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Chapter

Origin of Two Most Virulent Agents of Human Malaria: *Plasmodium falciparum* and *Plasmodium vivax*

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Abstract

Malaria is a protozoan disease caused by a parasite belonging to *Plasmodium* genus. Five species are known to infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium knowlesi, Plasmodium ovale*, and *Plasmodium malariae*. Among these species, *Plasmodium falciparum* and *Plasmodium vivax* account for more than 95% of all human malaria infections and thus pose a serious public health challenge. *Plasmodium falciparum* is highly prevalent in sub-Saharan Africa, while *Plasmodium vivax* is rare in sub-Saharan Africa but endemic in many parts of Asia. The recent studies using the development of molecular tools have shown that a large diversity of malaria parasites circulate among the nonhuman primates and certainly present a similarity with human parasites. For a long time, the question of the origin of its parasites that infect human population has been the subject of much debate. Today, it would seem that both most virulent agents of human malaria would come from African apes. Thus, this chapter tries to review available data about the origin of these two *Plasmodium* species.

Keywords: *Plasmodium*, nonhuman primate, human, Africa, origin, host switching

1. Introduction

Malaria is a serious infectious disease. It is caused by parasites of the genus *Plasmodium* and transmitted by *Anopheles* mosquitoes to its vertebrate hosts. This disease is an important global health problem, especially in sub-Saharan Africa [1] (Figure 1). Indeed, the African region continues to carry a disproportionately high share of the global malaria burden [1, 2]. Among five *Plasmodium* species which infect human, two species *Plasmodium falciparum* and *Plasmodium vivax* pose the greatest threat for human health. For example, *P. falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally [3], while *P. vivax* is rare in sub-Saharan Africa, but it is the major malaria parasite in most countries outside of sub-Saharan Africa [4].

The origin of parasites responsible of human malaria has always been at the center of the debate [5, 6]. Understanding the origin of its infectious agents could open a door in the improvement of strategies to fight against the malaria agents which constantly surprise us by their abilities to adapt to the different means of fight put in place. So then, the questions are as follows: Where do the pathogens...
Malaria

responsible for this disease come from in humans? This chapter is a synthesis of the available data on the origin of two most virulent agents of human malaria: \( P. falciparum \) and \( P. vivax \).

2. Nonhuman primate natural hosts of a large \textit{Plasmodium} diversity

Today, the diversity of \textit{Plasmodium} parasites infecting primates is well documented. First studies based in morphological analysis have reported three species which infect African apes (\textit{Plasmodium reichenowi}, \textit{Plasmodium schwetzii}, and \textit{Plasmodium rodhaini}), and some of these were found to resemble human parasites \textit{Plasmodium malariae}, \textit{Plasmodium vivax}, and \textit{Plasmodium ovale} \cite{7}. The development of molecular tools allowed for a re-examination of \textit{Plasmodium} diversity \cite{8–10}. Data collected over the past years have shown that NHPs are infected with large diversity of \textit{Plasmodium} belonging to two subgenera (\textit{Laverania} and \textit{Plasmodium}) \cite{11} (\textbf{Figure 2}).

2.1 \textit{Laverania} subgenus

Among species classified into \textit{Laverania} group, four species infect chimpanzees (\textit{P. gaboni}, \textit{P. billcollinsi}, \textit{P. billbrayi}, and \textit{P. reichenowi}), only three infect gorillas (\textit{P. adleri}, \textit{P. blacklocki}, and \textit{P. praefalciparum}), and only one infect bonobo (\textit{P. lomamiensis}) \cite{8, 9, 12}. Therefore, \textit{P. billbrayi} \cite{10} is not accepted as a new species by some authors \cite{6, 13} who reported that these isolates did not seem to be sufficiently distinct from \textit{P. gaboni} to warrant a separate species designation \cite{6}. However, this species was described only in \textit{Pan troglodytes schweinfurthii} and hence is the reason why we believe that could be another species \cite{10} (\textbf{Figure 2}). Moreover, Mapua and colleagues reported recently several lineages of these parasites among African apes \cite{14}.

To date, all studies on natural populations of apes (based on the analysis of fecal samples) have shown that no \textit{Plasmodium} species from the \textit{Laverania} subgenus is able to infect \textit{in natura} both hosts (gorillas and chimpanzees) \cite{8, 13}, thus suggesting the existence of a strong host specificity due to genetic barrier \cite{6, 15}. However, a recent study revealed that this genetic barrier is not completely impermeable \cite{16}; moreover, in this study, authors reported that the exchanges between gorillas
Figure 2.

Figure 3.
Distribution of the different subspecies of great apes in Africa and representation of the spread of the different Plasmodium species in these species [5].
Malaria and chimpanzees were possible in confined environments [16]. Second hypothesis was about the role played by potential vectors [17]. However, this hypothesis was refuted by a study which showed that vectors had no preference for hosts [18]. Thus, other ecological factors could play a potential role in host specificity. Furthermore, the simians’ species of this group seem to be geographically located in central Africa only (Figure 3).

2.2 Plasmodium subgenus

Conversely, subgenus Plasmodium (non-Laverania) includes several species infecting a large variety of primates of varied origins [Africa, Asia (catarrhines), South America (platyrrhines) and Human] [11]. Two major facts concerning this group were the emergence of P. knowlesi in human population [19, 20] and the characterization of P. vivax-like in chimpanzees and gorillas [21, 22] which completely changed our consideration of this malaria parasite subgenus [23, 24].

In Africa NHPs, five species of this subgenus circulate among monkeys and great apes, two for monkeys (P. gonderi and P. sp. DAJ-2004 [called now Plasmodium mandrilli [25]]) and three for great apes (P. vivax-like, P. malariae-like, and P. ovale-like) [13, 16]. In African great apes, both hosts (chimpanzee and gorilla) are infected with these parasites (P. vivax-like, P. malariae-like, and P. ovale-like) (Figures 3 and 4). Thus, these Plasmodium species are not specific hosts, and it would be very interesting to establish the mechanisms which favor host switching for these parasites. Several species were reported as implicated in circulation of malaria parasites in central Africa [17, 18]. In African apes three Anopheles species (An. moucheti, An. vinckei, and An. marshallii) are known to allow the circulation of malaria parasites in forest environment [18].

Apart from African apes, Asian monkeys are also infected by many other species of Plasmodium (P. cynomolgi, P. hylobati, P. knowlesi, P. coatneyi, P. fragile, P. fieldi,

Figure 4. Phyllogenetic tree of some Plasmodium species found in apes.
P. simiovale, and P. inui Plasmodium spp. \([26]\) (Figures 3 and 4). Several other species of Plasmodium were observed among Asian apes by microscopic analyses, but no molecular evidence of the existence of these lineages are available (e.g., P. pithecia and P. sandoshami). These malaria parasites could infect many apes' hosts. Several studies reported of the different NHP species with same parasites \([27]\) or many parasites which were found in one species of NHP, for example, four species of simian malaria parasites were characterized in the pig-tailed macaques (Macaca nemestrina) \([28, 29]\). In this part of the world, the situation of P. knowlesi gives a good example of the risk that these parasites could present to humans. Recently, the probable existence of three divergent subpopulations of P. knowlesi with the different origins was reported \([30]\).

Finally, in South America some Plasmodium species were described as infecting NHPs. The species found in Southern American primates are Plasmodium brasilianum and Plasmodium simium, and these parasite species naturally infect monkeys from the Cebidae and Atelidae families \([31]\) (Figure 3). However, P. brasilianum infects 11 species of monkeys (Alouatta spp, Ateles spp, Brachyteles arachnoides, Cacajao calvus, Calliebus spp, Cebus spp, Chiropterus satans, Lagothrix spp, Saimiri spp, Saguinus midas, and Pithecia pithecia), while Plasmodium simium infects only 2 species (Alouatta spp and Brachyteles arachnoides). In recent studies, P. simium was found for the first time in capuchin monkeys from the Brazilian Atlantic Forest \([32]\). P. brasilium and P. simium are similar and indistinguishable from human P. malariae and P. vivax. These similarities occur at the morphological, genetic, and immunological levels \([31, 32]\).

3. Where do the malaria parasites that infect men come from?

The understanding of origin of human malaria parasites has been the subject of numerous studies that have been based on the morphology, biology, and affiliation of parasites to their hosts \([33]\). However, recent development of molecular tools in diagnosis has made considerable progress in understanding the evolutionary history of malaria parasites. Indeed, the contribution of several new sequences by this new approach will clarify the debate on many theories developed on the subject \([34]\). Moreover, several of these parasites have been found to be associated with humans by lateral transfer from other vertebrate host species \([35, 36]\). We will present the probable origin of two most virulent Plasmodium species that infect human.

3.1 Plasmodium falciparum

The debate on the origin of P. falciparum most spread in world (Figure 5) was opened with the study of Waters and his collaborators who proposed an avian origin of this parasite that is to say that the man would have recently acquired this parasite of a transfer from birds to humans \([37]\). Indeed, phylogenetic analyses based on the study of ribosomal RNA subunit (rRNA) sequences showed that P. falciparum formed a monophyletic group with Plasmodium spp. of birds (see Figure 6), hence the conclusion of the authors.

Three years after the first hypothesis on the origin of P. falciparum, Escalante and Ayala \([38]\), in their study also based on 18S RNA, take into account for the first time P. reichenowi, an isolated parasite in a chimpanzee African (Figure 7). They will show that this parasite is the closest parent of P. falciparum; therefore, this observation allowed authors to conclude that Plasmodium falciparum origin was not a recent lateral transfer of this parasite of birds to humans \([38, 39]\). In this study, P. falciparum and P. reichenowi form a large group with primate parasites of the subgenus Plasmodium (non-Laverania), rodents, and birds \([38, 40, 41]\) (Figure 7). This will further fuel the debate on the origin of P. falciparum.
The disputes surround the probable origin of *P. falciparum*, whether it comes from birds or rodents, will be raging. Authors as Prugnolle et al. believe that the problems or weaknesses of many studies were based essentially on two aspects [5]: firstly the low number of plasmodial species and sequences integrated in these analyses and secondly the limited number of molecular markers used for the development of phylogenies. Despite all this controversy, *P. falciparum* will be considered to have an African origin [43–45].

The year 2009 will completely change our understanding of the evolutionary history of *P. falciparum*, because prior to this year, only one species (*P. reichenowi*) was known to be closer to *P. falciparum*. After the discovery of *Plasmodium gaboni* parasite that infects chimpanzees [46], several other sequences from African great apes will definitively bring elements of answers to question on the origin of this parasite.

Indeed, in 2010, Prugnolle and colleagues will highlight for the first time *P. falciparum*-like in gorillas and several other lineages. These studies will prove that the *Laverania* group that includes *P. falciparum* has a great diversity of species that circulate in African primates [9]. This will make it possible to show that the origin
of *P. falciparum* is not found in birds or rodents but in the gorillas that have recently transmitted it to humans via anopholic zoo-anthropophilic mosquito [17, 18]. *P. falciparum*-like of gorillas will be named *P. praefalciparum* to distinguish it from that which infects humans [11, 13].

In 2011, the hypothesis of a gorilla origin of *P. falciparum* seems to be weakened by the discovery of *P. praefalciparum* in a small African monkey (*Cercopithecus nictitans*) [47]. This study also will reveal the existence of at least two types of *P. praefalciparum*: 1 and 2. *P. praefalciparum*-1 infects gorillas and monkeys (*C. nictitans*), and *P. praefalciparum*-2 infects only gorillas [11]. Other studies will focus on African monkeys, but will not find *P. praefalciparum* [48]. Thus, we believe that the hypothesis of *Plasmodium falciparum* from monkeys is not solid and that *C. nictitans* species is not a natural reservoir for this parasite [48].

Today, after numerous studies that analyzed more than 5000 samples of wild and captives apes [8–10, 12, 13, 16, 21, 22, 47] (Figure 8), it appears that gorillas are...
the reservoir for the *P. praefalciparum*, even though several hypotheses concerning the origin of *P. falciparum* have been proposed for primates [10, 47].

The hypothesis according to which *Plasmodium falciparum* would come from gorillas seems to be the most plausible at the moment. Indeed, several *P. praefalciparum* sequences had been found from numerous wild-living gorillas in different areas [8, 13]. Loy and colleagues suggested that this parasite strain that was able to cross the host species barrier by carried one or more highly unusual mutations that conferred him an ability to colonize humans [49]. This theory comes to the fact that recent studies in human populations living close to the wild apes did not reveal the presence of parasites of great apes belonging to *Laverania* subgenus in humans [50, 51]. Thus, then it would seem that *P. falciparum* comes from African gorillas according to available data at the moment.

3.2 Origin of *Plasmodium vivax*

*Plasmodium vivax* is particularly prevalent in Asia, Southeast Asia, South America, and the Western Pacific region [52] (Figure 9). Already the first studies on malaria of the great apes had revealed the presence of parasites resembling *P. vivax* [53, 54]. Despite its first observations, the question on the origin of *P. vivax* remained uncertain for several years. Concerning this interesting question of the *P. vivax* origin, several hypotheses have been proposed in recent years.

The first hypotheses about the origin of *P. vivax* had suggested that it originated in Southeast Asia [24, 49]. These hypotheses were based on the fact that *P. vivax* shares morphological and biological traits with several macaque parasites and that *Plasmodium simian*’s species are abundant in this Asian region [36]. This hypothesis was supported by the phylogenetic analyses that placed *P. vivax* among the *Plasmodium* spp. of Asian monkeys with like closest parent, *Plasmodium cynomolgi*, which infects macaques in Asia [40, 55]. The consensus view has thus been that *P. vivax* emerged in southeastern Asia following the cross-species transmission of a macaque parasite [23, 56, 57].

In addition to the first hypothesis, another hypothesis will articulate around the negative Duffy receptor and would suggest African origin of *P. vivax* [58, 59]. Indeed, the presence of negative Duffy blood group in central and West African populations was correlated with the absence of *P. vivax*. This character would confer resistance to *P. vivax* infection, which suggested that this mutation arose in response to prolonged selection pressure from *P. vivax* [60]. Currently, Duffy antigen is the

Figure 9.
The spatial distribution of *Plasmodium vivax* in the world [52].
only receptor known to be used by parasite to invade the red blood cell. Thus, it has been proposed that *P. vivax* co-evolved with African populations for longer than with other human populations [24, 61].

However, the recent studies using the development of molecular tools allow to have a clear view on the origin of this parasite. These studies have shown that chimpanzees and gorillas from central and West Africa harbor a large diversity of *P. vivax*-like parasites [10, 21, 22, 62]. This discovery accentuates the African origin of *Plasmodium vivax* and reveals that African great apes are potential sylvatic reservoir of *P. vivax* [21, 22]. However, elucidation of the origin of *P. vivax* in African apes needed complementary studies of wild-living populations across central Africa [22].

Also, Prugnolle et al. have shown that *P. vivax*-like found among African great apes form a distinct and much more diverse genetic group than that of human parasites [21]. In this study authors revealed also an older origin of the African simian lineages and the fact that these lineages are able to infect the Caucasian population today [21] (Figure 10). Thus, the discovery of *P. vivax* in large numbers of chimpanzees and gorillas provides compelling evidence for an African, rather than an Asian, origin of human *P. vivax*.

Today, an interesting question would be to understand how this passage of apes to man had been done. To this question, in view of current data and analyses, we agree to say, instead, it is much more likely that extant human *P. vivax* could represent a lineage that survived after spreading out of Africa [21, 64, 65], because this theory could explain the fact that we observed today a reduced diversity of the human parasites which would result from an out-of-Africa bottleneck, such as observed in *P. falciparum* [45, 66].

4. Malaria like a zoonotic disease: the running toward new environments is a wont for *Plasmodium*

It is true that many *Plasmodium* parasites circulating in African NHPs could produce symptoms of this disease in apes [67]. However, no *Plasmodium* species particularly parasites belonging to *Laverania* subgenus has been found to infect human to date. Studies conducted in rural population in central Africa (Cameroon and Gabon) have shown that *Laverania* parasites were absent of human populations living in villages that are in very close proximity to wild forest [50, 51] and even
those working in very close contact with NHPs [16]. On the other hand, several studies reported that *P. falciparum* is able to infect African apes, for example, Bonobos, chimpanzees [10, 26], and recently the mandrills [16]. The question is why these transfers are rare or why the ancestral parent of *P. falciparum* (*P. praefalciparum*) appear incapable of infecting humans today. Loy et al. suggest that gorilla parasite strain that was able to cross the host species barrier must have carried one or more highly unusual mutations that enable it to colonize humans [49]. But, supplementary studies would be necessary to support this hypothesis.

In contrast, many parasites of *Plasmodium* subgenus were reported to infect humans. The major case known is *P. knowlesi* that infects NHPs in south Asia and now is considered as the fifth *Plasmodium* species that infects human and cause malaria in southern Asian population [19]. Other cases of natural or accidental infections of humans with simians *Plasmodium* were reported in literature. Indeed, a total of seven species of monkey malaria have been reported via mosquitoes (*P. cynomolgi*, *P. brasilianum*, *P. eylesi*, *P. knowlesi*, *P. inui*, *P. schwetzii*, and *P. simium*) [11, 68, 69]. Recently, ape *P. vivax* has been found to cause clinical malaria in Caucasians who stayed during some days in African forest [21]. Thus, parasites of *Plasmodium* subgenus are apparently able to cross the species barrier to humans. So the emergence of these parasites should be monitored in areas where an influx of contact between humans and NHPs increases with anthropization, which destroys ape habitat and favors contact. In view of the rare faction of monkeys and the increase of the human population, it is feared that human infection of simians *Plasmodium* will become more frequent which could lead to humans becoming simians’ major host [70].

5. Prevention

The potential for zoonosis is influenced by human habitation and behavior as well as the adaptive capabilities of parasites and vectors. Indeed, the existence of potential sylvatic reservoirs of *P. vivax* and *P. falciparum* in Africa could compromise malaria control and eradication efforts. Actually, there is lack of knowledge about the real extent of malaria zoonosis. Thus, this aspect of zoonosis malaria parasites must be taken into account by the public health authorities responsible for the fight against malaria. African structures health need to put appropriate strategies of prevention against zoonotic malaria parasites that could be developed. However, they must be based on good data of research on diagnosis and treatment of zoonotic malaria. Moreover, all people living in the locality or monkeys are known to grass a large variety of malaria parasite, which must take their precaution when they venture into forest environment, in order to avoid mosquito bites.

6. Conclusion

The development of the tools of molecular biology allowed us to see clearer in the history of parasite that infects the man, especially *Plasmodium* species. Indeed, these tools allowed us to highlight large diversity of the malaria parasites that circulate to the nonhuman primates, so to understand better the origin of the most virulent parasite responsible for human malaria (*Plasmodium falciparum* and *Plasmodium vivax*). Therefore, on the basis of available data, it is more than likely that its parasites have an African origin and that African gorillas and chimpanzees would constitute potential reservoirs of its parasites. Thus, in this context, it is important to determine or develop appropriate preventive strategies. It is necessary to set up monitoring systems in forest areas and to make sensitization campaigns.
Annex for reader

Diversity: the condition of having or being composed of differing elements (variety). It can also include of different species or genetic lineages.

Gorilla sp.: designs all species belonging to Gorilla genus. This genus has three subspecies of gorilla (Gorilla gorilla gorilla; Gorilla gorilla graueri and Gorilla gorilla beringei).

Laverania: is a subgenus of the Plasmodium genus of parasites. The parasites belonging to this subgenus have a strong host specificity.

Outgroup: outgroup is a more distantly related group of organisms that serves as a reference group when determining the evolutionary relationships of the ingroup, and it is used as a point of comparison for the ingroup and specifically allows for the phylogeny to be rooted.

Phylogenetic tree: a phylogenetic tree is a diagram that represents evolutionary relationships among organisms.

Plasmodium GorA (Prugnolle et al. 2010): Plasmodium adleri.
Plasmodium (non-Laverania): non-Laverania subgenus includes many parasites such as P. malariae, P. vivax, P. ovale-curtisi, and P. ovale-wallikeri as well as the monkey parasites P. inui and P. hylobati.
Pan sp.: Pan sp. designs all species belonging to Pan genus (the common name of member of this genus chimpanzees and bonobo).

RNA subunit (rRNA): ribosomal ribonucleic acid (rRNA) is the RNA component of the ribosome and is an essential element for protein synthesis in all living organisms.

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15


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