specific counterpart, *P. falciparum* EBA-140, recognizes GPC on human erythrocytes. GPC also plays an important role in infection by *P. berghei* (a rodent parasite) and mediates red cell rosetting in malaria caused by *P. falciparum* (through interactions with the STEVOR protein) and *P. vivax*. In summary, in addition to the many well-known roles of GPC and GPD, new important functions continue to be discovered. Here, we revisit the Gerbich blood group system and discuss the emerging data about GPC and GPD function.

Glycophorins C and D as structural membrane proteins

Antigens of the Gerbich blood group system are expressed on glycophorin C (GPC, CD236C) and glycophorin D (GPD, CD236D), which

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are minor sialoglycoproteins of human RBCs [1-3]. GPC is primarily expressed early during normal and leukemic erythroid differentiation [4,5]. However, GPC, unlike GPA and GPB, is not restricted to the erythroid lineage and is also found on B and T lymphocytes, monocytes, and myeloid precursors [6]. Moreover, GPC mRNA was detected in many non-hematopoietic tissues, including the thymus, stomach, breast, and fetal and adult liver [7].

GPC and GPD are type I transmembrane proteins that consist of three domains: an extracellular N-terminal domain, a transmembrane domain, and a cytoplasmic C-terminal domain (Fig 1). GPC and GPD are encoded by the same gene (*GYPC*) and arise as the result of leaky translation from two initiation codons; thus, GPD is a truncated version of GPC [8]. The polypeptide chain of GPC is composed of 128 a.a. residues with one N-glycan (at Asn8) and approximately 12 O-glycans (Fig 1) [9,10]. GPD starts from what is Met22 in GPC; thus, it consists of 107 a.a. residues and lacks the N-glycan.

GPC and GPD play important roles in maintaining RBC shape and mechanically stabilizing the RBC membrane [11,12]. They form complexes with proteins 4.1 and p55, which provide a membrane mooring system for the spectrin-actin network [13,14] (Fig 2). C-terminal a.a. residues 86–88 (RHK) of GPC interact with protein 4.1, while p55 engages residues 126–128 (YFI) [15,16]. The similarity of the GPC cytoplasmic tail sequences in many evolutionarily distant mammals underscores its importance as a plasma membrane link to the cytoskeleton (Fig 3).

The absence of GPC and GPD or protein 4.1 causes hereditary elliptocytosis [17]. Protein 4.1 deficiency causes a 70–90% decrease of GPC and GPD content in the RBC membrane [18]. Conversely, GPC/GPD-deficient RBCs show a 25% reduction of protein 4.1 [19,20]. Depression of the Kell blood group antigens in the Ge:-2,-3 (Gerbich) rare type was also described, initially reported in a K+ woman and her brother, with approximately half the number of K antigen sites compared to K + k+, Ge:2,3 control RBCs [21]. Daniels described various degrees of weakening of high-frequency Kell antigens, especially K11, in 9 out of 11 Ge:-2,-3 subjects [22]. Another group observed that K + k+, Ge:-2,-3 RBCs showed a K antigen density three times lower than K + k-, Ge:2,3 RBCs [23]. A weakened expression of the k antigen in Ge:-2,-3 people was recently confirmed with the use of a monoclonal anti-k [24]. However, this k antigen depression appeared to be moderate (about −25%) and not easily detected with standard typing procedures. The authors also unexpectedly found a seemingly higher expression of the k antigen in Ge:-2,3 (Yus) RBCs when compared to standard RBCs, though this is still not explained. Thus, these effects may suggest conformational changes of Kell epitopes due to perturbation of macromolecular protein 4.1 complex with transmembrane proteins including GPC (Gerbich) and Kell [13].

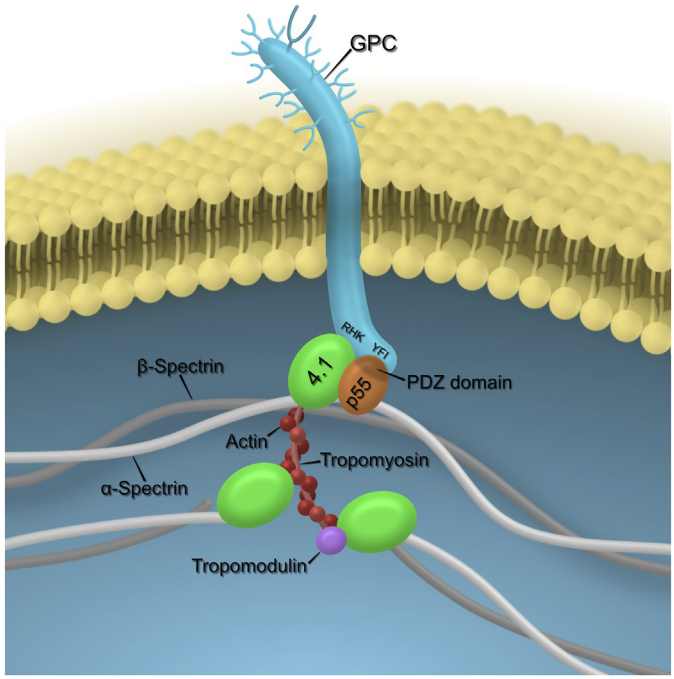

Fig 2. GPC ternary complex with protein 4.1 and p55 linked to red cell cytoskeleton. The binding sites in GPC polypeptide chain: (RHK) for protein 4.1 [15] and (YFI) for p55 [16] are indicated.

Glycophorins C and D carry the Gerbich blood group antigens

The *GYPC* gene (13.5 kbp) contains four exons and is on chromosome 2q14-q21 [25]. The high degree of homology between exons 2 and 3 may lead to unequal crossing over and loss of exon 2 or 3, causing

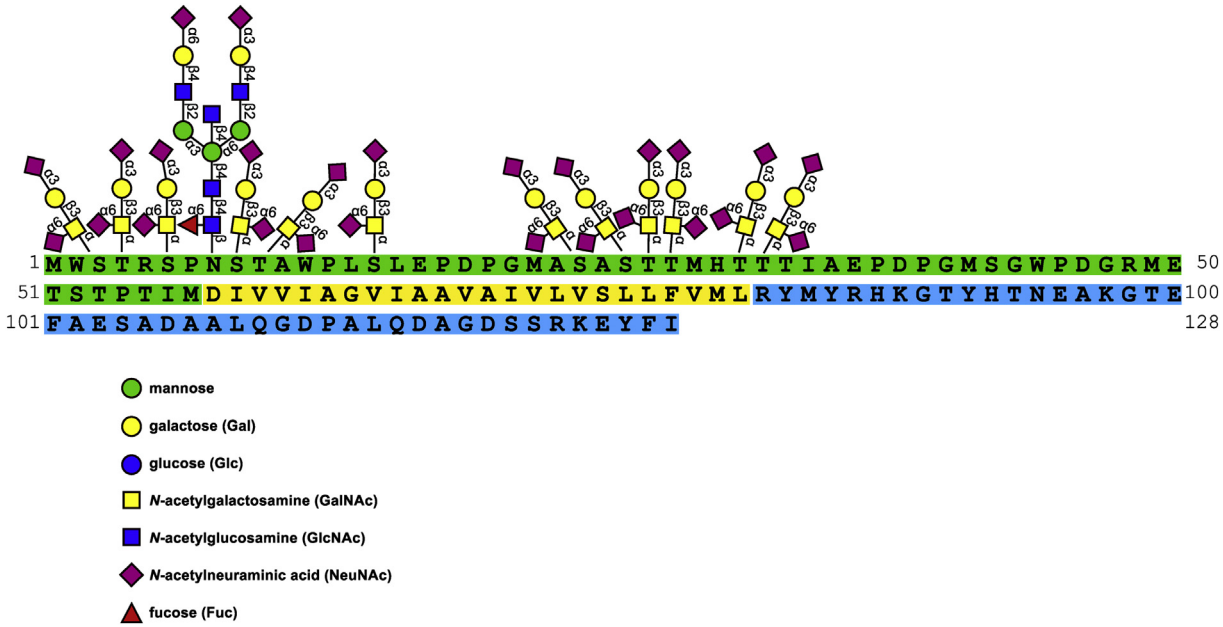

Fig 1. Amino acid sequence and domain structure of GPC and its glycan structure and attachment sites [9,10]. The external (aa 1–57), transmembrane (aa 58–81) and cytoplasmic (aa 82–128) domains are marked in green, yellow, and blue, respectively.

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