IMMUNITY TO PARASITIC AND FUNGAL INFECTIONS

- Chapter 20

Topics Covered

- Overview of parasitic diseases
- Immune response to parasitic infections
- Immunity to malaria
- Immunity to schistosomiasis
- Immune effectors in parasitic infections
- How parasites evade the immune response
- General features of fungal pathogens
- Immunity to fungal infections

Overview of parasitic diseases

- Parasites live in or on a host and cause harm to the host while they derive benefits from the host
- Specifically the Protozoa and the Helminths
  - Protozoa are single celled eukaryotic organisms
    - pathogenic protists
  - Helminths are multicellular eukaryotic organisms (worms)
    - Nematodes or roundworms
    - Trematodes or flukes
    - Cestodes or tapeworms

Overview of parasitic diseases

Table 20.1 Major parasitic infections of humans

Disease	Major species	Areas of endemicity	Infections (millions)
Protozoa			
Malaria	*Plasmodium falciparum, P. vivax, P. ovale, P. malariae*	Worldwide in tropics and subtropics	300
Leishmaniasis, visceral	*Leishmania donovani*	India, China, Africa	<1
Leishmaniasis, cutaneous	*Leishmania major*, others	Worldwide in tropics and subtropics	12
Trypanosomiasis, African (sleeping sickness)	*Trypanosoma brucei*	Sub-Saharan Africa	<1
Trypanosomiasis, South American (Chagas' disease)	*Trypanosoma cruzi*	Latin America	20
Toxoplasmosis	*Toxoplasma gondii*	Worldwide	>100

Overview of parasitic diseases

Table 20.1 Major parasitic

Disease	Mode of transmission	Site of parasitism	Duration of infection (yr)
Protozoa			
Malaria	*Anopheles* mosquito bite	Erythrocytes	1–2
Leishmaniasis, visceral	Sand fly bite	Macrophages	Lifelong
Leishmaniasis, cutaneous	Sand fly bite	Macrophages	Lifelong
Trypanosomiasis, African (sleeping sickness)	Tsetse fly bite	Bloodstream	Months
Trypanosomiasis, South American (Chagas' disease)	Reduviid bug bite	Blood, muscle	Lifelong
Toxoplasmosis	Infective stages in cat feces, undercooked meat	Many cell types	Lifelong

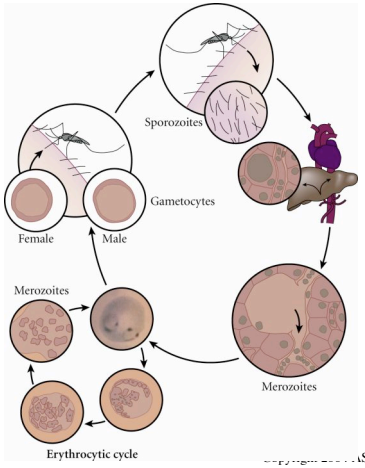
Protozoa are single celled eukaryotic organisms

- The most serious and intensely studied protozoal infections include:
- Malaria
  - *Plasmodium falciparum*
- Leishmaniasis
  - *Leishmania donovani or L. major*
- Trypanosomiasis
  - *Trypanosoma brucei or T. cruzi*
- Toxoplasmosis
  - *Toxoplasma gondii*

Malaria *Plasmodium falciparum*

- Leading cause of death worldwide
- Protective immunity does not develop after first episode or exposure
- only after many years of repeated exposure does individual become more resistant to infection
  - Fewer parasites in bloodstream
  - Less fever and clinical signs of disease
- No strong immunity to malaria due to
  - the tremendous strain diversity
  - and remarkable level of antigenic drift or variation
- Disease symptoms are due to intra-erythrocytic cycles of infection that result in
  - High fever
  - Anemia
  - Cerebral disease
    - Acute infection of the central nervous system
    - Leads to disorientation, delirium, coma, and death

Malaria: Life Cycle of *Plasmodium falciparum*

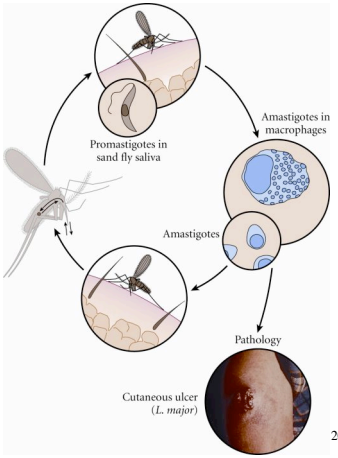


- Sporozoites from anopheline mosquito bite
- Invade and replicate in the liver
- Emerge as merozoites and infect red blood cells (erythrocytes)
- Get sucked back up into another anopheline mosquito during another bite

Leishmaniasis:
Leishmania donovani or L. major

- Parasitize Mϕ of skin, liver, spleen, and bone marrow
- Causes skin ulcers and permanent scars
- Cutaneous leishmaniasis is the only major human parasitic infection that there appears to be immunity to reinfection
- CMI most important -little role for antibodies
- TH1 are most critical part of CMI
  - Produce cytokines for Mf activation
  - Destroy intracellular parasites with Nitric Oxide (NO) and reactive oxygen intermediates (ROI)

Life Cycle of *Leishmania* species

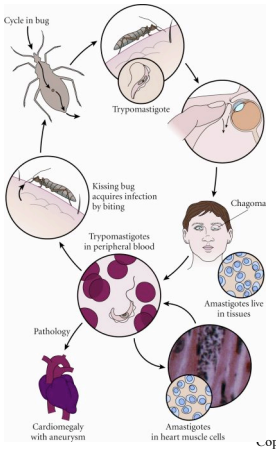


- promastigotes from infected female sand fly bite enter wound
- Activate complement and are taken up by Mϕ
- Inside the phagolysosome they transform to amastigotes and replicate -filling the cytoplasm
- They rupture the Mϕ and are taken up by new Mϕ
- Get sucked back up into another sand fly during another bite and develop into infectious promastigotes

Trypanosomiasis: *Trypanosoma brucei or T. cruzi*

- *T. cruzi* causes Chagas' disease in S. and Central America
  - Intracellular parasite infects Mϕ, muscle and nerve cells
  - Transmitted by bite and subsequent contact with reduviid bug feces or through mucous membrane contamination with feces
  - Activation of Mϕ and generation of NO are critical for parasite killing
  - CTL, specific antibodies and complement are important to kill infected cells and parasites directly
  - *T. cruzi* antigens cross react with human cardiac muscle and mesenteric nerve antigens causing severe damage to these host tissues
  - Acute phase of Chagas' disease may be asymptomatic, but chronic infection can lead to cardiac arrhythmias, cardiomyopathy, or megacolon/megaesophagus.
- *T. brucei* causes African sleeping sickness
  - Strictly extracellular parasite
  - Transmitted by the bite of the tsetse fly
  - Intermittent fevers associated with antigenic drift of the parasite
  - Invasion of central nervous system leads to coma and death if untreated

Trypanosomiasis: Life Cycle of *T. cruzi*

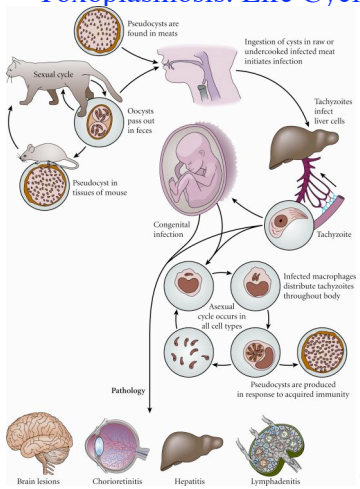


- Trypomastigotes from infected hematophagous reduviid bugs bite enter wound from bug feces (or infect eyes from contaminated hands)
- Infect a wide variety of cells and cause a infammatory lesion or chagoma at site of parasite entry
- Inside the host cells they transform to amastigotes and replicate -filling the cytoplasm
- They rupture the host cells and are released to infect new host cells
- Get sucked back up into another reduviid bug during another bite and develop into infectious trypomastigotes

Toxoplasmosis: *Toxoplasma gondii*

- Intracellular pathogen that can infect virtually any warm-blooded animal
  - where asexual reproduction occurs and pseudocyst formation occurs
- The definitive host is the cat (wild and domestic)
  - Where sexual reproduction and egg prodcution of parasite occurs
- Other hosts become infected upon ingestion of eggs found in cat feces or eat undercooked meat of an infected animal
- Normally remains in encysted in CNS
- Infection is very common, 1/3 of the world has been exposed
- Generally asymptomatic, but 2 high risk groups
  - Immunocompromised and pregnant women
    - Toxoplasmic encephalitis in HIV+
    - Primary infection during pregnancy can lead to infected fetus and spontaneous abortion or congenital disease including mental retardation and blindness

Toxoplasmosis: Life Cycle of *Toxoplasma gondii*



- Pseudocysts from meat or eggs from cat feces are ingested
- Become tachyzoites and infect and replicate in any nucleated cell
- Immune system clears tachyzoites but some transform into bradyzoites and form pseudocysts to evade T cell response
- Tachyzoites can infect the fetus, cause damage, and form pseudocysts here as well

ASM press

Table 20.1 Major parasitic infections of humans

Disease	Major species	Areas of endemicity	Infections (millions)
Helminths			
Intestinal nematodes			
Ascariasis (roundworms)	*Ascaris lumbricoides*	Worldwide in tropics and subtropics	1,000
Hookworm	*Ancylostoma duodenale*, *Necator americanum*	Worldwide in tropics and subtropics	900
Trichuriasis (whipworm)	*Trichuris trichiura*	Worldwide in tropics and subtropics	500
Tissue nematodes			
Lymphatic filariasis	*Wuchereria bancrofti*	Worldwide in tropics and subtropics	>100
Onchocerciasis (river blindness)	*Onchocerca volvulus*	Sub-Saharan Africa, Central and South America	20
Trematodes			
Schistosomiasis	*Schistosoma mansoni*	Africa, Arabia, South America, East and Southeast Asia	>200
	S. japonicum	East Asia	
	S. haematobium	Africa, Middle East	
Cestodes			
Cysticercosis (tissue)	*Taenia solium* (pig tapeworm)	Worldwide	>10

Overview of parasitic diseases

Table 20.1 Major para

Disease	Mode of transmission	Site of parasitism	Duration of infection (yr)
Helminths			
Intestinal nematodes			
Ascariasis (roundworms)	Infective eggs in fecally contaminated soil	Small intestine	1–2
Hookworm	Infective larvae in fecally contaminated soil	Small intestine	2–3
Trichuriasis (whipworm)	Infective eggs in fecally contaminated soil	Colon and cecum	5
Tissue nematodes			
Lymphatic filariasis	Mosquito bite	Lymphatics	>10
Onchocerciasis (river blindness)	Blackfly bite	Subcutaneous	>10
Trematodes			
Schistosomiasis	Infective cercariae from freshwater snails	Mesenteric veins	>10
		Mesenteric veins Vesical plexus veins	
Cestodes			
Cysticercosis (tissue)	Infected pork	Subcutaneous tissues, brain	Lifelong

Overview of parasitic diseases

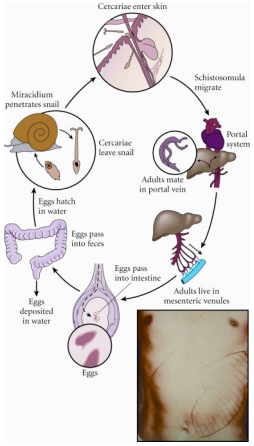
Helminths are multicellular eukaryotic organisms (worms)

- Trematodes or flukes
  - Schistosomiasis = Bowel, Bladder, and Liver Infection
    - *Schistosoma mansoni* or *S. japonicum, S. haematobium*, and ALL three res.
- Nematodes or roundworms
  - Lymphatic Filariasis = Intravascular Infection - "elephantitis"
    - *Wuchereria bancrofti* and *Brugia* species
  - Intestinal Nematodes
    - *Trichuris trichiura*

Trematodes or flukes: Schistosomiasis

- Caused by highly immunogenic eggs deposited in tissues
- Triggers chronic inflammation and immunopathic reactions
- T cell-mediated host reaction to eggs results in granuloma formation
- Cause hepatic fibrosis = liver scarring
- Portal hypertension = high blood pressure in liver vein
- Bladder and urinary tract fibrosis
- No strong immunity to schistosomes
- Decreased susceptibility to additional infection of adults
  - Selective immunity to the larvae
  - Does not decrease number of adult worms in residence
  - Adult worms induce immune response that are protective against the larvae but not the adult worms themselves

Trematodes or flukes:Schistosomiasis Life Cycle of *Schistosoma mansoni*

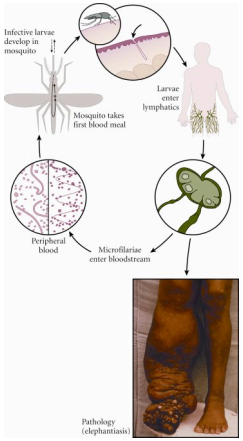


- Infective schistosome larvae called cercariae leave snail and bore into human skin
- Become schistosomula in skin and migrate to lungs and portal vein
- Males and females pair settle into gut veins and mature into adult worms
- Female lives "inside" male and continuously produces eggs
- Eggs expelled in feces and travel to liver
- T cell mediated granuloma formation around the eggs causes disease

Nematodes or roundworms

- Lymphatic Filariasis = Intravascular Infection - "elephantitis"
  - *Wuchereria bancrofti* and *Brugia* species
  - Damage to lymphatic vessels
  - Episodic lymphatic inflammation, pain , and fever
  - Adult worms can cause lymph stasis and gross enlargement of the limbs, scrotum, or breast
  - Lymphatic lesions likely casued by mechanical damage by worms and immune mediated inflamatory responses
- Onchocerciasis = Tissue Infection - "river blindness"
  - *Onchocerca volvulvus*
  - Severe eye disease and dermatitis in Africa and Central America
  - Transmitted by black flies near fast flowing waters
  - Adult worms reside in cutaneous tissues
  - Microfilariae migrate to ocular tissues
  - Disease is caused by immune responses to the circulating Microfilariae

Lymphatic Filariasis: Life Cycle of *Wuchereria bancrofti*



- Infective larvae from Culex, Anopheles, and Aedes mosquito bite
- Migrate to lymphatic vessels and lymph nodes where they mature into adult worms
- Adults produce offspring or microfilariae which enter the bloodstream
- Get sucked back up into another mosquito during another bite
- Chromic inflammation and vessel damage cause pathology

Nematodes or roundworms

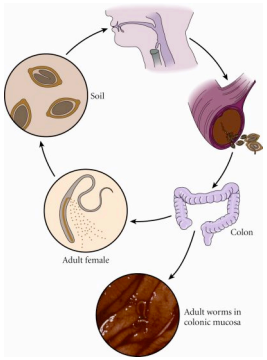
Intestinal Nematodes
- *Ascaris lumbricoides,* hookworm, and *Trichuris trichiura*

– Infect 1/4 of World's people
– Do not cause overt clinical problems in most cases
– Problems with massive infections or inappropriate immune response

Tissue Nematodes
– *Trichinella spiralis*
– Larvae become encysted in striated muscle
– Eat undercooked meat, larvae hatch, migrate to gut, mature into adult worms, lay eggs and larvae migrate to muscle

Both provoke TH2 immune response
– with cytokines IL-4, IL-9, and IL-13
– important for expelling worms from the gut

Intestinal Nematode: Life Cycle of *Trichuris trichiura*



- Direct Infection by a human fecal-oral route with no intermediate vector
- Adult whipworms live in the colon and cecum
- Adult females produce thousands of unembryonated eggs daily which pass though the feces and embryonate in the soil
- Eggs are transpprted to mouth via unclean hands, contaminated food or water and are swallowed
- Eggs hatch into larvae in the small intestine and larvae mature and then migrate to the large intestine

T cells and Cytokines Regulate Immune Responses in Parasitic Infections

- T cells are critical to control all parasitic infections
- Do not provide protective immunity against reinfection
- Are required to control parasitic infection
- Genetically deficient mice lacking B and T cells and athymic mice with few T cells are
  – unable to control infections and
  – develop overwhelming parasite burdens that are fatal

T cells and Cytokines Regulate Immune Responses in Parasitic Infections

- Development of tissue injury is often due to
  - Inappropriate immune response
  - rather than insufficient immune response
- T cells are usually responsible for immune mediated injury and disease progression
- TH cell subsets (TH1 and TH2) were discovered through
  - dissecting disease resolution versus disease progression
  - and immune-mediated injury in parasitic infections

Table 20.2 The potential role of T-cell subsets in parasitic diseases

Parasite	T-cell subset(s)	Potential function in disease[a]
Protozoa		
Leishmania major (murine)	TH1 TH2	Protection Exacerbation
Trypanosoma cruzi	$CD8^+$	Protection
Plasmodium		
Liver stage	$CD8^+$	Protection
Cerebral	TH1	Immunopathology
Toxoplasma gondii	$CD8^+$, TH1	Protection
Helminths		
Schistosoma mansoni (murine)	TH1 TH2	Protection Immunopathology
Trichuris muris	TH2 TH1	Protection Exacerbation

[a]The association of specific T-cell subsets with disease outcome derives from animal models and is not always mutually exclusive and generally is not as clear-cut in human infections.

TH cell subsets and their cytokines regulate immune responses to parasites

- Expansion of TH1 or TH2 cells in response to infection is dependent on
  - Nature of the invading organism
  - Genetics of the host
- Host genetic importance demonstrated in inbred mouse strains where difference in genetic background can determine whether an infection is
  - Harmless or Lethal
- First shown with *Leishmania*
  - Induction of TH1 leads to disease resolution
  - Induction of TH2 leads to disease progression

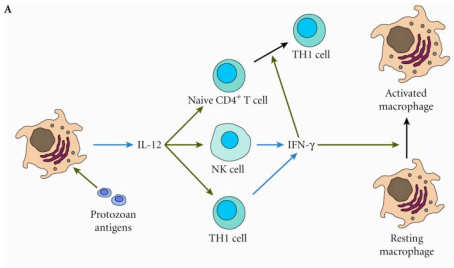
TH cell subsets and their cytokines regulate immune responses to parasites

- Many Studies have shown:
- Activation of TH1 lymphocytes is usually necessary for the destruction of protozoa
- Activation of TH2 lymphocytes occurs in Helminth infections
  - Characterized by increase in eosinophils and mast cells
  - and upregulated IgE levels
- TH2 bias has been studied in murine models and humans infected with schistosomes or filarial nematodes
- For tissue helminths, it is unclear whether the TH2 response benefits the the host or the parasite
- For Gut nematodes, it is clear that TH2 cytokines are necessary for clearance of the parasites

IL-12 drives TH1 responses

- IL-12 initiates TH1-dependent cell-mediated immune responses
- IL-12 Is produced by phagocytic cells and B cells
  - in response to infection with protozoan parasites
- IL-12 is a Critical component in the early response to infection that drives TH1 cell expansion
- IL-12 Directly stimulates the production of IFN-γ
  - by T cells and NK cells

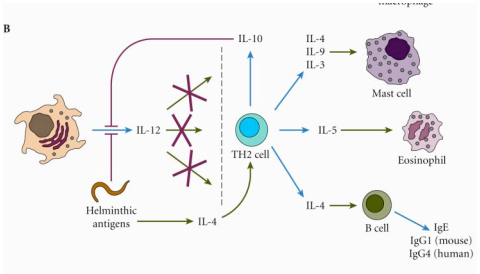
IL-12 and parasite infection



- Intracellular parasites in Mϕ activate the production of IL-12
- Induces production of IFN-γ by T cells and NK cells
- Immediately activates more Mϕ
- IL-12 and IFN-γ favor development of more TH1 cells
- IL-12 and IFN-γ favor the additional production of IFN-γ by established TH1 cells

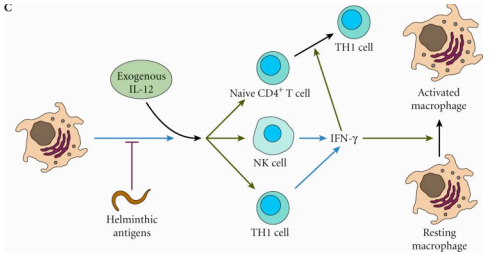
IL-12 and parasite infection

- Helminthic Antigens induce the production of IL-4
- IL-4 drives TH2 development
- Helminthic parasites do not induce production of IL-12
- and may directly block production of IFN-γ
- TH2 cells produce IL-10 which directly blocks IL-12 production



IL-12 and parasite infection

- When exogenous IL-12 is added to helminthic infections:
- Normal production of TH2 cells is prevented
- TH1 cell development follows pathway of protozoan parasitic infection



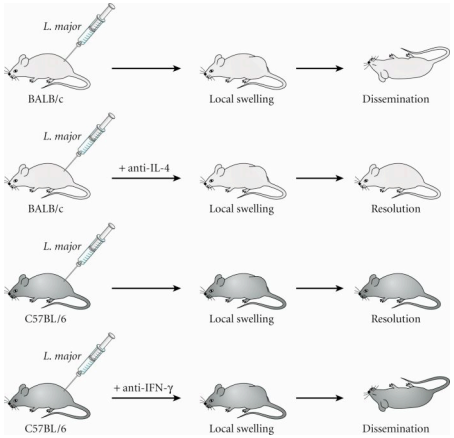
IFN-γ

- For intracellular protozoan parasites:
  - IFN-γ Is the major cytokine responsible for disease resolution
  - Because it activates macrophages
- Inbred mouse strains BALB/c and C57BL/6
  - BALB/c: produces IL-4 and TH2 response to *L. major*
  - C57BL/6: produces IL-12 and TH1 response to *L. major*
- TH2 is not protective and mice die (no IFN -γ)
- TH1 is protective and mice clear infection and remain resistant to reinfection (yes IFN -γ)

IFN-γ

- BALB/c: IL-4/TH2 response/no IFN-γ/death
- C57BL/6: IL-12/TH1 response/yes IFN-γ/lives
- Give BALB/c mice anti-IL-4 antibody
  - Binds up all IL-4 so it cannot work
  - No TH2 response that usually downreg TH1 response
  - Get a TH1 response and yes IFN-γ
  - Mice live and are resistent to reinfection
- Give C57BL/6 mice anti-IFN-γ antibody
  - Binds up all IFN-γ so it cannot activate Mϕ
  - No TH1 response to downreg TH2 response
  - Mice die

Leishmaniasis: cleared by TH 1 response



IL-4 initiates TH2 response to Helminths

- Hallmarks of Helminthic infection :
  - Elevated IgE
  - Elevated eosinophils in blood and tissue
  - Mast cell hyperplasia
- Above are Induced by TH2 responses
- IL-4 is critical for inducing TH2 response
- Cells that can produce IL-4 include specialized T cells like NK1.1 and γδ, mast cells, basophils, and eosinophils
- After initial induction, TH2 cells take over IL-4 production
  - And IL-5, IL-6, IL-9, and IL-13
- It is not yet known what helminthic signal caused initial production of IL-4

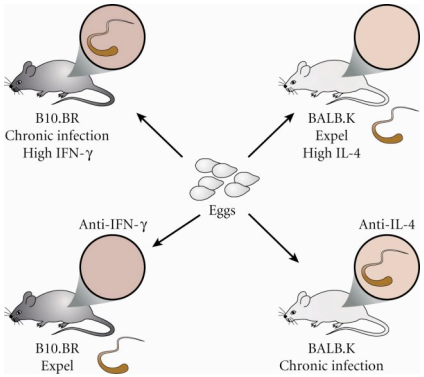
TH2 responses to Helminths clears parasites

- BALB.K: IL-4 / TH2 response / no IFN-γ / clears parasite
- B10.BR: IL-12 / TH1 response / yes IFN-γ / chronic infection

- Give BALB.K mice anti-IL-4 antibody
  - Binds up all IL-4 so it cannot work
  - No TH2 response that usually downreg TH1 response
  - Get a TH1 response and yes IFN-γ
  - Mice have chronic infection

- Give B10.BR mice anti-IFN-γ antibody
  - Binds up all IFN-γ so it cannot activate Mϕ
  - No TH1 response to downreg TH2 response
  - Mice clear the parasites

Trichuriasis: cleared by TH 2 response



TH2 responses to Helminths

- Universal feature of worm expulsion (nematode species) is the TH2 response

- The specific TH2 cytokines that are needed for expulsion differ for different parasite species

- Represents different effector mechanisms that mediate the expulsion of the different parasite species