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Molecular interactions governing host-specificity of blood stage malaria parasites

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Non-human primates harbor diverse species of malaria parasites, including the progenitors of *Plasmodium falciparum* and *Plasmodium vivax*. Cross-species transmission of some malaria parasites — most notably the macaque parasite, *Plasmodium knowlesi* — continues to this day, compelling the scientific community to ask whether these zoonoses could impede malaria control efforts by acting as a source of recurrent human infection. Host-restriction varies considerably among parasite species and is governed by both ecological and molecular variables. In particular, the efficiency of red blood cell invasion constitutes a prominent barrier to zoonotic emergence. Although proteins expressed upon the erythrocyte surface exhibit considerable diversity both within and among hosts, malaria parasites have adapted to this heterogeneity via the expansion of protein families associated with invasion, offering redundant mechanisms of host cell entry. This molecular toolkit may enable some parasites to circumvent host barriers, potentially yielding host shifts upon subsequent adaptation. Recent studies have begun to elucidate the molecular determinants of host-specificity, as well as the mechanisms that malaria parasites use to overcome these restrictions. We review recent studies concerning host tropism in the context of erythrocyte invasion by focusing on three malaria parasites that span the zoonotic spectrum: *P. falciparum*, *P. knowlesi*, and *P. vivax*.

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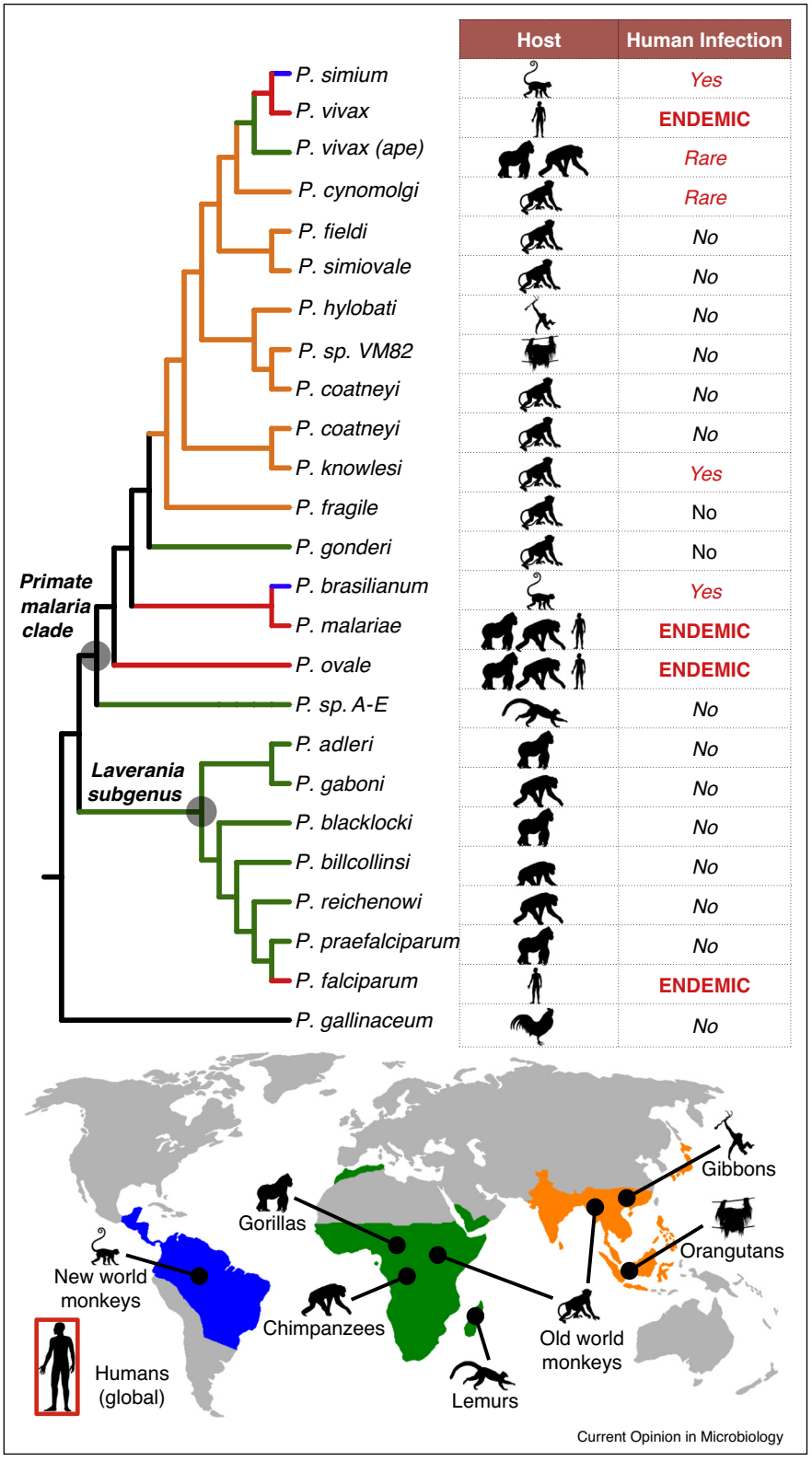
Introduction

Malaria is an infectious disease caused by a diverse clade of vector-borne Apicomplexan parasites that replicate asexually in the red blood cells of vertebrate hosts. Although over 500 malaria parasites have been isolated from avian, reptilian, and mammalian hosts [1], only five species — *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi* — commonly produce human infections (Figure 1) [2]. While cross-species transmission of most mammalian *Plasmodium* species is rarely observed in nature, the expansion of human populations into biodiversity hotspots has presented opportunities for exposure to novel zoonotic parasites. This paradigm is underscored by the growing health burden posed by *P. knowlesi*, a parasite of macaque monkeys, which now accounts for over 70% of human malaria infections in parts of Southeast Asia [3,4].

However, recent advances in molecular diagnostics and the expanded sampling of wild primates have revealed that *P. knowlesi* is not the only malaria parasite to transcend species boundaries. The precivilization origins of both *P. falciparum* [5,6] and *P. vivax* [7,8] — pandemic malaria parasites, which underlie the majority of human malaria infections globally [2,9] — have recently been traced to African great apes, and cross-species transmission of other malaria parasites continues to this day (Figure 1). Indeed, the observation that most, if not all, contemporary human malaria parasites originated in non-human primate hosts has compelled the scientific community to ask whether these zoonotic reservoirs could impede malaria control efforts by acting as a source of recurrent human infection [10–12].

While it is true that the primate origins of the human malaria parasites suggest that we are predisposed to these host shifts on evolutionary timescales, the low frequency of contemporary cross-species transmission indicates that most malaria parasites must nevertheless overcome substantial ecological and molecular barriers to cross species boundaries (Box 1). Ecological factors may present barriers to cross-species transmission by influencing the probability of human exposure to the zoonotic parasite. For example, the incidence of infection in the primate reservoir, the host biting preferences of the mosquito vector, and the degree of spatial overlap between human and reservoir hosts are all ecological factors that mediate cross-species transmission potential. Given a sufficient magnitude of exposure, molecular factors may present additional barriers to emergence by influencing the

Figure 1



Evolutionary relationships of primate malaria parasites. Neighbor-joining tree was derived from a 3486-bp gapped mtDNA alignment encompassing the cytochrome oxidase subunit 3, cytochrome oxidase subunit 1-like, and cytochrome b genes of 24 previously published non-human primate malaria parasite sequences and outgroup *P. gallinaceum* (GenBank accession numbers: AB354571-AB354575, AB434918,