PROTOZOAN DISEASES

Protozoa is a unicellular, eukaryotic organism that may cause several serious diseases in humans such as malaria, sleeping sickness, leishmaniasis and ameobiasis. Protozoan infection stimulates both defence mechanisms—humoral as well as cell-mediated. Humoral responses are elicited when a protozoan parasite is outside the cell; while the same pathogen if it has an intracellular part of the life cycle will induce a cell-mediated immune response.

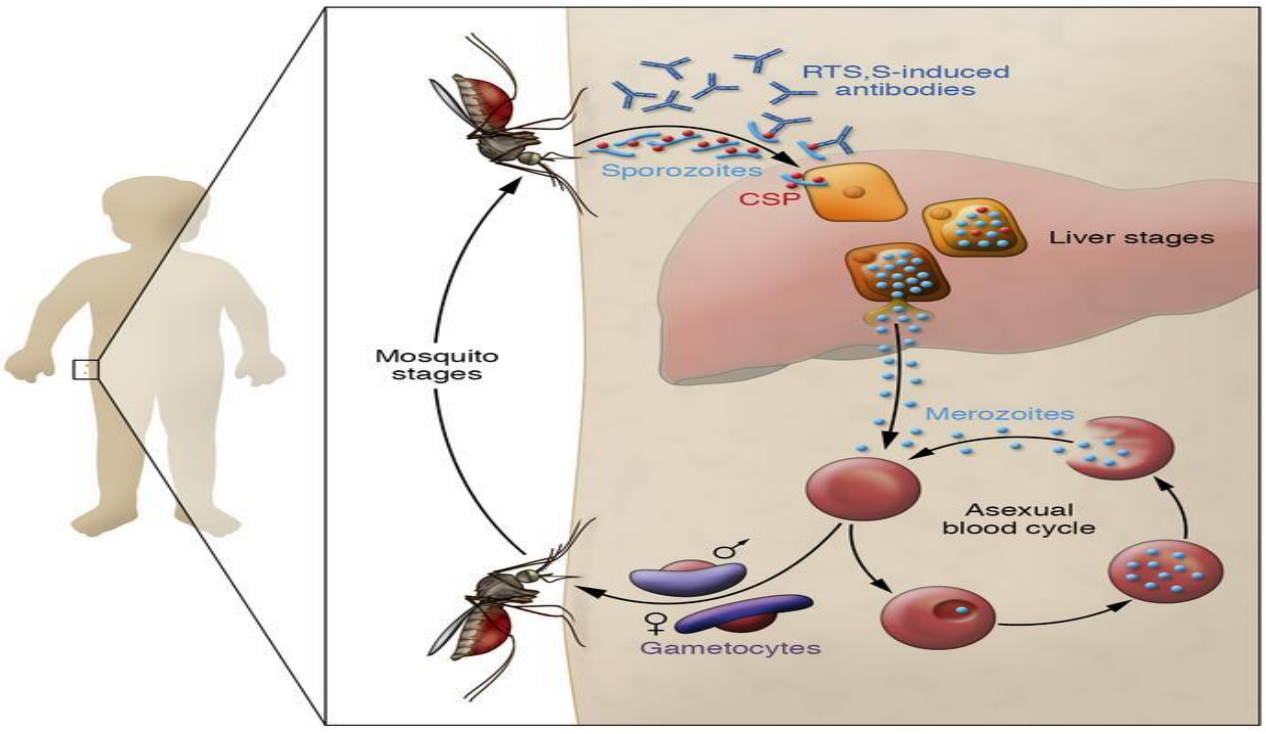
MALARIA

Malaria is a serious and sometimes fatal disease that affects about 500 million people worldwide; about 1 million die in Africa alone. About 1,000 cases of malaria are diagnosed in USA each year. Malaria is caused by four species of protozoa plasmodium—P. falciparum, P. vivax, P. ovale and P. malariae. P. falciparum is the most virulent and most prevalent of these protozoan species. Symptoms of malaria include shaking chills, fever, headache, muscle aches, tiredness and nausea. Vomiting and diarrhoea may also occur. Jaundice and anaemia can also occur because of loss of blood cells.

PATHOGENESIS OF MALARIA

Humans get malaria from the bite of the malaria-infested female anopheles mosquitoes which feed on human blood. The female anopheles mosquito serves as the biological vector for malaria and a part of the parasite's life cycle occurs in it. When plasmodium-infected mosquito bites a healthy human, sporozoites migrate from the mosquito's mouth into the subcutaneous tissue and from there into the blood. Once sporozoites leave the bloodstream, they enter the liver within half an hour. Sporozoites are a part of the plasmodium life cycle and are equipped with a specialized adhesion protein, circumsporozoite, that binds liver cells. Once inside

the liver cells, they multiply and result in the formation of the next stage in the life cycle, merozoites. During the time in which the parasite is in the liver, the infected person does not feel ill. The merozoites then leave the liver cells and enter into the red blood cells. Merozoites then transform to a large uninucleate, trophozoite. This trophozoite then divides asexually to produce a large number of merozoites again, causing red blood cells to burst. This frees the parasite to attack other red blood cells. Every 48 hours, merozoites, together with merozoite toxins (which are believed to be cytokines), are released. These merozoite toxins, erythrocyte debris released from lysed red blood cells, cause the characteristic recurrent chills, shivering, fever and sweating associated with malaria. Eventually some (asexual) merozoites differentiat into male and female gametocytes which are ingested by the female anopheles mosquito during the mosquito bite. Within the mosquito gut, male and female gametocytes form gametes which fuse to form a zygote. This differentiates into a sporozoite within the salivary gland. The infected female anopheles is ready for yet another round of infection. Malarial parasite is shown in Figure below.



HOST IMMUNE RESPONSE TO PLASMODIUM

Infants and children less than 14 years have poorly developed immune systems, consequently they are most likely to develop this disease. Unless malaria is properly treated with chemotherapy, mortality rate of children can reach up to 50 per cent. BothTH cells and Tcyt cells render some protection against different stages of plasmodium. Studies on mice have led us to believe that TH cells mediate immunity against malarial parasite when they are in the blood, while Tcyt cells inhibit multiplication of parasite in heptocytes. TH cells do not act on heptocytes as they do not express class II MHC molecules. The low host immune response to malarial parasite is due to several reasons:

• The humoral and cell-mediated immune responses to sporozoites does not occur because sporozoites remain for only about 30 minutes in blood. Such a short duration is ineff ective in inducing immune response.

• P. falciparum present in blood releases a soluble parasite antigen that binds to the antibody generated and hence protects the parasite from host antibodies. This process is called immune distraction, and involves the shedding of cell-surface antigen. Immune distraction is mediated by endogenous phospholipase(s). Table 15.3 provides some interesting insights into the mechanisms used by Plasmodium and other parasites in evading immune response.

• Macrophages in malaria endocytose hemozone—a breakdown product of malaria which makes them less responsive.

• The surface molecules of the parasite undergo several changes of life cycle within the host cell. The immune system cannot cope fully with this continuous changes of antigen.

• The parasite hides from the immune system by multiplying and living mostly inside the body cells.

LEISHMANIASIS

Leishmaniasis is a protozoan disease that is spread by the bite of infected sand flies (of genera Lutzomyia and Phlebotomus). There are two forms of this disease—cutaneous and visceral. The symptoms of the cutaneous form of the disease are sores on the skin which are usually covered by a scab. The visceral form of leishmaniasis is exhibited by enlarged liver and spleen (in some cases spleen becomes larger than the liver), low RBC and platelet count and continual fever.

There are about 1–2 million cases of the cutaneous form, while the visceral form of the disease affects 500,000 individuals per year. Cutaneous leishmaniasis is mainly caused by L. tropica, while the visceral disease is caused by L. donovani.

HOST RESPONSE TO LEISHMANIA SPP.

The resistance of individuals to leishmaniasis infection varies and may be controlled by number of factors. Once inside the blood stream, the leishmania parasite, which is a flagellated protozoa, enters the macrophage. Figure 15.16 shows a leishmania parasite getting endocytosed by a macrophage. Since it spends most of the time inside the macrophage, the main human defence mechanisms are generation of reactive oxygen species, reactive nitrogen species and lysosomal enzymes within the macrophages so that intracellular pathogens are killed. Studies in mice have shown that IFN-γ produced by activated TH- (TH1) cells activates macrophages to kill the protozoa (L. major) that live within them. IL-4, if produced by TH2 cells, inhibits the production of IFN-γ and makes mice more susceptible to leishmania parasite.Parasites can resist host defences in naïve individuals (individuals not immunized) in a number of ways, as follows:

• Certain species of leishmania parasite (for example, L. donovani) have a membrane that can resist complement-mediated cell lysis.

• Certain species can protect themselves from killer oxidative burst within the macrophage by synthesizing the enzyme superoxide dismutase that neutralizes injurious oxidative free radicals.

• Certain species have specialized lipophosphoglycan coat and glycoproteinins (eggp 63) that provide protection against lysosomal enzymes as well reactive oxygen species generated within the cell. They also downregulate class II MHC molecules making the cells immune to T-cell surveillance. These protozoan diseases clearly point to one thing. Prevention (through vaccine) is better than cure, as the pathogen, even though unicellular, has evolved complex defence mechanisms over the years. Chemotherapy is the last and perhaps the only alternative for the several of these diseases.

DISEASES CAUSED BY PARASITIC

WORMS

Parasitic worms are responsible for a wide variety of diseases in humans. Parasitic worms that infect humans include trematodes or flukes (Schistosoma) roundworm (Ascaris), filarial worms (Wuchereria spp.) and several other helminths that can enter the human body via food, such as tapeworm (Ancyclostoma spp.) round worm (Trichinella spiralis), and hookworm. Hookworms and schistoma larva enter via skin; tapeworm, pinworm and roundworm via contaminated food; and filarial worm through the bite of intermediate insect vector. These parasitic worms reside in the human body, outside the cell and usually do not multiply in the host.

HOST IMMUNE RESPONSE

Helminths, being extracellular parasites, are easily accessible to immune surveillance. However, since the number of parasitic worms that enter the human body is quite small, a low level of immune response to helminths occurs. These parasites are too large to be phagocytosed by neutrophils and macrophages which help clear extracellular pathogens. The major defence against worms are IgE and eosinophils. Eosinophils react to IgE- or IgG-coated worms causing degranulation onto the surface of the worms, killing them. It is believed that TH2 subsets of TH cells play an important role in helminth infection. Cytokines released by TH2 cells such as IL-4 induces class switching to IgE, IL-5 induces eosinophilia (increase in the number of eosinophils) and IL-3 activates mast cells to degranulate. IgE antibodies bind to the surface of the parasite. The free Fc region of helminth-bound antibody attaches to the Fc receptor present on eosinophils. The cross-linking of the Fc receptor causes the secretion of granules from eosinophils (and mast cells) that destroys the parasite. Eosinophils may be more effective at killing helminth parasites than other leukocytes because the major basic protein of eosinophils is more toxic to helminths, than reactive oxygen and reactive nitrogen species and proteolytic enzymes produced by macrophages and neutrophils. Major basic protein is a non-specific protein, but still does more harm to the parasite because it is secreted in close proximity to the parasite, doing little damage to nearby host cells. Sometimes, the immune system cannot completely eliminate the parasite, so it “isolates” the organism (or its eggs) by “walling off ” the parasite. This walling off effect is a chronic cell-mediated response, that leads to the formation of fibrosis and granulomatous lesion. Schistoma mansoni eggs in the liver stimulate TH cells that activate macrophages and induce delayed type hypersensitivity reactions. Chronic delayed type hypersensitivity results in the formation of granuloma around the eggs.

Though the granuloma localize the Schistoma eggs and prevents their dispersal to other places such as the intestine or bladder, fi brosis associated with granuloma disrupts blood flow in the liver inducing hypertension and cirrhosis. Schistosoma parasites can elicit antibody formation, resulting in the formation of an immune complex. These complexes can be deposited in the kidneys, and blood vessels producing vasculitis and nephrites.

EVASION OF IMMUNE MECHANISM BY HELMINTHS

Heminths evade the immune mechanism in the following ways:

• Antigenic disguise: Some helminths such as schistosomes acquire a surface layer of host antigen (such as blood group A, B, and MHC molecules) which allows them to remain in the host body, as the host is unable to distinguish them from self.

• Many parasitic worms develop thick integuments that make them resistant to complementmediated cell lysis, cytolytic action of Tcyt and cytocidal mechanisms of neutrophils and macrophages. The best example is Schistosoma larvae which develop teguments during their migration to lungs.

• Some parasitic worms induce generalized immunosupression as well as specific anergy to parasite antigens. Filarial worms infect and disrupt lymph nodes contributing to deficient immunity.

• Some parasitic worms express or secrete certain antioxidant enzymes/molecules that resist the oxidative burst of phagocytes. Schistosomes have the antioxidant enzyme glutathione-S-transferase, while filarial worms can secrete glutathione peroxidase.