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Red cell receptors as access points for malaria infection

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Abstract

Purpose of Review—Red cell receptors provide unique entry points for *Plasmodium* parasites to initiate blood-stage malaria infection. Parasites encode distinct ligands that bind specifically to both highly abundant and low copy receptors. Recent advances in the understanding of molecular and structural mechanisms of these interactions provide fundamental insights into receptor-ligand biology and molecular targets for intervention.

Recent Findings—This review focuses on the requirements for known interactions, insight derived from complex structures, and mechanisms of receptor/ligand engagement. Further, novel roles for established red cell membrane proteins, parasite ligands and associated interacting partners have recently been established in red cell invasion.

Summary—This new knowledge underlines the intricacies involved in invasion by a eukaryotic parasite into a eukaryotic host cell demonstrated by expanded parasite ligand families, redundancy in red cell receptor engagement, multi-tiered temporal binding, and the breadth of receptors engaged.

Keywords

Receptor; Malaria; Ligand; Interaction; Host-pathogen

Introduction

Forty percent of the world's population is at risk for malaria leading to 800,000 deaths each year, predominantly in children. Malaria is caused by *Plasmodium* parasites which have a complicated lifecycle involving two different hosts, the Anopheles mosquito and the human, and three distinct stages of development: exo-erythrocytic, erythrocytic, and sporogonic stage. All stages are required to establish an infection and continue the cycle of transmission.

Within the human host, the erythrocytic stage consists of multiple cycles of red blood cell (RBC) invasion, replication, and lysis that lead to the anemia and fatigue associated with this disease. RBC invasion occurs in four distinct steps: low affinity interactions between the merozoite and RBC; apical reorientation and tight junction formation; active invasion and

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Conflicts of Interest

None Declared.

surface shedding; and formation of the parasitophorous vacuole for parasite replication. The first two steps rely on distinct receptor-ligand interactions between the host RBC and *Plasmodium* merozoite that are essential for parasite survival. Recently, great strides in understanding these interactions have been made and those efforts are described here.

Band 3

Band 3 (anion exchanger-1) is the most abundant integral membrane protein on the surface of RBCs with approximately 1.2 million copies per cell (Table 1) [2]. It is a 100 kDa multipass transmembrane channel for anions that forms dimers, tetramers, and higher-order oligomers as a result of interactions with cytoskeletal proteins [2].

Plasmodium parasites exploit the high abundance of Band 3 and employ a variety of ligands to engage this receptor (Figure 1, Table 2) including the multimeric *Plasmodium falciparum* (Pf) Merozoite surface protein 1 (MSP1) complex. The PfMSP1 complex is composed of PfMSP1, PfMSP6, PfMSP7, PfMSP9, PfMSPDBL1, PfMSPDBL2, PfRhoph3, PfRhoph1/Clag, PfRAP-1, and PfRAP-2 proteins [10,12,15,49]. PfMSP1, a 200 kDa protein, facilitates the majority of the interactions of the complex with Band 3 and undergoes proteolytic processing to produce the truncated proteins identified by their molecular weight as PfMSP1₈₃, PfMSP1₃₀, PfMSP1₄₂, PfMSP1₃₈, and PfMSP1₁₉. Of these products, PfMSP1₁₉ is proposed to mediate the principal interaction with Band 3 and binds to amino acids (aa) 720–761 with an apparent nanomolar affinity [10]. Additional proteins including PfMSP9, aa 77–183 and 364–528, and PfRhoph3 also interact with aa 720–761 of Band 3 albeit with lesser affinities [12,15]. PfMSP1₁₉ also contacts PfRhoph3 by immuno-precipitation and is able to compete for binding of PfRhoph3 to Band 3 [12].

An unanswered question remains how do these competing proteins interact with Band 3 as a complex? The first model relies on the multimeric state of Band 3 (Figure 1A). In the example of binding to a dimer, two independent binding sites on Band 3 exist in the right configuration to support independent binding. PfMSP1₁₉, PfMSP9, and PfRhoph3 could each bind an independent Band 3 monomer resulting in increased avidity that drives attachment. An alternate model is that each component binds the same Band 3 monomer. While this is possible, the competitive binding of PfMSP1₁₉ and PfRhoph3 suggests this is unlikely [12].

Glycophorin A and B

GpA is the most abundant glycoprotein on the surface of the RBC with 1 million copies per cell (Table 1) [2]. GpA is a single span transmembrane protein and part of a gene family that includes Glycophorin B (GpB) and Glycophorin E (GpE). GpB and GpE arose from gene duplication and share 95% sequence similarity and exon structure with GpA [4]. GpA is comprised of seven exons and exons 2 through 6 form the mature receptor. In contrast, the mature form of GpB consists of exons 2, 4, and 5. Exon 5 forms a constitutive transmembrane dimer that allows for both homodimers and heterodimers of GpA and GpB on the RBC surface [4].

Mature GpA is heavily glycosylated with 16 O-linked glycans and 1 N-linked glycan on exons 2 and 3 that make up 50% of the molecular weight of the receptor [2,4,52]. Five O-linked glycans are located in exon 3 and are unique to GpA [2,4,52]. O-linked glycosylation on GpA is essential for binding to *P. falciparum* EBA-175, a member of the Erythrocyte Binding Like (EBL) family of proteins (Figure 1B, Table 2) [17]. Region II of PfEBA-175 (RII-175) contains two Duffy Binding Like (DBL) domains that bind to GpA [18]. The crystal structure of RII-175 in complex with α -2,3-sialyllactose, a trisaccharide similar to O-linked glycans from GpA, revealed that the glycan binding sites are located at the dimer interface of RII-175 [16] implicating multimeric assembly of PfEBA-175 around a dimeric GpA during invasion [19,21].

Recently, production of fully glycosylated recombinant GpA (rGpA) in a mammalian tissue culture system enabled careful interrogation of the binding requirements for malaria infection [20,22]. This system overcomes the poor yield, poor solubility, and contamination with GpB observed when GpA is extracted from RBCs. Multiple glycans in exon 3 of GpA are critical for *P. falciparum* invasion as mutation of three glycosylation sites within, or elimination of, exon 3 from rGpA abrogated binding to RII-175 [20]. These glycans are also critical during *in vitro* infection as loss of these glycosylation sites prevented inhibition of *P. falciparum* growth observed with rGpA [20]. Therefore, PfEBA-175 differentiates between GpA and GpB by engaging glycans unique to GpA [20]. It is possible that GpB arose due to evolutionary pressure driven by malaria infection to lose the PfEBA-175 binding site in GpA [20]. Finally, GpB is engaged by PfEBL-1, a related protein to PfEBA-175, [24,25] although little is currently known about the mechanisms of this interaction (Table 2).

PfMSP1₈₃, a member of the PfMSP1 complex, also binds to GpA purified from RBCs (Figure 1A, Table 2) [23]. Binding is not affected by trypsin or neuraminidase treatment and contrasts that of PfEBA-175 binding to GpA [18]. Trypsin treatment cuts GpA at two arginine residues in exon 3 and removes all but three glycans while neuraminidase removes sialic acid from glycans of GpA. Further analysis using protease treatment of GpA indicated that the PfMSP1₈₃ binding site is in amino acids 53 to 84 of GpA [49] and overlaps with, but is not identical to, the PfEBA-175 binding site [20]. GpA can form a complex with Band 3 [2] and the PfMSP1₈₃:GpA interaction likely augments the Band 3 contacts mediated by other PfMSP1 complex components (Figure 1A). It is not yet clear how these two *Plasmodium* proteins can bind the same receptor region during invasion. However, it is plausible that PfMSP-1 binding occurs first during the initial cell-cell contact and is supplanted by PfEBA-175 during tight junction formation and invasion.

Glycophorin C and D

Glycophorin C (GpC) and Glycophorin D (GpD) are ~40kDa single span transmembrane glycoproteins unrelated to GpA/B/E and are present on the surface of RBCs in levels of 143,000 and 82,000 copies/cell respectively (Table 1) [2,5]. GpD results from an alternate start codon in exon 2 generating a protein that is 22 amino acids shorter, however, both proteins retain the cytoplasmic domain that is responsible for binding to the cytoskeleton [2]. GpC is heavily glycosylated with 1 N-linked glycan and 12 O-linked glycans. The alternate start codon of GpD eliminates the N-linked glycan and 6 O-linked glycans [2].

GpC, but not GpD, is the receptor for PfEBA-140, another member of the EBL family (Figure 1C, Table 2) [27]. PfEBA-140 is unable to bind RBCs lacking GpC or lacking exon 2 of GpC, and antibodies targeting exon 2 of GpC block binding of PfEBA-140 to normal RBCs [27]. Together, this data argues that exon 2 is critical for binding. However, PfEBA-140 cannot bind GpC lacking the single N-linked glycan, indicating that this glycan in exon 1 also contributes to the GpC: PfEBA-140 interaction [28].

Crystal structures of the minimal RBC binding domain of PfEBA-140 (region II, RII-140) were solved with and without sialyllactose [26,29]. RII-140 consists of two DBL domains named F1 and F2 that share an overall fold with PfEBA-175, although RII-140 is monomeric instead of dimeric [26,29]. F1 and F2 use the same region of the DBL domain to bind receptor glycans and these receptor binding pockets are structurally similar to each other, but distinct from the pockets in PfEBA-175 [26]. However, mutational data revealed that the binding pocket in F1, but not F2, is essential for receptor binding [26].

Polymorphisms in the F1 domain of PfEBA-140 alter receptor specificity and affinity [30,53]. The polymorphism I185V is located in the F1 binding pocket [26], and parasite strains with V185 have reduced binding to RBCs compared to strains with I185 [30,53]. The larger Ile creates a tight binding pocket for glycans in F1, and substitution by the smaller Val creates a cavity in the glycan binding pocket increasing solvent accessibility and reducing affinity for the receptor [26]. The structure of EBA-140 has answered a number of questions relevant for engagement of GpC although the exact mechanism remains to be determined.

Duffy antigen/Receptor for chemokines

The Duffy antigen/Receptor for chemokines (DARC) is a 35–50 kDa glycoprotein with 7 transmembrane spanning regions and three N-linked glycans (Table 1) [1]. It is expressed on the surface of RBCs and endothelial tissue and belongs to the G protein-coupled receptor family [1,3]. DARC exists with either a glycine or an aspartate at amino acid position 42 resulting in the Duffy blood groups Fy^a and Fy^b, respectively. A Fy-null phenotype is also observed and is caused by a mutation of the GATA consensus translation sequence that eliminates DARC expression in RBCs but not in endothelial tissues. In DARC expressing erythrocytes, DARC is present at levels of 6,000–13,000 copies per cell. Antibody staining using the DARC specific antibody Fy6 that recognizes aa 19–26 of DARC shows that levels of DARC are 50% greater in reticulocytes than erythrocytes [1].

DARC is the receptor for Duffy Binding Protein (DBP) ligand from *P. vivax* (Pv) and *P. knowlesi* (Pk), and PvDBP is the sole member of the EBL family found in *P. vivax* (Figure 1D, Table 2) [32]. Loss of DARC on RBCs is protective against *P. vivax* malaria making DBP a high priority vaccine candidate [54]. DBP contains a single DBL domain in Region II (RII-DBP) that is sufficient to bind DARC on RBCs.

Residues 1–60 form the N-terminal ectodomain of DARC (DARC_{1–60}) and are sufficient for DBP binding [32,33]. In the absence of DARC_{1–60}, PvDBP is monomeric in solution [34] consistent with the monomeric structure of PkDBP α , which represents the unbound monomeric form of DBP [35]. Strikingly, addition of DARC_{1–60} induces dimerization of

PvDBP to form an oligomeric complex [34]. Two distinct crystal structures of the PvDBP:DARC complex have been determined: a heterotrimer (2 RII-DBP: 1 DARC) and a heterotetramer (2 RII-DBP: 2 DARC) [31]. In both structures, only residues 19–30 of DARC are engaged by PvDBP, and this segment includes the Fy6 antigen [1,3]. Isothermal titration calorimetry demonstrated a stepwise assembly mechanism in solution: the heterotrimer forms first with micromolar affinity followed by a second binding event to form the heterotetramer with nanomolar affinity. This stepwise binding mechanism results in a stable high affinity complex to initiate invasion [31].

Although these structural and biophysical studies provide deep mechanistic insight into DARC engagement by DBP, several unanswered questions remain. The glycine to aspartate change at residue 42 (FyB) increased DBP binding and *P. vivax* infection [55] and sulfation at residues 30 and 41 of DARC also increase binding to DBP [33]. However, residues 41 and 42 of DARC do not make direct contacts with DBP in the crystal structures [31]. It is therefore plausible that these modifications to DARC may alter the surface exposure or presentation of the DARC N-terminus rather than facilitating a direct contact with DBP. Further studies are required to address these models.

Basigin

Basigin (BSG) is a 35–65 kDa glycoprotein composed of two to three extracellular Immunoglobulin-like domains, a single span transmembrane domain, and a short cytoplasmic domain (Table 1) [1,6]. BSG is expressed on number of cell types including erythrocytes with 3,000 copies per RBC [1,3,6] and has a broad range of functions. In RBCs, BSG is necessary for the correct surface targeting and activity of monocarboxylate transporters [1,6].

An avidity-based screen optimized to detect low affinity interactions identified BSG as the receptor for *P. falciparum* reticulocyte-binding homology 5 (PfRh5), a member of the reticulocyte binding like homolog proteins (RBPs or Rh) (Figure 1E, Table 2) [37]. PfRh5 binds to the short isoform of BSG that contains two Ig-like domains with a K_d of 0.43–1.3 μ M [37,38]. Crystal structures of PfRh5 [36,38] and PfRh5 in complex with BSG [36] were also recently reported. PfRh5 is a 60 kDa protein that is processed upon secretion to remove 139 residues from the N-terminus [36,38]. The mature form of PfRh5 is composed of two alpha-helix bundles that form a flat kite like shape [36,38]. BSG binds the end of the alpha-helical bundles closest to the C-terminus of PfRh5 and engages both Ig-like domains of BSG forming a 1:1 complex [36]. Surprisingly, interactions in the complex are primarily between the backbone of BSG and the loops of PfRh5 [36].

PfRh5 does not contain a transmembrane domain or a GPI-anchor but still localizes to the surface of merozoites. PfRh5 immunoprecipitated from parasite cultures revealed a multiprotein complex of 200 kDa [39,40] that includes PfRipr, a large 123 kDa protein containing multiple EGF-like domains [40], and PfCyRPA, a 35 kDa GPI-anchored protein [39]. These weights suggest the 200 kDa complex is a 1:1:1 association of PfRH5, PfRIPR and PfCyRPA. However, the molecular interactions within this complex are still unknown. BSG is an essential receptor for invasion by all strains of *P. falciparum* investigated [37] making this interaction central for malaria infection despite its relatively low abundance.

Complement Receptor 1

Complement Receptor 1 (CR1) is a relatively low abundance, 50–1200 copies/cell, type 1 transmembrane protein on the surface of RBCs (Table 1) [7]. CR1 consists of up to 44 control protein repeats (CCPs) organized into long homologous repeats (LHRs) composed of seven CCPs resulting in a protein of 190–280 kDa. CR1 binds C3b and C4b immune complexes resulting in transport of the complexes to the spleen and liver for clearance [7].

CR1 is the receptor for PfRh4, a member of the RBP/Rh family, [41–43] as anti-CR1 antibodies block native PfRh4 binding to RBCs and soluble CR1 binds soluble PfRh4 with a K_d of 2.9 μ M (Figure 1F, Table 2) [41]. PfRh4 binds to CCP1–3, which are also the repeats responsible for binding C4b and convertase decay-accelerating activity (DAA) [42]. Surprisingly, C4b and PfRh4 are able to bind to CR1 at the same time. However, PfRh4 engagement of CR1 disrupts DAA activity in a dose dependent manner [42].

More recently, the PfRh4 binding site was narrowed to CCP1 [43]. Amino acid residues 18 and 20 are essential for binding and mutation of amino acids 7–9 and 19 greatly reduced binding to PfRh4. These residues form a continuous patch on one face of CCP1 [43]. While the regions of CR1 that interact with PfRh4 have been identified, the molecular architecture of the interaction remains unknown.

Semaphorin 7A

Semaphorin 7A (Sema7A) is an 80 kDa GPI-anchored member of the semaphorin family [8,9] composed of three domains: a sema domain, PSI domain, and Ig domain (Table 1) [8]. Sema7A is the receptor for the *P. falciparum* MTRAP (Figure 1G, Table 2) [44]. PfMTRAP, a member of the thrombospondin-related anonymous protein (TRAP) family, is composed of receptor-binding extracellular domains, a transmembrane domain, and a cytoplasmic domain that facilitates active invasion utilizing an actin-myosin motor complex.

PfMTRAP's extracellular domain contains two thrombospondin repeat (TSR)-like domains that are required to bind RBCs [45]. Direct binding studies showed the two TSR domains alone were necessary and sufficient to bind Sema7A with similar kinetics as the full length PfMTRAP ectodomain ($K_d = 1.96 \mu$ M and 1.18 μ M respectively) [44]. The interaction is dependent on the sema domain, which promotes homodimerization of Sema7A [8], and each PfMTRAP molecule binds a Sema7A monomer [44].

Novel receptors and ligands with roles in invasion

There are currently RBC receptors for which no parasite ligand has been defined and vice versa. CD55 and ICAM-4 are RBC receptors without known parasite ligands identified through forward genetics [46] and parasite inhibition studies [47], respectively (Table 2). Conversely, parasite ligands without known receptors include PfMSPDBL 1 & 2 [49], PfRh2 [50], PFEBA-181 [48], and PfTRAMP (Table 2) [51]. These proteins remain an area of active study to fully define the range of RBC interactions available to the malaria parasite.

Consequences for therapeutic design

A mechanistic understanding of host-parasite receptor-ligand interactions and a mechanistic framework for antibody neutralization are crucial for the design of effective vaccines that will prevent malaria. Antibodies are a critical component of naturally acquired immunity to malaria. While antibodies that target blood-stage parasites can prevent interactions, not all antibodies are inhibitory [36,44,56]. It is clear that antibodies that target protein function by engaging to receptor-binding pockets or dimerization interfaces are potentially neutralizing while antibodies that engage non-functional or decoy epitopes have no effect on parasite viability [56]. In addition, multiple interactions for RBC invasion indicate that targeting multiple parasite ligands will be necessary to prevent blood-stage infection. Lastly, polymorphic variation in parasite ligands results in immune evasion, and this phenomenon must also be addressed during vaccine design. This is best exemplified in PvDBP where recent efforts have proven successful in eliminating highly immunogenic polymorphic segments that result in strain-specific responses while retaining broadly neutralizing segments [57,58].

Conclusion

Recent advances have defined some of the interactions involved in malaria parasite invasion into RBCs. Receptors have been identified for four major families of *Plasmodium* invasion ligands (EBL, Rh, MSP, and TRAP) and the mechanisms of the interactions have been determined for a handful of the family members. Crystal structures of *Plasmodium* ligands alone and in complex with receptors have contributed greatly to the mechanisms of invasion. For those receptor/ligand pairs that have not been crystallized, mutagenesis studies have further elucidated how these pairs interact. In conclusion, red cell receptor engagement by malaria parasites is far more intricate than initially anticipated. Molecular mechanistic studies of host-parasite interactions remain an active area of research, and are desperately needed not only for the fundamental understanding of receptor biology but also for the rational design of vaccines and therapeutics for malaria.

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Keypoints

- Malaria parasites must engage distinct red cell receptors for disease pathogenesis
- Multimeric assembly is critical for receptor-ligand engagement
- Parasites engage a wide range of red cell receptors to ensure invasion
- Identification of novel receptors and ligands inform receptor biology and host-pathogen interactions.
- Recent advances have defined the molecular mechanisms that underpin receptor-ligand interactions

Figure 1.

Molecular interactions between RBC receptors and malaria parasite ligands. A) Band 3 (left) and Band 3/GpA (right) bind the PfMSP1 complex. PfMSP1₁₉, PfMSP9 and PfRhopH3 can independently bind Band 3 leading to multiple binding configurations raising the possibility for engagement of multiple Band 3 dimers (dotted lines), B) Glycophorin A (GpA) drives dimerization of PfEBA-175 upon engagement, C) Glycophorin C binding to PfEBA-140, D) Duffy antigen receptor for chemokines (DARC) engages PvDBP via a model of receptor-induced ligand dimerization, E) Basigin (BSG) interacts with the multiprotein complex of PfRh5, PfRIPR and PfCyRPA, F) Complement receptor 1 (CR1) in complex with PfRh4, G) Each monomer of the Semaphorin 7A (Sema7A) dimer binds a monomer of PfMTRAP. Available structures are shown in surface representation. Domains, transmembrane segments (long cylinders) and GPI anchors (short cylinders) are shown as cartoons wherever structural information is lacking.

Table 1

Molecular and Functional Description of RBC Receptors for *Plasmodium* Parasites

RBC receptor	Alternate Names	Malaria Ligand(s) Engaged	Copies per RBC	Blood Groups	Domains	Endogenous Function	Refs
Band 3	AE-1	PMSP1 ₁₉ , PIRhoph3, PMSP9	1.2 million	Di, Wr	N-terminal cytoplasmic C-terminal transmembrane spanning	Binding to cytoskeletal proteins, Oligomerization Anion transport channel for bicarbonate and chloride anions	[1–3]
Glycophorin A	CD235A	PfEBA-175, PfMSP1 ₈₃	1 million	M, N, S, s	Extracellular Transmembrane	Unknown Oligomerization	[1–4]
Glycophorin B	CD235B	PfEBL-1	150,000	N, S, s	Extracellular Transmembrane	Unknown Oligomerization	[1–4]
Glycophorin C	CD236	PfEBA-140	143,000	Ge	Extracellular Cytoplasmic	Unknown Binding to cytoskeletal proteins	[1–3,5]
CD55	DAF	Unknown	20,000	CROM	Control protein repeats (CCP) 2–4	Complement decay-accelerating activity	[1,3]
Duffy antigen/Receptor for chemokines	CD234	PvDBP	6,000–13,000	Fy	Seven-span transmembrane GPCR	Receptor for CC and CXC chemokines	[1,3]
Intracellular adhesion molecule 4	CD242	Unknown	2,800–5,100	LW	Immunoglobulin-like	Intercellular adhesion	[1,3]
Basigin	CD147, EMMPRIN, TCSE, Neurothelin, 5A11, HT7, OX47, CE9, gp42	PfRh5	3,000	Ok	Extracellular	Transport and function of monocarboxylate transporters, binding to integrins, cyclophilins, and caveolin-1	[1,3,6]
Complement Receptor 1	CD35, C3b/C4b adherence receptor, immune adherence receptor	PfRh4	50–1200	Kn	CCP 1–3, CCP 7–9, CCP 15–17 CCP 1–3 CCP 7–9 and CCP 15–17	Binding of C4b Complement decay-accelerating activity Binding of C3b	[1,3,7]
Semaphorin 7A	CDw108	PfMTRAP	unknown	JMH	Ectodomain Sema Immunoglobulin-like	T-cell maturation, T-cell/macrophage interactions, regulation of TGF-β1 Binding to PlexinC1 and β1-Integrin and oligomerization Oligomerization	[1,3,8,9]

Table 2

Malaria Parasite Ligand/RBC Receptor Pairs and Their Interactions

RBC receptor	Receptor binding region (aa)	Receptor MW (kDa)	Malaria Ligand	Ligand MW (kDa)	Ligand binding region (aa)	PDB ID of receptor/ligand complex structure	Refs
Band 3							
	720–761	100	PFMSPI ₁₉	19	1517–1640		[10,11]
	720–761		PFRhoph3	110	620–897		[12]
	720–761		PFMSPI ₃₈	38	931–1348		[10,13]
	720–761		PFMSPI ₄₂	42	1255–1640		[10,11,14]
	720–761		PFMSPI ₉	88.6	77–183, 364–528		[15]
Glycophorin A	50–84 53–84	43	PFEBa-175 PFMSPI ₈₃	175 83	145–760 194–296	1ZRO [16]	[16–22] [23]
Glycophorin B	Unknown	25	PFEBL-1	300	601–669		[24,25]
Glycophorin C	Unknown	40	PFEBa-140	140	143–740	4JNO [26]	[26–30]
Duffy antigen/Receptor for chemokines	14–43	35–45	PvDBP	120	211–525	4NUU, 4NUV [31]	[31–35]
Basigin	22–205	35–65	PFH5	45–63	140–526	4U0Q [36]	[36–40]
Complement receptor 1	7–9, 18–20	190–280	PFH4	205	104–465		[41–43]
Semaphorin 7A	54–491	80	PFMTRAP	58	23–105		[44,45]
CD55	Unknown	60–70	Unknown				[46]
ICAM 4	Unknown	40	Unknown				[47]
Unknown			PFEBa-181	181	Unknown		[48]
Unknown			PFMSPDBL1	80	143–443, 542–696		[49]
Unknown			PFMSPDBL2	88	161–457, 571–672		[49]
Unknown			PFH2	370	495–860		[50]

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RBC receptor	Receptor binding region (aa)	Receptor MW (kDa)	Malaria Ligand	Ligand MW (kDa)	Ligand binding region (aa)	PDB ID of receptor/ligand complex structure	Refs
Unknown			PFTRAMP	37	26–307		[51]