Plasmodium

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Plasmodium is a genus of parasitic alveolates, many of which cause malaria in their hosts.[1] The parasite always has two hosts in its life cycle: a Dipteran insect host and a vertebrate host. Sexual reproduction always occurs in the insect, making it the definitive host.[2]

The life-cycles of Plasmodium species involve several different stages both in the insect and the vertebrate host. These stages include sporozoites, which are injected by the insect vector into the vertebrate host's blood. Sporozoites infect the host liver, giving rise to merozoites and (in some species) hypnozoites. These move into the blood where they infect red blood cells. In the red blood cells, the parasites can either form more merozoites to infect more red blood cells, or produce gametocytes which are taken up by insects which feed on the vertebrate host. In the insect host, gametocytes merge to sexually reproduce. After sexual reproduction, parasites grow into new sporozoites, which move to the insect's salivary glands, from which they can infect a vertebrate host bitten by the insect.[1]

The genus Plasmodium was first described in 1885. It now contains about 200 species, which are spread across the world where both the insect and vertebrate hosts are present. Five species regularly infect humans, while many others infect birds, reptiles, rodents, and various primates.

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History

Plasmodia were first identified when Charles Louis Alphonse Laveran described parasites in the blood of malaria patients in 1880.[3] He named the parasite Oscillaria malariae.[3] The fact that several species may be involved in causing different forms of malaria was first recognized by Camillo Golgi in 1886.[3] Soon thereafter, Giovanni Batista Grassi and Raimondo Filetti named the parasites causing two different types of human malaria Plasmodium vivax and Plasmodium malariae.[3] In 1897, William Welch identified and named Plasmodium falciparum. This was followed by the recognition of the other two species of Plasmodium which infect humans: Plasmodium ovale (1922) and Plasmodium knowlesi (identified in long-tailed macaques in 1931; in humans in 1965).[3] The contribution of insect hosts to the Plasmodium life cycle was described in 1897 by Ronald Ross and in 1899 by Giovanni Batista Grassi, Amico Bignami and Giuseppe Bastianelli.[3]

Life cycle

The life cycle of Plasmodium involves several distinct stages in the insect and vertebrate hosts. In infected mosquitoes, parasites in the salivary gland are called sporozoites. When the mosquito bites a vertebrate host, sporozoites are injected into the host with the saliva. From there, the sporozoites enter the bloodstream and are transported to the liver, where they invade and replicate within hepatocytes. At this point, some species of Plasmodium can form a long-lived dormant stage called a hypnozoite which can remain in the liver for many years.[2] The parasites that emerge from infected hepatocytes are called merozoites, and these return to the blood to infect red blood cells.

Within the red blood cells, the merozoites grow first to a ring-shaped form and then to a larger form called a trophozoite. Trophozoites then mature to schizonts which divide several times to produce new merozoites. The infected red blood cell eventually bursts, allowing the new merozoites to travel within the bloodstream to infect new red blood cells. Most merozoites continue this replicative cycle, however some merozoites differentiate into male or female sexual forms called gametocytes. These gametocytes circulate in the blood until they are taken up when a mosquito feeds on the infected vertebrate host, taking up blood which includes the gametocytes.[2]

In the mosquito, the gametocytes move along with the blood meal to the mosquito's midgut. Here the gametocytes develop into male and female gametes which fertilize each other, forming a zygote. Zygotes then develop into a motile form called an ookinete, which penetrates the wall of the midgut. Upon traversing the midgut wall, the ookinete embeds into the gut's exterior membrane and develops into an oocyst. Oocysts divide many times to produce large numbers of small elongated sporozoites. These sporozoites migrate to the salivary glands of the mosquito where they can be injected into the blood of the next host the mosquito bites, repeating the cycle.[2]
**Description**

*Plasmodium* species each have 14 chromosomes in the nucleus, as well as genetic material in the mitochondrion and in the apicoplast. The chromosomes vary from 500 kilobases to 3.5 megabases in length. The apicoplast is involved in isoprenoid metabolism, Fe-S cluster synthesis, fatty acid synthesis, and phospholipid biosynthesis.[4]

On a molecular level, the parasite damages red blood cells using plasmepsin enzymes — aspartic acid proteases which degrade hemoglobin.

**Taxonomy**

*Plasmodium* is a member of the family Plasmodiidae, order Haemosporidia and phylum Apicomplexa which, along with dinoflagellates and ciliates, make up the taxonomic group Alveolata.[5]

*Plasmodium* species were originally classified into subgenera based on their morphology, location, and host specificity. However, more recent studies of *Plasmodium* species using molecular methods have occasionally given results which conflict with the original taxonomic system.[6]

**Evolution**

Evolutionary relationships of species within the genus *Plasmodium* have been controversial.[6] *Plasmodium* species were originally divided by morphology, life-cycle characteristics, and host species. However, modern molecular approaches for determining evolutionary relationships have given results which conflict with older classification methods.[6] Many attempts to clarify *Plasmodium* taxonomy with molecular methods have also run into technical challenges. Ribosomal RNA sequencing, which is often used in other organisms to determine evolutionary relationships, is challenging to interpret from *Plasmodium* species as *Plasmodia* maintain several different copies of ribosomal RNA which are expressed at different stages of the life cycle and which may be able to recombine with one another.[6] Another commonly used marker for evolutionary studies has been the circumsporozoite protein (CSP) which is present in all *Plasmodium* species.[6] However, analyses of CSP sequences are complicated by the fact that the sequence of CSP, which is present on the surface of the parasite during infection, is under heavy selective pressure from the host immune system.[6] This could potentially obscure relevant changes.[6]

Environmental factors play a considerable role in the evolution of *Plasmodium* and the transmission of malaria.
The genetic information of *Plasmodium falciparum* has signaled a recent expansion that coincides with the agricultural revolution. It is likely that the development of extensive agriculture increased mosquito population densities by giving rise to more breeding sites, which may have triggered the evolution and expansion of *Plasmodium falciparum*.\[7\]

There are over one hundred species of mosquito-transmitted *Plasmodium*. The phylogeny of these malarial parasites suggests that the *Plasmodium* of mammalian hosts forms a well-defined clade strongly associated with the specialization to the *Anopheles* mosquito vector. This was a major evolutionary transition that allowed Plasmodium to exploit humans and other mammals.\[8\][9]

*P. falciparum*, the most lethal malaria parasite of humans, evolved from a "nearly identical" parasite of western gorillas.\[10\]

The high mortality and morbidity caused by malaria—especially that caused by *P. falciparum*—has placed the greatest selective pressure on the human genome in recent history. Several genetic factors provide some resistance to *Plasmodium* infection, including sickle cell trait, thalassaemia traits, glucose-6-phosphate dehydrogenase deficiency, and the absence of Duffy antigens on red blood cells.\[11\] [12]

Although there are therapeutic medications to treat malaria, *Plasmodium* has accumulated increasing drug resistance over time. A recent examination has shown that even artemisinin, one of the most powerful anti-malarial drugs, has been experiencing decreased efficacy due to the development of resistance.\[13\]

**Subgenera**

*Plasmodium* species have been subdivided into subgenera, which group species of similar morphology and with similar hosts.

- Subgenus *Asiamoeba* (lizards)
- Subgenus *Bennettinia* (birds)
- Subgenus *Carinamoeba* (reptiles)
- Subgenus *Giovannolaia* (birds)
- Subgenus *Haemamoeba* (birds)
- Subgenus *Huffia* (birds)
- Subgenus *Lacertamoeba* (reptiles)
- Subgenus *Laverania* (higher primates)
- Subgenus *Novyella* (birds)
- Subgenus *Paraplasmodium* (lizards)
- Subgenus *Plasmodium* (monkeys, higher primates)
- Subgenus *Sauramoeba* (reptiles)
- Subgenus *Vinckeia* (non-primate mammals)

Species infecting monkeys and apes (the higher primates) with the exceptions of *P. falciparum* and *P. reichenowi* (which together make up the subgenus *Laverania*) are classified in the subgenus *Plasmodium*. Parasites infecting other mammals including lower primates (lemurs and others) are classified in the subgenus *Vinckeia*. The distinction between *P. falciparum* and *P. reichenowi* and the other species infecting higher primates was based on morphological findings but have since been confirmed by DNA analysis.

The four subgenera *Giovannolaia*, *Haemamoeba*, *Huffia* and *Novyella* were created by Corradetti et al.\[14\] for the known avian malarial species. A fifth — *Bennettinia* — was created in 1997 by Valkiunas.\[15\] The
relationships between the subgenera are a matter of current investigation.[16]

*P. juxtanucleare* is the only member of the subgenus *Bennettinia*.

Unlike the mammalian and bird malarias those affecting reptiles have been more difficult to classify. In 1966 Garnham classified those with large schizonts as *Sauramoeba*, those with small schizonts as *Carinamoeba* and the single then-known species infecting snakes (*Plasmodium wenyoni*) as *Ophidiella*. In 1988, Telford used this scheme as the basis for the current system.[18]

### Hosts

All *Plasmodia* are parasitic and require both a vertebrate host and an insect host to reproduce. Known vertebrate hosts include various primates (including humans), birds, rodents, bats, porcupines and squirrels. Mosquitoes of the genera *Culex*, *Anopheles*, *Culiseta*, *Mansonía* and *Aedes* often serve as insect hosts for various *Plasmodium* species.

### Humans

The species of *Plasmodium* that infect humans include:

- *Plasmodium falciparum* (the cause of malignant tertian malaria)
- *Plasmodium vivax* (the most frequent cause of benign tertian malaria)
- *Plasmodium ovale* (the other, less frequent, cause of benign tertian malaria)
- *Plasmodium malariae* (the cause of benign quartan malaria)
- *Plasmodium knowlesi* (the cause of severe quotidian malaria in South East Asia since 1965)

*C. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* together account for nearly all human infections with *Plasmodium* species, with *P. falciparum* accounting for the overwhelming majority of malaria deaths. An increasing number of cases of severe malaria in Southeast Asia have been attributed to *P. knowlesi*.

With the use of the polymerase chain reaction additional species have been identified in humans, although whether these species can regularly infect humans is not known. An experimental infection of a human volunteer with *Plasmodium eylesi* and *Plasmodium cynomolgi* has been reported, although the infection was not able to be transferred to another susceptible host, suggesting the parasites may not be able to productively infect humans.[19] A possible infection with *Plasmodium tenue* has also been reported, however doubts have been raised as to the validity of this diagnosis.[20] Other species which have been reportedly isolated from humans include *Plasmodium brasilianum*, *Plasmodium inui*, *Plasmodium rhodiani*, *Plasmodium schweizti*, *Plasmodium semiouve*, and *Plasmodium simium*.

In addition to humans, *P. vivax* can infect chimpanzees and orangutans. In these hosts, infection tends to not cause severe disease, but may persist for some time.[21]
Species of Plasmodium infect many primates across the world, such as the brown lemur, *Eulemur fulvus*, of Madagascar. Many non-primate mammals, such as mouse-deer (*Tragulus kanchil*) can carry malaria parasites.

Non-human primates

The species that infect primates other than humans include: *P. bouillize*, *P. brasilianum*, *P. bucki*, *P. cercopithecus*, *P. coatneyi*, *P. coulangesi*, *P. cynomolgi*, *P. eylesi*, *P. fieldi*, *P. foleyi*, *P. fragile*, *P. girardi*, *P. georgesi*, *P. gonderi*, *P. hylobati*, *P. inui*, *P. jefferyi*, *P. joyeuxi*, *P. knowlesi*, *P. lemuris*, *P. percygarnhami*, *P. petersi*, *P. reichenowii*, *P. rodhaini*, *P. sandoshami*, *P. semnopithecus*, *P. silvaticum*, *P. simiovale*, *P. simium*, *P. uilenbergi*, *P. vivax* and *P. youngei*.

Many *Plasmodium* species infect more than one primate host species. Primates which have been found to be infected with *Plasmodium* include species of the genera *Alouatta* (also known as howler monkeys), *Ateles* (spider monkeys), *Brachyteles* (muriqui or wooly spider monkeys), *Callicebus* (titi monkeys), *Chiropotes* (bearded sakis), *Lagothrix* (woolly monkeys), *Lemur* (lemurs), *Macaca* (macaques), *Pan* (chimpanzees), *Pongo* (orangutans), and *Saimiri* (squirrel monkeys).[22][23]

The insect hosts of the *Plasmodium* species which infect primates are various species of *Anopheles* mosquitoes. Different species of *Plasmmodium* generally infect different species of mosquito, although some mosquito species can carry several *Plasmodium* species.

Non-primate mammals

The subgenus *Vinckeia* was created by Cyril Garnham to accommodate the mammalian parasites other than those infecting primates. Species infecting lemurs have also been included in this subgenus. *Plasmodium* species can infect a wide variety of mammals including rodents, ungulates, and bats. Several of the species which infect rodents have been shown to also infect the mosquito *Anopheles stephensi*.

*P. aegyptensis*, *P. bergei*, *P. chabaudi*, *P. inopinatum*, *P. yoelli* and *P. vinckei* infect rodents. *P. bergei*, *P. chabaudi*, *P. yoelli* and *P. vinckei* have been used to study malarial infections in the laboratory. Other members of this subgenus infect other mammalian hosts.

Birds

Species in five *Plasmodium* subgenera infect birds — *Bennettinia*, *Giovannolaia*, *Haemamoeba*, *Huffia* and *Novyella*. *Giovannolaia* appears to be a polyphyletic group and may be subdivided in the future.[16] Species that infect birds include *P. accipiteris*, *P. allopontatum*, *P. ansam*, *P. ashfordi*, *P. bambusicolai*, *P. bigueti*, *P. biziurae*, *P. buteonis*, *P. cathemerium*, *P. circumflexum*, *P. coggshalli*, *P. corradetti*, *P. coturnix*, *P. dissanaikai*, *P. durae*, *P. elongatum*, *P. fallax*, *P. forresteri*, *P. gallinacium*, *P. garnhami*, *P. giovannolai*, *P. griffithsi*, *P. guindersi*, *P. guangdong*, *P. hegneri*, *P. hermani*, *P. hexamerium*, *P. huffi*, *P. jiangi*, *P. juxtanucleare*, *P. kempi*, *P. lophurae*, *P. lutzi*, *P. matutinum*, *P.

These infect a variety of bird species. In general each species of *Plasmodium* infects one to a few species of birds. Each species is also generally transmitted by a single insect species. Insect hosts include *Aedes aegypti*, *Mansonia crassipes*, and various *Culex* species.

**Reptiles**

Species in the subgenera *Asiamoeba*, *Carinamoeba*, *Lacertaemoba*, *Paraplasmodium* and *Sauramoeba* infect reptiles.[26] These species of *Plasmodium* include: *P. achiotense*, *P. aeuminatum*, *P. agamae*, *P. arachniformis*, *P. attenuatum*, *P. aurulentum*, *P. australis*, *P. azurophilum*, *P. balli*, *P. basilisci*, *P. beebei*, *P. beltrani*, *P. brumpti*, *P. brygooi*, *P. chiricahuae*, *P. circularis*, *P. cnemaspi*, *P. cnemidophori*, *P. colombiense*, *P. cordyli*, *P. diminutivum*, *P. diploglossi*, *P. egerniae*, *P. fairchilid*, *P. floridense*, *P. gabaldoni*, *P. giganteum*, *P. gologoense*, *P. gracilis*, *P. guyannense*, *P. heischi*, *P. holaspi*, *P. icipeensis*, *P. iguanae*, *P. josephiniae*, *P. kentropyxi*, *P. lacertiliae*, *P. lainsoni*, *P. lepidoptiformis*, *P. lionatum*, *P. loveridgei*, *P. lgmosomae*, *P. mabuiae*, *P. mackerrasae*, *P. maculilabre*, *P. marginatum*, *P. mexicanum*, *P. michikoa*, *P. minasense*, *P. pelaizi*, *P. pessoai*, *P. pijanoi*, *P. pitmani*, *P. rhoadinum*, *P. sasai*, *P. saurocaudatum*, *P. scorzai*, *P. siamense*, *P. robinsoni*, *P. sasai*, *P. scorzai*, *P. tanzaniae*, *P. tomodoni*, *P. torrealbai*, *P. tribolonoti*, *P. tropiduri*, *P. uluguruense*, *P. uzungwiense*, *P. vacuolatum*, *P. vastator*, *P. volans*, *P. wenyoni* and *P. zonuriae*.

*Plasmodium* species have been reported from over 3200 species of lizard and 29 species of snake. Only three species — *P. pessoai*, *P. tomodoni* and *P. wenyoni* — infect snakes. Species infecting lizards have been reported in relatively few insect hosts, including *Lutzomyia* and *Culicoides* species, *Culex fatigans* and *Aedes aegypti*.

**Insects**

Mosquitoes of the genera *Culex*, *Anopheles*, *Culiseta*, *Mansonia* and *Aedes* may act as insect hosts for various *Plasmodia* species. The best studies of these have been the *Anopheles* mosquitoes which host *Plasmodia* which cause human malaria, as well as *Culex* mosquitoes which host the *Plasmodia* that cause malaria in birds. In all cases, only female mosquitoes can be infected with *Plasmodia* species, since only the females feed on the blood of vertebrate hosts.

The survivorship and relative fitness of mosquitoes are not adversely affected by *Plasmodium* infection, which indicates the importance of vector fitness in shaping the evolution of *Plasmodium*. [27] *Plasmodium* has evolved the capability to manipulate mosquito feeding behavior. Mosquitoes harboring *Plasmodium* have a higher propensity to bite than uninfected mosquitoes. This tendency has facilitated the spread of *Plasmodium* to the various hosts.[28]
Species reclassified into other genera

Several species of *Plasmodium* have been reclassified, mostly to *Hepatocystis*. These include:

- *Plasmodium epomophori* to *Hepatocystis epomophori*
- *Plasmodium kochi* to *Hepatocystis kochi*
- *Plasmodium limnotragi* to *Hepatocystis limnotragi* (Van Denberghe 1937)
- *Plasmodium pteropi* to *Hepatocystis pteropi* (Breinl 1911)
- *Plasmodium ratufae* to *Hepatocystis ratufae* (Donavan 1920)
- *Plasmodium vassali* to *Hepatocystis vassali* (Laveran 1905)
- *Plasmodium gonatodi* to *Garnia gonatodi*

Link to Ebola virus

In August 2016, the National Institute Of Allergy and Infectious Diseases (NIAID) came out with a study that showed that people with the Ebola virus were 20 percent more likely to survive it if they were infected with the *Plasmodium* parasite. The study was published in *Clinical Infectious Diseases*. Researchers did their work at an ebola treatment unit in Monrovia, Liberia.[29] Researchers also found that the greater the number of *Plasmodium* parasites in the body, the greater the rate of Ebola survival. NIAID is part of the National Institutes of Health.[30]

Nomenclature

As with many other genera, the genus name also yields a common noun; thus species of the genus are known as *plasmodia*.

See also

- *Plasmodium* molecular tools

References


17. Garnham 1966


Further reading

Identification


Biology


History


External links

- Malaria Atlas Project (http://www.map.ox.ac.uk/)
- "Plasmodium". *NCBI Taxonomy Browser*. 5820.


Categories: Apicomplexa genera | Malaria | Plasmodium

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