Plasmodium vivax Malaria

Subjects: Microbiology
Contributor: Lemu Golassa

Plasmodium vivax malaria is a neglected tropical disease, despite being more geographically widespread than any other form of malaria.

Keywords: Plasmodium vivax ; erythrocyte invasion mechanisms

1. Introduction

Plasmodium vivax malaria is a neglected tropical disease, despite being more geographically widespread than any other form of malaria [1], and causes 132–391 million clinical infections each year [2]. Compared to *P. falciparum*, *P. vivax* has a broader temperature tolerance and an earlier onset of gametocyte development, enabling the parasites to spread through diverse climates [3] and making them more difficult to control and eliminate [4]. Currently, there is no vaccine available for *P. vivax*, though several preventative medications have been shown to be effective [5][6]. The epidemiology of *P. vivax* malaria is further complicated by the pathogen's unique ability to form dormant-stage hypnozoites in the host liver cells, giving rise to recurrent relapse infections from weeks/months to years later [7][8]. Relapse infections have substantially impacted progress in malaria control, especially in countries that are approaching elimination [9][10][11].

Plasmodium vivax was previously thought to be rare or absent in Africa because people of African descent often lack the expression of a Duffy blood group antigen, known as the Duffy antigen–chemokine receptor (DARC). It is believed that the fixation of the Duffy negativity trait, and the rarity *of P. vivax* infection in Africa supports that Duffy-negative individuals are refractory to *P. vivax.* Unlike *P. falciparum*, which utilizes multiple erythrocyte receptors for invasion and has merozoite proteins with overlapping and redundant receptor-binding functions, invasion of erythrocyte by *P. vivax* merozoites exclusively relies on the interaction between PvDBP and DARC expressed on the surface of erythrocytes and reticulocytes. DARC is a glycoprotein on the surface of red blood cells (RBCs) that allows *P. vivax* to bind and invade human erythrocytes at the cysteine-rich region II of Duffy Binding Protein 1 (DBP1) [12][13][14]. However, recent studies have reported several cases of *P. vivax* in Duffy-negative people in different parts of Africa where Duffy-negative populations are predominant [15][16][17]. It is apparent that Duffy-negative individuals are no longer resistant to *P. vivax* malaria [16][17]. This phenomenon raises important questions of how *P. vivax* invades erythrocytes of Duffy-negative individuals. To date, only a single *P. vivax* ligand protein PvDBP1 has been studied in great detail [17]. It has been hypothesized that either mutations in *PvDBP*1 provided a new pathway of entry, or a low expression of DARC in Duffy-negative individuals binds readily with parasites that contain high copies of *PvDBP*1 [18][19]. Recent studies have shown that, despite several mutational differences observed in *PvDBP*1 between Duffy-positive and Duffy-negative infections, none of them bind to Duffy-negative erythrocytes [17], implying that an alternative parasite ligand is being used.

The investigation of erythrocyte invasion mechanisms in *P. vivax* could be complicated by the genetic characteristics and epidemiology of *P. vivax* in Duffy-negative individuals. *P. vivax* has a significantly higher nucleotide diversity at the genome level, compared to *P. falciparum* [20]. Such a contrast could be attributed to frequent gene flow via human movement, intense transmission, and variation in host susceptibility [21][22][23]. Genes associated with erythrocyte binding, such as Duffy binding protein (*PvDBP*), erythrocyte binding protein (*PvEBP*), reticulocyte binding protein (*PvRBP*), merozoite surface protein (*PvMSP*), apical membrane antigen 1 (*PvAMA*1), and tryptophan-rich antigen genes (*PvTRAg*) families, are highly diverse in *P. vivax* from Africa and Southeast Asia [24][25][26][27][28]. These genes have been shown to play a role in reticulocyte invasion [24][28] and patient antigenicity [29][30] and provide explanations to high levels of selection detected at the genome levels in *P. vivax* from South Korea [31], Kyrgyz Republic [32], New Guinea [33], and Thailand [34]. Proteins such as RBP, TRAg, anchored micronemal antigen (GAMA), and Rhoptry neck protein (RON) have been suggested to play a role in red cell invasion, especially in low-density infections [35][36][37][38][39]. Unfortunately, studies that investigated erythrocyte invasion pathways are scattered with no definitive evidence and systematic approaches to clarify the exact role of these target genes. Due to a lack of reliable and logistical long-term in vitro methods [40], *P. vivax* remains a parasite for which it is difficult to effectively study the molecular mechanisms and biology in detail, beyond genetic characterizations.

2. Pathogenesis of *P. vivax*

Recent findings of *P. vivax* cases in Duffy-negative individuals suggest that some lineages may have evolved to use ligands other than Duffy for erythrocyte invasion [17]. This significantly increases the risk of *P. vivax* infection in the African populations and may eventually become a new cause of epidemics and severe disease across Africa. To establish how the phenomenon of *P. vivax* infection of Duffy-negative individuals has evolved and identify potential vaccine candidates to target it, it is important to understand how this parasite invades Duffy-negative erythrocytes and, hence, causes malaria. The investigations of *P. vivax* at the cellular and molecular levels have been restricted by the lack of a continuous in vitro culturing of live parasites. With the advancement in *P. vivax* genome sequencing technology, coupled with the ability to mature ex vivo isolates, it is now possible to obtain high-quality transcriptomes of the blood stages. However, there is still a lack of viable methods to indefinitely culture *P. vivax*, due to the need for young reticulocytes to sustain long-term culture. Strategies to overcoming this problem have been proposed but remain impractical due to a large initial and continuous investment of labor and infrastructure [41]. The successes of short-term culture utilizing young reticulocytes from placental blood [40][42] and indefinite culture in *Saimiri boliviensis* and *Aotus nancymae* monkeys [43][44] shed light on pathogenesis in humans and potential ligands for invasion [39][44]; however, several unanswered questions remain.

While mature asexual *P. vivax* and its transmissive gametocytes occur in peripheral blood, histological analyses of *P. vivax* in *Aotus* and *Saimiri* monkeys have shown immature gametocytes and few asexual schizonts present in the parenchyma of bone marrow [45]. Asexual schizonts appear to be more concentrated in the sinusoids of the liver [45], suggesting that bone marrow could be a critical reservoir for *P. vivax* gametocyte development and proliferation. Indeed, the bone marrow reservoirs may suggest that microscopic detection is not ideal for active case detection and treatment of *P. vivax* until bone marrow samples are accessible. As *P. vivax* requires reticulocytes for growth [46][47][48][49], the general low proportion of reticulocytes (that make up only 1% of the total number of host erythrocytes) may explain low parasite loads in symptomatic patients [50][51][52] and a lack of observable schizonts in blood circulation [52][53]. Additionally, pathological analyses of *S. boliviensis* tissues showed that *P. vivax* infections also affect the lungs and kidneys, both of which had mononuclear infiltrates, higher macrophage levels, alveolar wall thickening, collagen deposition, and type II pneumocyte hyperplasia [44]. The level of tissue damage is parasite-load dependent and determined by the amount of by-product, namely hemozoin, being produced [44]. These findings may imply a large number of asymptomatic *P. vivax* carriers in the general populations. It is well-known that *P. vivax* has the ability to relapse from dormant liver-stage hypnozoites, from weeks to years after the clearance of the primary blood-stage infection, and this is a major obstacle to its control and elimination [20][54]. The liver and bone marrow have been shown to be major parasite reservoirs for *P. vivax* hypnozoites in *Saimiri* monkey models [45][55], but mechanisms of hypnozoite development remain largely unknown and are difficult to study due to a lack of long-term in vitro culture. Moreover, relapse varies systemically by geographic region and/or seasonal changes in the environment [54]. In regions where *P. vivax* transmission is intense and stable, relapse is common and enhances local transmission [20][54], whereas, in Africa, *P. vivax* transmission is relatively low and usually seasonal and unstable [56][57][58]. The rate of relapse is largely unknown. There is, as of yet, no information on the frequency and clinical impacts of relapse in Duffy-negative *P. vivax* infections, nor reliable biomarkers for relapse detection, due to limited technologies and substantial knowledge gaps in the biology of *P. vivax* hypnozoites and relapse. Future investigations employing a longitudinal study design that monitors the dynamics and consequences of relapse infections in both Duffy-positive and Duffy-negative individuals will offer deep insights into the epidemiology and biology of *P. vivax* infections.

3. Erythrocyte Invasion Mechanisms in Non-*Plasmodium vivax*

3.1. Plasmodium falciparum

Our current knowledge of the molecular mechanisms of erythrocyte invasion in several *Plasmodium* species offers a reference model on candidate invasion ligands in *P. vivax*. *Plasmodium falciparum* invades a wide range of red blood cells, from young reticulocytes to mature normocytes. One of the main binding protein ligands is the erythrocyte binding ligand (EBL) family, which includes multiple members, such as EBA-175, EBA-140, EBL-1, and EBA-181. EBA-175 binds to the sialic acid–containing structure on human erythrocyte receptor glycophorin A (GpA) during invasion [59]. The role of the EBA-175 protein has been shown to be critical for erythrocyte invasion, as antibodies raised against EBA-175 prevent binding to GpA in vitro [60][61]. EBA-175 triggers changes in the erythrocyte membrane [62][63], and the shedding of EBA-175 causes uninfected red blood cells to cluster or form rosette, which allows for immune evasion [64]. The host immune responses may explain the polymorphisms and diversifying selection observed in EBA-175 [65]. Other ligands, such as EBA-140 and EBL-1, are known to bind to glycophorin C (GpC) [66] and glycophorin B (GpB), respectively, on the erythrocytes. Unlike GpA and GpC, the GpB exhibits high levels of polymorphisms, particularly in people of African ancestry, suggesting that a strong selective pressure may have provided an evolutionary advantage to parasite invasion [67]. For example, the S-s-U- and Dantu GpB phenotypes both showed moderate protection against invasion; however,

this does not hold true for all GpB phenotypes [67][68][69][70]. To the best of our knowledge, the specific receptor for EBA-181 is chymotrypsin-sensitive, trypsin-resistant, and neuraminidase-sensitive to erythrocytic treatment [71][72], although it remains to be identified.

Another important binding protein family of *P. falciparum* is the reticulocyte-binding homologue (PfRh) that includes PfRh1, PfRh2a, PfRh2b, PfRh4, and PfRh5. PfRh1 binds to an unidentified receptor “Y”, which has been characterized to be trypsin- and chymotrypsin-resistant and neuraminidase-sensitive [73][74]. PfRh1 is necessary for sialic acid–dependent invasion of human red blood cells [74]. Antibodies raised against PfRh1 have been shown to block invasion by inhibiting calcium signaling in the merozoite [75]. PfRh2a and PfRh2b are identical for much of the N-terminus region, but each has a unique 500 C-terminus region [76] and differential expressions in various *P. falciparum* lines, including deletions, such as a deletion of PfRh2b in *P. falciparum* D10 [76][77]. The loss of PfRh2b does not appear to impact invasion or growth of the parasites and suggests compensatory mechanisms for the loss of PfRh2b [78]. PfRh2a binds to more than one receptor on erythrocytes, but these receptors have yet to be identified [79][80]. PfRh2b has been shown to be involved in merozoite calcium signaling [80]. It binds to an unknown receptor “Z” on erythrocytes, which is neuraminidase- and trypsin-resistant and chymotrypsin-sensitive [81]. PfRh4 has been shown to have sialic acid–independent binding activity with the complement receptor type I (CR1) on erythrocytes [82][83]. The PfRh5 complex is composed of PfRh5, Ripr, CyRPA, and Pf113, which collectively promote successful merozoite invasion of erythrocytes by binding to basigin (BSG, CD147) [84] [85]. A BSG variant on erythrocytes, known as Ok^{a-}, has been shown to reduce merozoite binding affinities and invasion efficiencies [86]. This variant was reported so far only from people of Japanese ancestry [87]. Previous knockout or double-knockout experiments have indicated that the *EBL* and *PfRh* gene families work cooperatively or can functionally compensate for the loss of each other [88][89]. For example, a loss of *EBA*-175 can activate *PfRh*4 [88][89]. When *EBA*-181 expression was disrupted, *PfRH*2b was no longer functional [89]. When *EBA*-181 and *EBA*-140 genes were disrupted, the parasite deleted the *PfRh2b* gene [89]. Further study is needed to gain a deeper understanding of how they may work synergistically to promote invasion and immune evasion.

3.2. Plasmodium knowlesi

Until recently, *P. knowlesi* was considered primarily a simian malaria that infects *Macaca fascicularis*, *Macaca nemestrina,* and *Presbystis melalophos* [90]*. P. knowlesi* is now confirmed to cause malarial infections in humans [91]. *P. knowlesi* has been shown to use different ligands to invade macaques and human erythrocytes [90]. Two gene families, *DBL* and *RBP*, are responsible for erythrocyte binding. The *DBL* gene family comprises *PkDBP*-α, *PkDBP*-β, and *PkDBP*-γ. In humans, the parasite ligand responsible for erythrocyte invasion is PkDBP-α, which binds to the DARC receptor. The other two Duffy-binding proteins, PkDBP-β and PkDBP-γ, bind only to macaque but not human erythrocytes [14]. The normocyte-binding protein Xa (NBPXa) is required for binding in human erythrocytes, but it is not necessary for invasion of *Macaca mulatta* erythrocytes [92]. Variation in PkNBPXa has been shown to be linked with parasite virulence and severity of disease [93]. The receptors for NBPXa and NBPXb necessary for invasion for either human or *M. mulatta* erythrocytes have yet to be identified [90]. Unlike *P. vivax*, both *P. falciparum* and *P. knowlesi* can be maintained in long-term culture, making them ideal systems for studying invasion mechanisms [94][95].

3.3. Plasmodium cynomolgi

P. cynomolgi is a vivax-like simian malaria that shares many genomic and phenotypic characteristics with *P. vivax* and has been often used as a reference model of *P. vivax* [96]. Two gene families, erythrocyte binding-like (*EBL*) and reticulocyte binding-like (*RBL*), are responsible for erythrocyte binding and invasion in *P. cynomolgi* [97][98][99]. The *EBL* gene family encodes *PcyDBP*-1 and *PcyDBP*-2, similar to *PkDBP,* which binds to the complementary DARC receptor on Duffy-positive erythrocytes. *PcyDBP-1* is an ortholog for *PkDBP*-α, while *PcyDBP*-2 has no known orthologs with other *Plasmodium DBP*s [100]. Previous studies have shown no variation in gene copy number of either *PcyDBP-1* or *PcyDBP-2* among *P. cynomolgi* laboratory strains [101]. Studies of field isolates of both *P. cynomolgi* and *P. knowlesi* have shown that *PcyDBP-1* exhibits high levels of nucleotide diversity, as compared to *PcyDBP2* or *PkDBP*s [102]. The *RBL* gene family is composed of *PcyRBP*1, *PcyRBP*1a, *PcyRBP*1b, *PcyRBP*2a, *PcyRBP*2b, *PcyRBP*2c, *PcyRBP*2d, *PcyRBP*2e, *PcyRBP*2f, and *PcyRBP*3, most of which are responsible for mediating parasite invasion into reticulocytes [101]. Functional studies of *PcyRBP*s are further complicated, as different strains of *P. cynomolgi* have a different set of *RBL* genes. For example, *PcyRBP2a* is present in the *P. cynomolgi* B and *P. cynomolgi* Cambodian strains but absent in the *P. cynomolgi* Berok strain. Similarly, *PcyRBP*1b is present in the *P. cynomolgi* Berok and Gombak strain but absent in the *P. cynomolgi* B, Cambodian and Rossan strain [96]. While it is possible that the loss of *PcyRBP1b* can be compensated by the presence of *PcyRBP2a* [101], the relative role of *PcyRBP1b* and *PcyRBP2a* in RBC invasion requires further investigations [103].

References

1. World Health Organization. World Malaria Report; WHO: Geneva, Switzerland, 2018.
2. Price, R.N.; Anstey, N.M.; Guerra, C.A.; Yeung, S.; Tjitra, E.; White. N.J. Vivax Malaria: Neglected and Not Benign. J. Trop. Med. Hyg. 2007, 77, 79–87.
3. Elgoraish, A.G.; Elzaki, S.E.G.; Ahmed, R.T.; Ahmed, A.I.; Fadlalmula, H.A.; Mohamed, S.A.; Abdallah N.I.; Abdelgadir, O; Ageep, T.B.; El-Sayed B.B. Epidemiology and distribution of Plasmodium vivax malaria in Sudan. R. Soc. Trop. Med. Hyg. 2019, 113, 517–524.
4. Lo, E.; Hemming-Schroeder, E.; Yewhalaw, D.; Nguyen, J.; Kebede, E.; Zemene, E.; Getachew, S.; Tushine, K.; Zhong, D.; Zhou, G.; et al. Transmission dynamics of co-endemic Plasmodium vivax and P. falciparum in Ethiopia and prevalence of antimalarial resistant genotypes. PLoS Negl. Trop. Dis. 2017, 11, e0005806.
5. White, N.J. The role of anti-malarial drugs in eliminating malaria. J. 2008, 7, 1–6.
6. Herrera, S.; Corradin, G.; Arévalo-Herrera, M. An update on the search for a Plasmodium vivax Trends Parasitol. 2007, 23, 122–128.
7. Chu, C. Management of relapsing Plasmodium vivax Int. J. Infect. Dis. 2016, 45, 16.
8. White, N.J. Determinants of relapse periodicity in Plasmodium vivax Malar. J. 2011, 10, 297.
9. Taylor, A.R.; Watson, J.A.; Chu, C.S.; Puaprasert, K.; Duanguppama, J.; Day, N.P.J.; Nosten, F.; Neafsey, D.E.; Buckee, C.O.; Imwong, M.; et al. Resolving the cause of recurrent Plasmodium vivax malaria probabilistically. Commun. 2019, 10, 1–11.
10. Lawpoolsri, S.; Sattabongkot, J.; Sirichaisinthop, J.; Cui, L.; Kiattibutr, K.; Rachaphaew, N.; Suk-uam, K.; Khamsiriwatchara, A.; Kaewkungwal, J. Epidemiological profiles of recurrent malaria episodes in an endemic area along the Thailand-Myanmar border: A prospective cohort study. J. 2019, 18, 124.
11. Robinson, L.J.; Wampfler, R.; Betuela, I.; Karl, S.; White, M.T.; Connie, S.N.; Suen, L.W.; Hofmann, N.E.; Kinboro, B.; Waltmann, A.; Brewster, J.; et al. Strategies for Understanding and Reducing the Plasmodium vivax and Plasmodium ovale Hypnozoite Reservoir in Papua New Guinean Children: A Randomised Placebo-Controlled Trial and Mathematical Model. PLoS Med. 2015, 12, e1001891.
12. Howes, R.E.; Patil, A.P.; Piel, F.B.; Nyangiri, O.A.; Kabaria, C.W.; Gething, P.W.; Zimmerman, P.A.; Barnadas, C.; Beall, C.M.; Gebremedhin, A.; et al. The global distribution of the Duffy blood group. Commun. 2011, 2, 1–10.
13. Fang, X.; Kaslow, D.; Adams, J.; Miller, L. Cloning of the Plasmodium vivax Duffy receptor. Biochem. Parasitol. 1991, 44, 125–132.
14. Chitnis, C.E.; Miller, L.H. Identification of the erythrocyte binding domains of Plasmodium vivax and Plasmodium knowlesi proteins involved in erythrocyte invasion. Exp. Med. 1994, 180, 497–506.
15. Howes, R.E.; Reiner, R.C.; Jr.; Battle, K.E.; Longbottom, J.; Mappin, B.; Ordanovich, D.; Tatem, A.J.; Drakeley, C.; Gething, P.W.; Zimmerman, P.A.; et al. Plasmodium vivax Transmission in Africa. PLoS Negl. Trop. Dis. 2015, 9,
16. Gunalan, K.; Niangaly, A.; Thera, M.A.; Doumbo, O.K.; Miller, L.H. Plasmodium vivax Infections of Duffy-Negative Erythrocytes: Historically Undetected or a Recent Adaptation? Trends Parasitol. 2018, 34, 420–429.
17. Gunalana, K.; Lo, E.; Hostetler, J.B.; Yewhalaw, D.; Mu, J.; Neafsey, D.E.; Yan, G.; Miller, L.H. Role of Plasmodium vivax Duffy-binding protein 1 in invasion of Duffy-null Africans. Natl. Acad. Sci. USA 2016, 113, 6271.
18. Menard, D.; Chan, E.R.; Benedet, C.; Ratsimbasoa, A.; Kim, S.; Chim, P.; Do, C.; Witkowski, B.; Durand, R.; Thellier, M.; et al. Whole Genome Sequencing of Field Isolates Reveals a Common Duplication of the Duffy Binding Protein Gene in Malagasy Plasmodium vivax PLoS Negl. Trop. Dis. 2013, 7, e2489.
19. Menard, D.; Barnadas, C.; Bouchier, C.; Henry-Halldin, C.; Gray, L.R.; Ratsimbasoa, A.; Thonier, V.; Carod, J.F.; Domarle, O.; Colin, Y.; et al. Plasmodium vivax clinical malaria is commonly observed in Duffy-negative Malagasy people. Natl. Acad. Sci. USA 2010, 107, 5967–5971.
20. White, M.T.; Shirreff, G.; Karl, S.; Ghani, A.C.; Mueller, I. Variation in relapse frequency and the transmission potential of Plasmodium vivax Proc. Royal Soc. B 2016, 283, 20160048.
21. Parobek, C.M.; Lin, J.T.; Saunders, D.L.; Barnett, E.J.; Lon, C.; Lanteri, C.A.; Balasubramanian, S.; Brazeau, N.; DeConti, D.K.; Garba, D.L.; et al. Selective sweep suggests transcriptional regulation may underlie Plasmodium vivax resilience to malaria control measures in Cambodia. Natl. Acad. Sci. USA 2016, 113, E8096–E8105.
22. Auburn, S.; Benavente, E.D.; Miotto, O.; Pearson, R.D.; Amato, R.; Grigg, M.J.; Barber, B.E.; William, T.; Handayuni, I.; Marfurt, J.; et al. Genomic analysis of a pre-elimination Malaysian Plasmodium vivax population reveals selective pressures and changing transmission dynamics. Commun. 2018, 9, 1–12.

23. Benavente, E.D.; Ward, Z.; Chan, W.; Mohareb, F.R.; Sutherland, C.J.; Roper, C.; Campino, S.; Clark, T.G. Genomic variation in Plasmodium vivax malaria reveals regions under selective pressure. PLoS ONE. 2017, 12, e0177134.

24. Ford, A.; Kepple, D.; Abagero, B.R.; Connors, J.; Pearson, R.; Auburn, S.; Getachew, S.; Ford, C.; Gunalan, K.; Miller, L.H.; et al. Whole genome sequencing of Plasmodium vivax isolates reveals frequent sequence and structural polymorphisms in erythrocyte binding genes. PLoS Negl. Trop. Dis. 2020, 14, e0008234.

25. Lo, E.; Hostetler, J.B.; Yewhalaw, D.; Pearson, R.D.; Hamid, M.M.A.; Gunalan, K.; Kepple, D.; Ford, A.; Janies, D.A.; Rayner, J.C.; et al. Frequent expansion of Plasmodium vivax Duffy Binding Protein in Ethiopia and its epidemiological significance. PLoS Negl. Trop. Dis. 2019, 13, e0007222.

26. Jang, J.W.; Yun, S.G.; Woo, M.-K.; Han, E.T.; Lu, F.; Gao, Q.; Yoon, S.Y.; An, S.S.; Lim, C.S. Sequence polymorphisms of Plasmodium vivax tryptophan and alanine rich antigen (PvTARAg55). Acta Trop. 2015, 142, 122–126.

27. Guy, A.J.; Irani, V.; Richards, J.S.; Ramsland, P.A. Structural patterns of selection and diversity for Plasmodium vivax antigens DBP and AMA1. J. 2018, 17, 183.

28. Roesch, C.; Popovici, J.; Bin, S.; Run, V.; Kim, S.; Ramboarina, S.; Rakotomalala, E.; Rakotoarison, R.L.; Rasholoharimanana, T.; Andriamanantena, Z.; et al. Genetic diversity in two Plasmodium vivax protein ligands for reticulocyte invasion. PLoS Negl. Trop. Dis. 2018, 12, e0006555.

29. Han, J.H.; Cho, J.-S.; Ong, J.J.Y.; Park, J.-H.; Nyunt, M.H.; Sutanto, E.; Trimarsanto, H.; Petros, B.; Aseffa, A.; Getachew, S.; et al. Genetic diversity and neutral selection in Plasmodium vivax erythrocyte binding protein correlates with patient antigenicity. PLoS Negl. Trop. Dis. 2020, 14, e0008202.

30. Zeeshan, M.; Bora, H.; Sharma, Y.D. Presence of Memory T Cells and Naturally Acquired Antibodies in Plasmodium vivax Malaria-Exposed Individuals Against a Group of Tryptophan-Rich Antigens With Conserved Sequences. Infect. Dis. 2012, 207, 175–185.

31. Hwang, S.-Y.; Kim, S.-H.; Kho, W.-G. Genetic Characteristics of Polymorphic Antigenic Markers among Korean Isolates of Plasmodium vivax. Korean J. Parasitol. 2009, 47, S51.

32. Goryacheva, I.; Baranova, A.; Lukashev, A.; Gordeev, M.; Usenbaev, N.; Shaikevich, E. Genetic characterization of Plasmodium vivax in the Kyrgyz Republic. Genet. Evol. 2018, 66, 262–268.

33. Xainli, J.; Adams, J.H.; King, C.L. The erythrocyte binding motif of Plasmodium vivax Duffy binding protein is highly polymorphic and functionally conserved in isolates from Papua New Guinea. Biochem. Parasitol. 2000, 111, 253–260.

34. Cheng, C.W.; Putaporntip, C.; Jongwutiwes, S. Polymorphism in merozoite surface protein-7E of Plasmodium vivax in Thailand: Natural selection related to protein secondary structure. PLoS ONE 2018, 13, e0196765.

35. Wang, B.; Lu, F.; Cheng, Y.; Chen, J.-H.; Jeon, H.-Y.; Ha, K.-S.; Cao, J.; Nyunt, M.H.; Han, J.H.; Lee, S.K.; et al. Correction for Wang et al., Immunoprofiling of the Tryptophan-Rich Antigen Family in Plasmodium vivax. Immun. 2018, 86, e00950-17.

36. Baquero, L.A.; Moreno-Pérez, D.A.; Garzón-Ospina, D.; Forero-Rodríguez, J.; Ortiz-Suárez, H.D.; Patarroyo, M.A. PvGAMA reticulocyte binding activity: Predicting conserved functional regions by natural selection analysis. Parasites Vectors 2017, 10, 1–11.

37. Arévalo-Pinzón,; Bermúdez, M.; Curtidor, H.; Patarroyo, M.A. The Plasmodium vivax rhoptry neck protein 5 is expressed in the apical pole of Plasmodium vivax VCG-1 strain schizonts and binds to human reticulocytes. Malar. J. 2015, 14, 106.

38. Tyagi, K.; Hossain, M.E.; Thakur, V.; Aggarwal, P.; Malhotra, P.; Mohmmed, A.; Sharma, Y.D. Plasmodium vivax Tryptophan Rich Antigen PvTRAg36.6 Interacts with PvETRAMP and PvTRAg56.6 Interacts with PvMSP7 during Erythrocytic Stages of the Parasite. PLoS ONE 2016, 11, e0151065.

39. Gunalan, K.; Sá, J.M.; Barros, R.R.M.; Anzick, S.L.; Caleon, R.L.; Mershon, J.P.; Kanakabandi, K.; Paneru, M.; Virtaneva, K.; Martens, C.; et al. Transcriptome profiling of Plasmodium vivax in Saimiri monkeys identifies potential ligands for invasion. Natl. Acad. Sci. USA 2019, 116, 7053–7061.

40. Udomsangpetch, R.; Somsri, S.; Panichakul, T.; Chotivanich, K.; Sirichaisinthop, J.; Yang, Z.; Cui, L.; Sattabongkot, J. Short-term in vitro culture of field isolates of Plasmodium vivax using umbilical cord blood. Int. 2007, 56, 65–69.

41. Golenda, C.F.; Li, J.; Rosenberg, R. Continuous in vitro propagation of the malaria parasite Plasmodium vivax. Natl. Acad. Sci. USA 1997, 94, 6786–6791.

42. Borlon, C.; Russell, B.; Sriprawat, K.; Suwanarusk, R.; Erhart, A.; Renia, L.; Nosten, F.; D'Alessandro, U. Cryopreserved Plasmodium vivax and cord blood reticulocytes can be used for invasion and short term culture. J. Parasitol. 2012, 42, 155–160.

43. Anderson, D.C.; Lapp, S.A.; Barnwell, J.W.; Galinski, M.R. A large scale Plasmodium vivax- Saimiri boliviensis trophozoite-schizont transition proteome. PLoS ONE. 2017, 12,

44. Peterson, M.S.; Joyner, C.J.; Cordy, R.J.; Salinas, J.L.; Machiah, D.; Lapp, S.A.; Consortium, M.; Meyer, E.V.S.; Gumber, S.; Galinski, M.R. Plasmodium vivax Parasite Load Is Associated With Histopathology in Saimiri boliviensis With Findings Comparable to P vivax Pathogenesis in Humans. Open Forum Infect. Dis. 2019, 6,

45. Obaldia, N.; Meibalan, E.; Sa, J.M.; Ma, S.; Clark, M.A.; Mejia, P.; Barros, R.R.M.; Otero, W.; Ferreira, M.U.; Mitchell, J.R.; et al. Bone Marrow Is a Major Parasite Reservoir in Plasmodium vivax mBio 2018, 9, doi:10.1128/mBio.00625-18.

46. Hadley, T.J.; Klotz, F.W.; Miller, L.H. Invasion of Erythrocytes by Malaria Parasites: A Cellular and Molecular Overview. Rev. Microbiol. 1986, 40, 451–477.

47. Galinski, M.R.; Medina, C.C.; Ingravallo, P.; Barnwell, J.W. A reticulocyte-binding protein complex of plasmodium vivax Cell. 1992, 69, 1213–1226.

48. Kanjee, U.; Rangel, G.W.; Clark, M.A.; Duraisingh, M.T. Molecular and cellular interactions defining the tropism of Plasmodium vivax for reticulocytes. Opin. Microbiol. 2018, 46, 109–115.

49. Malleret, B.; Rénia, L.; Russell, B. The unhealthy attraction of Plasmodium vivax to reticulocytes expressing transferrin receptor 1 (CD71). J. Parasitol. 2017, 47, 379–383.

50. Huh, A.-J.; Kwak, Y.G.; Kim, E.S.; Lee, K.S.; Yeom, J.-S.; Cho, Y.-K.; Kim, C.S.; Park, J.W. Parasitemia Characteristics of Plasmodium vivax Malaria Patients in the Republic of Korea. Korean Med. Sci. 2011, 26, 42.

51. Almeida, A.C.G.; Kuehn, A.; Castro, A.J.M.; Vitor-Silva, S.; Figueiredo, E.F.G.; Brasil, L.W.; Brito, M.A.M.; Sampaio, V.S.; Bassat, Q.; Felger, I.; et al. High proportions of asymptomatic and submicroscopic Plasmodium vivax infections in a peri-urban area of low transmission in the Brazilian Amazon. Parasites Vectors. 2018, 11, 1–13.

52. Siegel, S.V.; Chappell, L.; Hostetler, J.B.Amaratunga, C.; Suon, S.; Böhme, U.; Berriman, M.; Fairhurst, R.M.; Rayner, J.C. Analysis of Plasmodium vivax schizont transcriptomes from field isolates reveals heterogeneity of expression of genes involved in host-parasite interactions. Rep. 2020, 10, 16667.

53. Adams, J.H.; Mueller, I. The Biology of Plasmodium vivax. Cold Spring Harb. Med. 2017, 7, a025585.

54. Battle, K.E.; Karhunen, M.S.; Bhatt S, Gething PW, Howes RE, Golding, N.; Boeckel, T.P.V.; Messina, J.; Shanks, G.D.; Smith, D.L.; et al. Geographical variation in Plasmodium vivax Malar. J. 2014, 13, 1–16.

55. Mikolajczak, S.A.; Vaughan, A.M.; Kangwanrangsan, N.; Roobsoong, W.; Fishbaugher, M.; Yimamnuaychok, N.; Rezakhani, N.; Lakshmanan, V.; Singh, N.; Kaushansky, A.; et al. Plasmodium vivax Liver Stage Development and Hypnozoite Persistence in Human Liver-Chimeric Mice. Cell Host Microbe. 2015, 17, 536.

56. Craig, M.H.; Snow, R.W.; Sueur, D. A climate-based distribution model of malaria transmission in sub-Saharan Africa. Parasitol 1999, 15, 105–111.

57. Midekisa, A.; Beyene, B.; Mihretie, A.; Bayabil, E.; Wimberly, M.C. Seasonal associations of climatic drivers and malaria in the highlands of Ethiopia. Parasit Vectors 2015, 8, 339.

58. Ikeda, T.; Behera, S.K.; Morioka, Y.; Minakawa, N.; Hashizume, M.; Tsuzuki, A.; Maharaj, R.; Kruger, P. Seasonally lagged effects of climatic factors on malaria incidence in South Africa. Rep. 2017, 7, 2458.

59. Rodríguez, L.E.; Urquiza, M.; Ocampo, M.; Curtidor, H.; Suárez, J.; García, J.; Vera, R.; Puentes, A.; López, R.; Pinto, M.; et al. Plasmodium vivax MSP-1 peptides have high specific binding activity to human reticulocytes. Vaccine 2002, 20, 1331–1339.

60. Sim, B.K.L.; Narum, D.L.; Liang, H.; Fuhrmann, S.R.; Obaldia, N.; Gramzinski, R.; Aguiar, J.; Haynes, J.D.; Moch, J.K.; Hoffman, S.L. Induction of Biologically Active Antibodies in Mice, Rabbits, and Monkeys by Plasmodium falciparum EBA-175 Region II DNA vaccine. Med. 2001, 7, 247–254.

61. O'donnell, R.A.; Hackett, F.; Howell, S.A.; Treeck, M.Struck, N.; Krnajski, Z.; Martinez, C.W.; Gilberger, T.W.; Blackman, M.J. Intramembrane proteolysis mediates shedding of a key adhesin during erythrocyte invasion by the malaria parasite. Cell Biol. 2006, 174, 1023–1033.

62. Koch, M.; Wright, K.E.; Otto, O.; Herbig, M.; Salinas, N.D.; Tolia, N.H.; Satchwell, T.J.; Guck, J.; Brooks, N.J.; Baum, J. Plasmodium falciparum erythrocyte-binding antigen 175 triggers a biophysical change in the red blood cell that facilitates invasion. Natl. Acad. Sci. USA 2017, 114, 4225–4230.

63. Sisquella, X.; Nebl, T.; Thompson, J.K.; Whitehead, L.; Malpede, B.M.; Salinas, N.D.; Rogers, K.; Tolia, N.H.; Fleig, A.; O'Neill, J.; et al. Plasmodium falciparum ligand binding to erythrocytes induce alterations in deformability essential for invasion. Int. 2017, 6, e21083.

64. Paing, M.M.; Salinas, N.D.; Adams, Y.; Oksman, A.; Jensen, A.T.; Goldberg, D.E.; Tolia, N.H. Shed EBA-175 mediates red blood cell clustering that enhances malaria parasite growth and enables immune evasion. Int. 2018, 7, e43224.

65. Maier, A.G.; Baum, J.; Smith, B.; Conway, D.J.; Cowman, A.F. Polymorphisms in Erythrocyte Binding Antigens 140 and 181 Affect Function and Binding but Not Receptor Specificity in Plasmodium falciparum. Immun. 2009, 77, 1689–1699.

66. Mayer, D.C.G.; Jiang, L.; Achur, R.N.; Kakizaki, I.; Gowda, D.C.; Miller, L.H. The glycophorin C N-linked glycan is a critical component of the ligand for the Plasmodium falciparum erythrocyte receptor BAEBL. Natl. Acad. Sci. USA 2006, 103, 2358–2362.

67. Gaur, D.; Storry, J.R.; Reid, M.E.; Barnwell, J.W.; Miller, L.H. Plasmodium falciparum Is Able To Invade Erythrocytes through a Trypsin-Resistant Pathway Independent of Glycophorin-B. Immun. 2003, 71, 6742–6746.

68. Facer, C.A. Erythrocyte sialoglycoproteins and Plasmodium falciparum Trans. R Soc. Trop. Med. Hyg. 1983, 77, 524–530.

69. Field, S.; Hempelmann, E.; Mendelow, B.; Fleming, A. Glycophorin variants and Plasmodium falciparum: Protective effect of the Dantu phenotype in vitro. Genet. 1994, 93, 148–150.

70. Kariuki, S.N.; Marin-Menendez, A.; Introini, V.; Ravenhill, B.J.; Lin, Y.-C.; Macharia, A.; Makale, J.; Tendwa, M.; Nyamu, W.; Kotar, J.; et al. Red blood cell tension protects against severe malaria in the Dantu blood group. Nature 2020, 585, 579–583.

71. Vera-Bravo, R.; Valbuena, J.J.; Ocampo, M.; Garcia, J.E.; Rodriguez, L.E.; Puentes, A.; Lopez, R.; Curtidor, H.; Torres, E.; Trujillo, M.; et al. Amino terminal peptides from the Plasmodium falciparum EBA-181/JESEBL protein bind specifically to erythrocytes and inhibit in vitro merozoite invasion. Biochimie 2005, 87, 425–436.

72. Reyes, C.; Molina-Franky, J.; Aza-Conde, J.; Suárez, C.F.; Pabón, L.; Moreno-Vranich, A.; Patarroyo, M.A.; Patarroyo, M.E. Malaria: Paving the way to developing peptide-based vaccines against invasion in infectious diseases. Biophys. Res. Commun. 2020, 527, 1021–1026.

73. Rayner, J.C.; Vargas-Serrato, E.; Huber, C.S.; Galinski, M.R.; Barnwell, J.W. A Plasmodium falciparum Homologue of Plasmodium vivax Reticulocyte Binding Protein (PvRBP1) Defines a Trypsin-resistant Erythrocyte Invasion Pathway. Exp. Med. 2001, 194, 1571–1582.

74. Triglia, T.; Duraisingh, M.T.; Good, R.T.; Cowman, A.F. Reticulocyte-binding protein homologue 1 is required for sialic acid-dependent invasion into human erythrocytes by Plasmodium falciparum. Microbiol. 2004, 55, 162–174.

75. Gao, X.; Gunalan, K.; Yap, S.S.L.; Preiser, P.R. Triggers of key calcium signals during erythrocyte invasion by Plasmodium falciparum. Commun. 2013, 4, 1–11.

76. Dvorin, J.D.; Bei, A.K.; Coleman, B.I.; Duraisingh, M.T. Functional diversification between two related Plasmodium falciparum merozoite invasion ligands is determined by changes in the cytoplasmic domain. Microbiol. 2010, 75, 990–1006.

77. Duraisingh, M.T.; Triglia, T.; Ralph, S.A.; Rayner, J.C.; Barnwell, J.W.; Mcfadden, G.I.; Cowman, A.F. Phenotypic variation of Plasmodium falciparum merozoite proteins directs receptor targeting for invasion of human erythrocytes. EMBO J. 2003, 22, 1047–1057.

78. Espinosa, A.M.; Sierra, A.Y.; Barrero, C.A.; Cepeda, L.A.; Cantor, E.M.; Lombo, T.B.; Guzmán, F.; Avila, S.J.; Patarroyo, M.A. Expression, polymorphism analysis, reticulocyte binding and serological reactivity of two Plasmodium vivax MSP-1 protein recombinant fragments. Vaccine 2003, 21, 1033–1043.

79. Gunalan, K.; Gao, X.; Liew, K.J.L.; Preiser, P.R. Differences in Erythrocyte Receptor Specificity of Different Parts of the Plasmodium falciparum Reticulocyte Binding Protein Homologue 2a. Immun. 2011, 79, 3421–3430.

80. Aniweh, Y.; Gao, X.; Gunalan, K.; Preiser, P.R. PfRH2b specific monoclonal antibodies inhibit merozoite invasion. Microbiol. 2016, 102, 386–404.

81. Triglia, T.; Chen, L.; Lopaticki, S.; Dekiwadia, C.; Riglar, D.T.; Hodder, A.N.; Ralph, S.A.; Baum, J.; Cowman, A.F. Plasmodium falciparum Merozoite Invasion Is Inhibited by Antibodies that Target the PfRh2a and b Binding Domains. PLoS Pathog. 2011, 7, e1002075.

82. Tham, W.-H.; Wilson, D.W.; Lopaticki, S.; Schmidt, C.Q.; Tetteh-Quarcoo, P.B.; Barlow, P.N.; Richard, D.; Corbin, J.E.; Beeson, J.G.; Cowman, A.F. Complement receptor 1 is the host erythrocyte receptor for Plasmodium falciparum PfRh4 invasion ligand. Natl. Acad. Sci. USA 2010, 107, 17327–17332.

83. Han, J.-H.; Lee, S.-K.; Wang, B.; Muh, F.; Nyunt, M.H.; Na, S.; Ha, K.S.; Hong, S.; Park, W.S.; Sattabongkot, J.; et al. Identification of a reticulocyte-specific binding domain of Plasmodium vivax reticulocyte-binding protein 1 that is homologous to the PfRh4 erythrocyte-binding domain. Rep. 2016, 6, 1–12.

84. Volz, J.C.; Yap, A.; Sisquella, X.; Thompson, J.K.; Lim, N.T.; Whitehead, L.W.; Chen, L.; Lampe, M.; Tham, W.H.; Wilson, D.; et al. Essential Role of the PfRh5/PfRipr/CyRPA Complex during Plasmodium falciparum Invasion of Erythrocytes. Cell Host Microbe. 2016, 20, 60–71.

85. Partey, F.D.; Castberg, F.C.; Sarbah, E.W.; Silk, S.E.; Awandare, G.A.; Draper, S.J.; Opoku, N.; Kweky, M.; Ofori, M.F.; Hviid, L.; et al. Correction: Kinetics of antibody responses to PfRH5-complex antigens in Ghanaian children with Plasmodium falciparum PLoS ONE 2018, 13, e0198371.
86. Crosnier, C.; Bustamante, L.Y.; Bartholdson, S.J.; Bei, A.K.; Theron, M.; Uchikawa, M.; Mboup, S.; Ndir, O.; Kwiatkowski, D.P.; Duraisingh, M.T.; et al. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. Nature 2011, 480, 534–537.
87. Sierra, A. Splenectomised and spleen intact Aotus monkeys? immune response to Plasmodium vivax MSP-1 protein fragments and their high activity binding peptides. Vaccine 2003, 21, 4133–4144.
88. Stubbs, J. Molecular Mechanism for Switching of P. falciparum Invasion Pathways into Human Erythrocytes. Science 2005, 309, 1384–1387.
89. Lopaticki, S.; Maier, A.G.; Thompson, J.; Wilson, D.W.; Tham, W.-H.; Triglia, T.; Gout, A.; Speed, T.P.; Beeson, J.G.; Healer, J.; et al. Reticulocyte and Erythrocyte Binding-Like Proteins Function Cooperatively in Invasion of Human Erythrocytes by Malaria Parasites. Immun. 2010, 79, 1107–1117.
90. Amir, A.; Cheong, F.W.; Silva, J.R.D.; Liew, J.W.K.; Lau, Y.L. Plasmodium knowlesi malaria: Current research perspectives. Drug Resist. 2018, 11, 1145–1155.
91. Cox-Singh, J.; Davis, T.M.E.; Lee, K.-S.; Shamsul, S.S.G.; Matusop, A.; Ratnam, S.; Rahman, H.A.; Conway, D.J.; Singh, B. Plasmodium knowlesi Malaria in Humans Is Widely Distributed and Potentially Life Threatening. Infect. Dis. 2008, 46, 165–171.
92. Moon, R.W.; Sharaf, H.; Hastings, C.H.; Ho, Y.S.; Nair, M.B.; Rchiad, Z.; Knuepfer, E.; Ramaprasad, A.; Mohring, F.; Amir, A.; et al. Normocyte-binding protein required for human erythrocyte invasion by the zoonotic malaria parasite Plasmodium knowlesi. Natl. Acad. Sci. USA 2016, 113, 7231–7236.
93. Ahmed, A.M.; Pinheiro, M.M.; Divis, P.C.; Siner, A.; Zainudin, R.; Wong, I.T.; Lu, C.W.; Khaira, S.K.; Millar, S.B.; Lynch, S.; et al. Disease Progression in Plasmodium knowlesi Malaria Is Linked to Variation in Invasion Gene Family Members. PLoS Negl. Trop. Dis. 2014, 8, e3086.
94. Bermúdez, M.; Moreno-Pérez, D.A.; Arévalo-Pinzón, G.; Curtidor, H.; Patarroyo, M.A. Plasmodium vivax in vitro continuous culture: The spoke in the wheel. J. 2018, 17, 301.
95. Pasini, E.M.; Zeeman, A.-M.; Wel, A.V.-V.D.; Kocken, C.H.M. Plasmodium knowlesi: A relevant, versatile experimental malaria model. Parasitology 2016, 145, 56–70.
96. Tachibana, S.-I.; Sullivan, S.A.; Kawai, S.; Nakamura, S.; Kim, H.R.; Goto, N.; Arisue, N.; Palacpac, N.M.Q.; Honma, H.; Yagi, M.; et al. Plasmodium cynomolgi genome sequences provide insight into Plasmodium vivax and the monkey malaria clade. Genet. 2012, 44, 1051–1055.
97. Coatney, G.R.; Elder, H.A.; Contacos, P.G.; Getz, M.E.; Greenland, R.; Rossan, R.N.; Schmidt, L.H. Transmission of the M Strain of Plasmodium cynomolgi to Man *. J. Trop. Med. 1961, 10, 673–678.
98. Eyles, D.E.; Coatney, G.R.; Getz, M.E. Vivax-Type Malaria Parasite of Macaques Transmissible to Man. Science 1960, 131, 1812–1813.
99. Ta, T.H.; Hisam, S.; Lanza, M.; Jiram, A.I.; Ismail, N.; Rubio, J.M. First case of a naturally acquired human infection with Plasmodium Malar. J. 2014, 13, 68.
100. Tachibana, S.-I.; Kawai, S.; Katakai, Y.; Takahashi, H.; Nakade, T.; Yasutomi, Y.; Horii, T.; Tanabe, K. Contrasting infection susceptibility of the Japanese macaques and cynomolgus macaques to closely related malaria parasites, Plasmodium vivax and Plasmodium Parasitol. Int. 2015, 64, 274–281.
101. Sutton, P.L.; Luo, Z.; Divis, P.C.; Friedrich, V.K.; Conway, D.J.; Singh, B.; Barnwell, J.W.; Carlton, J.M.; Sullivan, S.A. Characterizing the genetic diversity of the monkey malaria parasite Plasmodium Infect. Genet. Evol. 2016, 40, 243–252.
102. Putaporntip, C.; Kuamsab, N.; Jongwutiwes, S. Sequence diversity and positive selection at the Duffy-binding protein genes of Plasmodium knowlesi and P. cynomolgi: Analysis of the complete coding sequences of Thai isolates. Genet. Evol. 2016, 44, 367–375.
103. Chua, A.C.Y.; Ong, J.J.Y.; Malleret, B.; Suwanarusk, R.; Kosaisavee, V.; Zeeman, A.-M.; Cooper, C.A.; Tan, K.S.W.; Zhang, R.; Tan, B.H.; et al. Robust continuous in vitro culture of the Plasmodium cynomolgi erythrocytic stages. Commun. 2019, 10, 1–13.