Parasitic Infections in Humans and Animals

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Abstract

Parasites are organisms that depend on a host for feeding and reproduction and belong to various unrelated taxa, primarily protozoa, helminths and arthropods. Complex life cycles have often lead to extreme adaptations; nevertheless parasites may harm their hosts and even cause serious disease and death. Transmission of parasite stages can be environmental, nutritional or vector-borne. Among the most important human protozoan parasites in a global context are *Leishmania*, *Plasmodium* (both transmitted by bloodsucking arthropods) and *Toxoplasma* which is soil- or food-borne. Parasitic worms (helminths) relevant for human health include *Echinococcus*, *Toxocara*, hookworms (all soil-borne) and *Dirofilaria* (transmitted by mosquitoes). Various arthropods (ticks, insects) are involved in the transmission of pathogens due to their blood-feeding behaviour. They are especially involved in transmission cycles between animals and humans (zoonotic infections). Research on parasites and their interactions with the host requires suitable animal models. For parasites with a wide host range or those naturally infecting rodent species available as laboratory animals, established models are available. Others, like the human malaria parasites, require sophisticated and often costly genetic manipulation to allow for infection in non-natural rodent hosts. Alternatively, surrogate models of closely related helminth species in rodent models are used to study human parasites.

12.1 Introduction

Parasitism is a lifestyle characterised by the dependency of the parasite on a host organism which has no benefit from its parasite. The most important groups are protozoa (i.e. unicellular eukaryotes from different taxa), helminths (i.e. parasitic worms from different taxa) and arthropods. Every organism may host several parasite species. Of all animals, humans have the greatest parasite diversity. While coevolution of the parasite with its host leads to adaptation limiting the damage to the host at the cost of parasite control, in a medical and veterinary context many parasites still cause considerable harm and, due to their infectious nature, can threaten human and animal health. Parasites often have complex life cycles which may involve stage conversion, metabolic and morphological changes during development and a switch from one host to another (heteroxenous development). Parasites frequently produce long-living stages that can persist in the environment for months and even years. While certain parasites are specialised on a single host species (stenoxeny), others are generalists (euryxeny) and can infect unrelated host species. Zoonotic infections are characterised by parasite transmission between humans and non-human vertebrates. In the following chapters, some examples of important parasitic infections are described with a focus on their relevance for human health, possible zoonotic transmission and animal models to study important human parasitic diseases.

12.2 Diseases Caused by Protozoa

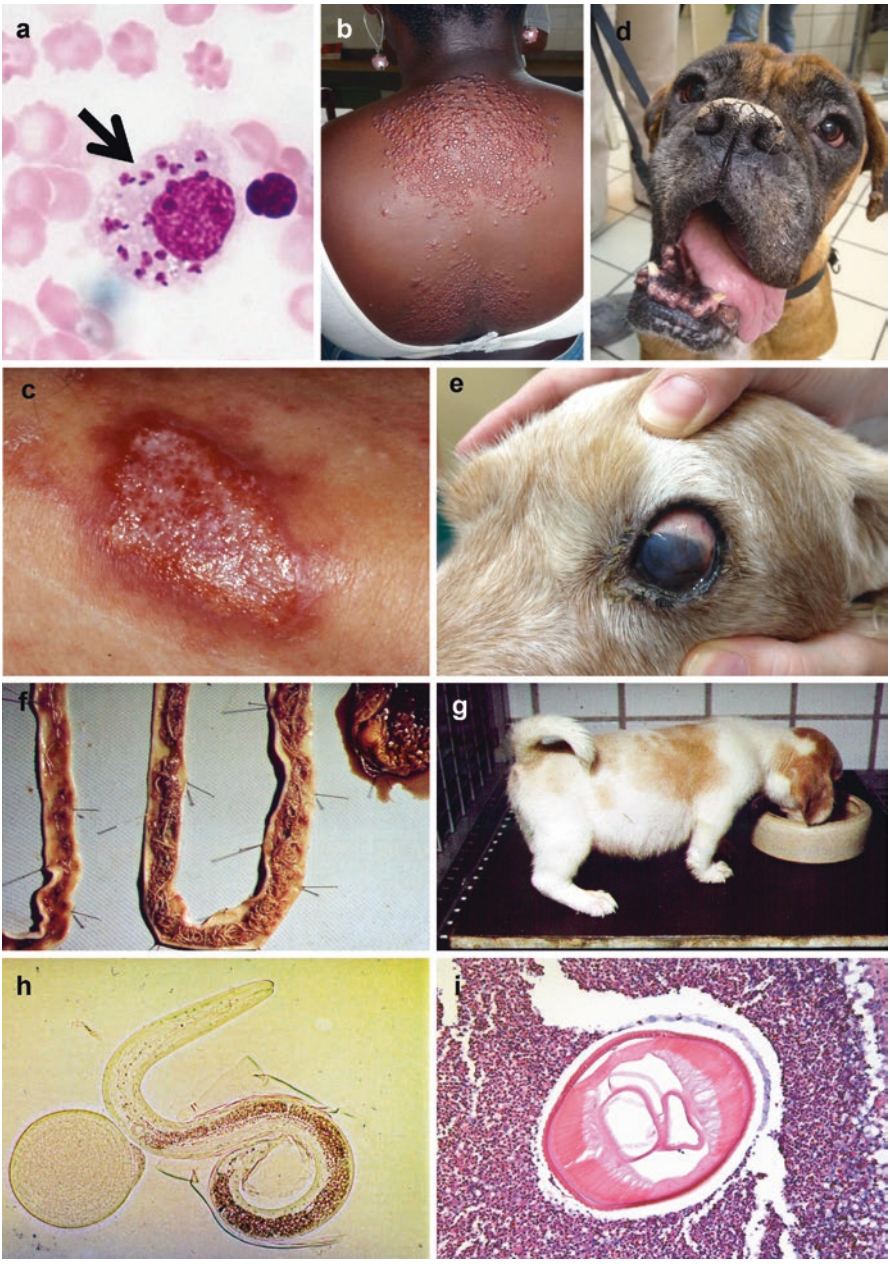
12.2.1 Leishmanioses

More than 30 *Leishmania* species are currently described, all exhibiting two different life cycle stages, one flagellated promastigote stage living extracellularly in the gut of the sandfly vector and one amastigote stage living intracellularly within macrophages and other cells of the reticuloendothelial system of the vertebrate host. Particularly dogs but also rodents play a significant role as reservoir hosts (Fig. 12.1a–e). Leishmaniae are transmitted by sandflies, *Phlebotomus* spp. in the Old World and *Lutzomyia* spp. in the New World.

Two different disease entities are caused by various *Leishmania* spp., the visceral leishmaniosis (VL) caused by representatives of the *L. donovani/L. infantum* complex and various forms of cutaneous leishmaniosis (CL) mainly caused by *L. tropica* and *L. major* in the Old World and representatives of the *L. mexicana* and *L. braziliensis* complexes in the New World. Worldwide around 12 million people are infected, and 350 million are assumed to be at risk of an infection. Approximately, 1.5 million new cases of CL and 500,000 new cases of VL occur every year, with 60,000 deaths annually. *Leishmania* infections are described from >90 countries, and the most affected are India, Nepal, Bangladesh, Sudan and Brazil for VL and Afghanistan, Iran, Saudi Arabia, Syria, Brazil and Peru for CL. The incubation period is highly variable, and infections may also remain without any symptoms. VL is characterised by diarrhoea, weight loss and high fever, children and immunocompromised individuals being at particular risk. Without therapy disease progression is usually fatal. CL can develop from a localised to a progredient form, depending on the parasite strain and the immune status of the patient. After an incubation period of several weeks or even months, a lesion around the site of infection is seen. While the localised form is usually self-limiting within less than one year, the disseminating mucocutaneous form, mainly caused by representatives of the *L. braziliensis* complex, leads to a gradual destruction of the skin, cartilage and even bone if left untreated.

Diagnosis relies on the examination of stained smears and tissue sections, respectively. In the recent past, PCR-based techniques have gained increasing importance for routine diagnostics. Alternatively, leishmanial antigens can be detected in clinical specimens, and a test for the detection of *Leishmania* antigens in urine is also commercially available. Serological tests are highly sensitive only for VL; a fast and easy strip test is available.

The most commonly used drugs are the pentavalent antimony compounds, but they can have severe side effects. Alternative drugs are amphotericin B, itraconazole and allopurinol for systemic and paromomycin for topical application. Miltefosine can be applied as an oral as well as a topical formulation. Generally it is assumed that even after successful therapy some leishmaniae may survive and persist within the host. Repellents and impregnated small-meshed mosquito nets help to avoid sandfly bites.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12.2.2 Malaria

Traditionally four *Plasmodium* spp. are recognised as human pathogens, namely, *Plasmodium falciparum, P. malariae*, *P. vivax* and *P. ovale*. However, in the recent past, an increasing number of human infections with the simian malaria parasite *P. knowlesi* have been reported. More than three billion people live in >100 countries with endemic malaria and are seasonally at risk of infection. Malaria is still one of the most important infectious diseases and the most important parasitic disease worldwide. An estimated 200 million cases of malaria occur every year, including at least 650,000 lethal cases. The vast majority of cases occur in Africa, and almost all fatal cases are caused by *P. falciparum*, the causative agent of malaria tropica. The population group at highest risk are children in sub-Saharan Africa under the age of 5 years. Historically, Europe was also endemic for malaria, mainly caused by *P. vivax*.

Malaria is transmitted by mosquitoes of the genus *Anopheles*. During the blood meal of the female mosquito, the so-called sporozoites are injected into the skin with the saliva. The parasites reach the bloodstream and undergo a first multiplication cycle in the liver. After approximately 1 week, they are released into the bloodstream where they infect the red blood cells and undergo successive cycles of multiplication. In infections with *P. vivax*, *P. ovale* and *P. malariae*, these cycles are synchronised, and every burst of red blood cells is accompanied by high fever (every 48 h in *P. vivax* and *P. ovale* and every 72 h in *P. malariae*). In *P. falciparum* malaria, the release of the parasites from the erythrocytes is not synchronised, more or less continuous or remittent fever occurs, which may be absent at the beginning of the infection.

Diagnosis still mainly relies on microscopic analysis of Giemsa-stained thick and thin smears of fresh finger-prick blood. In recent years, also rapid and simple dipstick tests have been developed. Due to the short incubation time, serodiagnosis only plays a role in advanced infections or in epidemiological studies, but not in the diagnosis of an acute malaria tropica.

Fig. 12.1 Zoonotic parasites can affect humans and animals in different ways. The protozoan *Leishmania* infects the macrophages: (**a**) microscopic view of an infected macrophage, arrow; it induces a variety of lesions; the location depends on the parasite and host species and the individual disposition. In humans it can cause cutaneous lesions, (**b**, **c**), whereas in dogs hyperkeratosis (**d**) and keratitis (**e**) are common. (**f**) The nematode *Toxocara* inhabits the small intestine of dogs; (**g**) in large numbers it impairs growth and leads to generally poor health of mostly puppies; (**h**) infection in humans takes place via ingestion of embryonated eggs from which a larva emerges and migrates through internal organs of the aberrant human host. In the case of the nematode *Dirofilaria repens* which is transmitted by mosquitoes, the larvae migrate into the tissue and are frequently enclosed in skin nodules in both the canine and the human host; (**i**) microscopic view of a nematode is enclosed in a skin nodule (Sources: **a**, **h**, **i**: Institute of Specific Prophylaxis and Tropical Medicine Medical University Vienna; b: by courtesy of Dr. R Moser, Eisenstadt, Austria; c: by courtesy of Prof W Bommer, Göttingen, Germany;**d**, **e**: by courtesy of Prof G Miró, Facultad de Veterinaria, Departamento de Sanidad Animal, UCM, Madrid, Spain; **f**, **g**: Institute for Parasitology, University of Veterinary Medicine Hannover, Hannover, Germany)

The most important drugs for the treatment of malaria are quinine, mefloquine, chloroquine, atovaquone/proguanil and artemether/lumefantrine, depending on the parasite species, the severity of the disease and the geographic region. In some African and Southeast Asian regions, resistance against several drugs is observed. An uncomplicated malaria which is promptly and appropriately treated has a very low mortality, but untreated severe malaria, particularly the cerebral form, is almost always fatal. Malaria is a preventable disease; mosquito nets and repellents can significantly reduce the risk of infection, and chemoprophylaxis with mefloquine and atoquavone/proguanil can prevent disease. Attempts to control and eradicate malaria include vector control, chemotherapy and the development of vaccines.

12.2.3 Toxoplasmosis

Toxoplasma gondii is one of the most prevalent human parasites worldwide; depending on the geographic region and age, up to 80 % of the population is infected. In Austria, infection rates are around 35 %. The only final hosts are cats and other felids which shed environmentally resistant oocysts with their faeces. Oocysts become infectious within a few days and can remain so for up to 1 year. Upon ingestion of these stages, sporozoites are released in the intestines and are spread in monocytes in the blood. After a phase of muliplication in various tissues and organs, the parasites form tissue cysts which can persist for years (probably for lifetime) and are infectious for other hosts after oral uptake.

Humans, other mammals or birds can become infected either by oral uptake of the oocysts or when ingesting undercooked meat from infected hosts. Transplacental transmission of circulating blood stages during gestation and infection of the foetus is possible and can lead to congenital toxoplasmosis with stillbirth, cerebral or ocular disease.

In the immunocompetent host, the infection usually remains without symptoms; however, the parasite survives within cysts in various organs, particularly in the brain, and remains viable throughout the host's entire life. In the immunocompromised patient, *T. gondii* can cause serious and also lethal diseases, mainly of the central nervous system and of the eye.

Diagnosis relies on serological tests detecting specific antibodies against *T. gondii* and PCR for direct detection of the parasite. A combination of serological tests is usually applied in order clarify the time point of infection. In immunocompromised individuals, diagnosis is achieved by PCR, and this technique can also be applied to umbilical cord blood to clarify the infection status of the foetus. Due to surveillance programs and adequate chemotherapy of infections during pregnancy, cases of congenital toxoplasmosis have been significantly reduced in most European countries.

Toxoplasmosis is usually treated with a combination of pyrimethamine and sulfadiazine plus folic acid. If a primary infection is diagnosed during pregnancy, the mother is treated in intervals until delivery. In the first trimenon, spiramycin is given as an alternative to the combination therapy. In AIDS patients, long-term treatment

may be necessary, at least during the phase of immunosuppression. Immunocompetent, nonpregnant patients do usually not require treatment. Complete prevention of infection is not possible, but pregnant women should avoid eating undercooked meat and raw vegetables possibly contaminated with oocysts, apply good hygiene when handling soil (during gardening) or raw meat and avoid contact with cat faeces.

12.3 Diseases Caused by Helminths

12.3.1 Alveolar Echinococcosis (AE)

AE is one of the most serious helminthic diseases of humans; it is caused by larval stages of *Echinococcus multilocularis*, the fox tapeworm.

The infection is acquired by oral ingestion of *Echinococcus* eggs excreted by foxes, dogs or (rarely) cats via contaminated vegetables, water, or the faecal-oral route upon direct contact with animal faeces. First larvae (oncospheres) hatch from the eggs in the small intestine of the intermediate host (humans and other mammals) and are transported with the blood stream to the liver where they develop to the metacestode stage infiltrating the liver parenchyma.

The incubation period varies from 5 to 25 years. Abdominal pain, hepatomegaly, malaise, icterus and fever are the most prominent clinical signs. AE is a chronic hepatic disease resembling hypertrophic liver cirrhosis or carcinomas of the liver or of the biliary system.

Diagnostic procedures consist of clinical and geographical anamnesis, imaging (e.g. ultrasound, CT or MRT scans) and – especially – of serological detection of specific antibodies. The stage of the disease (localisation and dimension of the parasitic lesions) can be categorised with the PMN system according to the WHO guidelines.

Treatment of choice is the surgical removal of the infiltrated liver parenchyma under pre- and postoperative anthelmintic therapy. In cases of inoperability, prolonged albendazole treatment for months, years or even lifelong are the alternatives, if albendazole is tolerated well.

AE has been known in Central Europe since the second half of the nineteenth century. In total 220 human AE cases have been diagnosed in Austria since 1897. The incidence of AE has increased significantly in recent years and now comprises about ten cases per year. The most affected provinces are Tyrol and Vorarlberg, but human infections could also be detected sporadically in all other provinces.

12.3.2 Toxocarosis (TC)

TC is a general term for different clinical manifestations caused by the nematode worms *Toxocara canis* and *T. cati* (large round worms of dogs and cats). *Toxocara* occurs worldwide in canids and felids.

Humans acquire the infection either by oral ingestion of infectious eggs via soil or hands, water or vegetables or by consumption of raw or undercooked meat from paratenic hosts (pig, poultry, rabbits, etc.) containing infectious larvae. After ingestion and passage of the portal venous system, larvae are distributed to nearly all organs via the blood stream. *Toxocara* larvae never become adult in humans but may have a life span of several years.

Most human infections may be clinically inapparent; however, severe clinical courses may occur (Fig. 12.1f–i). The most common forms are the visceral and ocular larva migrans (VLM, OLM) syndrome, covert (CT), general (GT), cerebral (NT) or cardiac toxocarosis (CT).

When clinical symptoms appear, diagnostic procedures consist of geographic and behavioural anamnesis, haematology (typical signs include eosinophilia, elevated IgE) and detection of antibodies by serological examination which has a high degree of sensitivity and also specificity. However, ocular or cerebral *Toxocara* infections are very often accompanied by low antibody levels. In general, asymptomatic infections require no treatment with anthelmintics. Patients suffering from VLM, CT and GT may receive albendazole, at least when eosinophilia is present or IgE is significantly elevated. OLM and NT have to be treated primarily with corticosteroids and afterwards or simultaneously with albendazole for 2–3 weeks.

Due to the fact that the knowledge about the epidemiology and nosology of human toxocarosis is rather limited in medical staff in Austria and other Central European countries, only very limited data are available on the prevalence and incidence of *Toxocara* infections and of human toxocarosis. However, several epidemiological studies in the past two decades revealed seroprevalences between 4 (average population) to 40 % (farmers). The incidence of toxocarosis comprises several hundred cases per year.

12.3.3 Subcutaneous Dirofilariosis (SD)

Dirofilaria repens is a filarial nematode of carnivores, particularly of dogs and cats, and is widely distributed in Southern and Eastern Europe and in Asia.

Humans can be accidental hosts when bitten by infected mosquitoes. Most transmitted larvae die off shortly after inoculation, but some may survive as immature worms. Maturation to the adult stage with production of microfilariae is seen very rarely.

SD manifests in skin nodules or as a migrating lump mostly on the head (eyes, orbita) and the upper thorax, less commonly the male genitalia (testes, epididymis). Diagnosis is mainly based upon histological and/or molecular biological examination of surgically removed nodules; serological tests are available in specialised laboratories. Resection of skin nodules is the therapy of choice. There is no experience with anthelminthic treatment (albendazole) of subcutaneous dirofilariosis so far.

SD is rarely seen in Austria. The first human case was observed in 1978, and between 1978 and 2014, 30 cases were registered in Austria; 29 infections were

imported from abroad (mainly in the Mediterranean region); one case was acquired autochthonously. Based on the fact that the incidence and prevalence of *D. repens* infections in animals and humans have increased in Hungary in recent years, it is likely that the incidence of subcutaneous dirofilariosis in humans will increase also in Austria in the future.

12.3.4 Larva Migrans Cutanea Syndrome (LMC)

LMC is an acute skin disease and is caused by larval stages of the animal hookworms *Ancylostoma braziliense* and *A. caninum,* which occur only in the (sub-) tropical regions. Humans acquire the infection by active penetration of the larvae during skin contact with faeces of infected definitive hosts. Neither species can mature in the human body nor can the larvae migrate subcutaneously in the erroneous human host. The clinical presentation (serpiginous, inflamed traces on the skin accompanied by intense pruritus) is pathognomonic. The therapy comprises symptomatic (antihistaminic, anti-inflammatory and antipruritic medication) as well as anthelmintic treatment (albendazole, tiabendazole). The incidence of LMC cases in Austria is low with no more than a few dozen cases per year.

12.4 Vectors

Two large groups of arthropods can serve as vectors for pathogens, the acari (mites and ticks) and the insects (e.g. bugs, lice, fleas or bloodsucking dipterans). Around 40 species of ticks are known to occur in Austria, belonging to two different families, the Ixodidae and the Argasidae. The so-called castor bean tick, *Ixodes ricinus*, is the most prevalent tick species and the most important vector of pathogens in Central Europe. It can transmit around 15 different pathogens, including tick-borne encephalitis (TBE) virus, various species of *Borrelia*, *Anaplasma phagocytophilum* and other bacteria as well as species of the protozoan genus *Babesia*. While it is assumed that only 1/1,000 ticks carries the TBE virus, infection rates in ticks with bacteria are usually much higher.

More than 50 species of mosquitoes (Culicidae), including also several species of *Anopheles*, are known to occur in Central Europe, and many of them also feed on human blood. Besides malaria, mosquitoes are the vectors of several nematodes (e.g. *Dirofilaria* spp.; see Sect. 12.3.3.) and a long list of viruses.

Sandflies (Phlebotominae) are vectors of *Leishmania* species and Phleboviruses. More than 800 sandfly species have been described, of which at least 80 are known to be vectors of *Leishmania* spp. Sandflies are widely distributed in the warmer regions of the world, including the Mediterranean countries, but in the recent past, small populations of sandflies have also been found to occur in Central Europe, including Austria. These populations may increase with global warming, but the emergence of *Leishmania* infections in Central Europe is mainly a result of globalisation.

The zoonotic transmission of pathogens by arthropod vectors is considered an emerging health problem since many arthropods display a low host specificity and feed on birds, mammals and humans.

12.5 Animal Models for Human Parasitic Diseases

Euryxenic protozoa, e.g. *T. gondii* or *Leishmania*, have been studied in great detail since they are able to naturally infect both humans and animals (including rodents). However, for most parasites, differences in susceptibility as well as size of, e.g. murine, models in comparison to humans often allow only for a part of the life cycle to be completed in a nontarget species. Nonpermissive models which do not support the completion of the full life cycle are useful when studying parasitic infections with humans as accidental (nonpermissive) hosts, such as larva migrans disease. The development of all stages, especially the long-lived adult metazoa, is however necessary to fully apprehend the course of disease and the host response to infection. To overcome the problem of host specificity of the target parasite, different options are available. One is the genetic manipulation of the parasite which is often technically not feasible since entry and development of a parasite in the host usually constitute a complex series of biological events that cannot easily be manipulated or mimicked. In a similar manner, well-defined murine models can be "humanised" to serve as suitable models as have been shown for human malaria. A third option is the use of surrogate models, i.e. closely related parasites infecting suitable animal models as natural hosts. This is often used for studies of helminths.

12.5.1 Models for *Toxoplasma gondii* Infection

The heteroxenic (two-host) development of *T. gondii* includes a natural prey–predator cycle involving the cat and its favourite prey, the mouse (as well as the rat). Different strains of mice display different susceptibilities to the parasite and this can be used to study clinical outcomes of infection, so this model allows for pathogenetic, immunological as well as genetic studies. *T. gondii* can be characterised on the subspecies level by genotyping using several PCR-RFLP genetic markers; these types vary in their virulence, host range and geographical distribution, and virulence in mice is one of the classical phenotypic traits by which such strains are characterised, which are recently complemented by genetic approaches.

12.5.2 Models for *Leishmania* Infection

Leishmania infantum (syn. *L. chagasi*) has a canine host which is considered the most important mammalian reservoir for this parasite. This has several implications

for human–animal interactions; firstly, dogs represent the reservoir host for this parasite and must be included in control measures (and large stray dog populations in many countries defy such measures); secondly, dogs maintain a synanthropic cycle of parasite transmission due to their close relationship with humans; and thirdly, dogs are important hosts that themselves may suffer from the disease. While rodent models for *Leishmania* infections have been used for a long time, and even formed the basis for the research on the Th1-Th2 paradigm in immunology, research on dogs as natural hosts for *Leishmania* is mainly driven by the requirement to develop a transmission-blocking vaccine for this host, as this may reduce the percentage of dogs infected in an endemic area and thus reduce the infection risk for humans; however, most studies on the immune response in dogs to infection or vaccination are restricted to (non-protective) antibody determination. Canine leishmaniosis due to *L. infantum* resembles human leishmaniasis in the development of progressive disease (often without clinical signs for long time periods), but the clinical signs differ between species. Dogs do not develop distinct pattern of cutaneous or visceral leishmaniosis; still they could serve as a model for human diseases as dogs also mirror the diverse genetic variability in natural populations. Mice, hamsters and monkeys are also used as models to study leishmaniosis.

12.5.3 Humanised Murine Models to Study Malaria

Besides the development of new drugs research on malaria control has mainly focused on the development of vaccines. Targets in malaria can be divided into three groups: (i) pre-erythrocytic stages, i.e. sporozoites and liver stages; (ii) erythrocytic stages in the red blood cells (merozoites and gametocytes); and (iii) sexual stages and ookinetes in the gut of the mosquito vector. One of the major obstacles in studying malaria is the high host specificity of most *Plasmodium* species; human malaria parasites cannot be transmitted to rodents, hampering both basic research on immunity and host-parasite interactions and preclinical testing of drugs. Surrogate models, i.e. rodent-specific *Plasmodium* species, such as *P. chabaudi*, *P. berghei* or *P. yoelii*, are used to investigate some aspects of infection and disease, e.g. immune responses in transgenic *P. berghei* expressing human malaria antigens, but the genetic differences between species are major and may account for human disease-specific traits, e.g. the development of cerebral symptoms upon infection with *P. falciparum*. Thus it is preferable to use human malaria species, and in order to be able to infect rodents, humanised models must be developed. Such models have been developed by using genetically manipulated mice that allow for the engraftment of human cells and tissue, both immune cells and, lately, also liver cells and erythrocytes which provide a localised “human environment” to study the development and immune response against the liver stages of *Plasmodium*. Correct expression of MHC I and MHC II is crucial in this model, and the successive replacement of murine tissue by human grafts is a technical challenge that is yet to be fully overcome; however, this technology provides new methods of studying vaccine efficacy before clinical trials.

12.5.4 Surrogate Rodent Models for Nematode Infections

Unlike the rarer "generalists" among the nematodes (e.g. *Trichinella spiralis* which naturally infects a range of mammalian hosts including rats and humans), most species are rather host specific and do not readily cross the species barrier and have so far defied attempts of genetic manipulation to achieve transfer of human parasites to murine models. In some cases, humans are aberrant hosts to migrating larvae of animal nematodes, and this can be mimicked in rodent models to a certain extent; however, the most important life history phase of a parasitic nematode is the development of fertile adults that can reproduce, if possible, for months to years. To investigate this stage, frequently surrogate models are used. These constitute infections of rodents with nematodes closely related to the respective human parasite. Humans have two anthroponotic species of hookworms, *Necator americanus* and *Ancylostoma duodenale*, but can also serve as final and aberrant hosts, respectively, for zoonotic species, including *A. ceylanicum*, *A. caninum* and *A. braziliense*. Due to the pathogenicity of these blood-feeding intestinal parasites and their worldwide distribution, attempts have been made to find adequate animal models of infection to support research on their control. Hamsters can be infected with *N. americanus*, and also with *A. ceylanicum*, dogs can harbour adult *A. ceylanicum* and *A. caninum*, and mice are hosts to the murine *Nippostrongylus brasiliensis*, all of which have a similar life cycle; however, the typical clinical feature of iron deficiency anaemia in human hookworm infection is not mimicked, and animals have a high rate of self-cure not mounted by humans – so the search for improved animal models is still ongoing.

12.6 Synopsis

Parasitic infections with protozoa, helminths or arthropods represent a considerable disease burden for humans and animals worldwide. Transmission to humans may be environmental, nutritional or via animals (zoonotic). Blood-feeding arthropods can serve as vectors of various pathogens including a number of parasites. Diseases caused by parasites may be chronic and debilitating or even acutely life-threatening. Research on them has focused on the interaction between host and parasite to improve current control measures. This involved the use of animal models which are sometimes challenging to obtain due to the specific requirements of parasitic life cycles.

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