Immune Mechanisms Against Intracellular Pathogens, Fungi, and Helminths

Overview of host immune responses to intracellular microbes (focus on viruses), fungi, and helminthic parasites.

Overview: Intracellular Pathogens

- Includes viruses, intracellular bacteria (e.g., Mycobacterium), and some protozoa (e.g., Toxoplasma).
- These pathogens replicate within host cells, evading many extracellular defenses.
- Control requires cytotoxic, macrophage- activating, and interferon-mediated responses.

Innate Immunity to Intracellular Pathogens

- PRRs: TLRs, RIG-I-like, and NOD-like receptors detect viral RNA/DNA or bacterial PAMPs.
- Type I interferons (IFN-α, IFN-β): inhibit viral replication, enhance NK cell activity.
- NK cells kill infected cells with reduced MHCI via perforin/granzyme.
- Macrophages phagocytose and release IL-12 → promotes Th1 differentiation.

Adaptive Immunity: T Cell Responses

- Dendritic cells present antigens on MHC I and II.
- CD8+ cytotoxic T lymphocytes (CTLs) recognize MHC I and kill infected cells.
- CD4+ Th1 cells produce IFN-γ, activating macrophages.
- Memory T cells ensure long-term protection.

Effector Mechanisms in Viral Immunity

- IFN-γ and TNF-α activate antiviral states in surrounding cells.
- CTLs destroy infected host cells directly.
- NK cells act early before CTLs expand.
- Neutralizing antibodies block viral entry and enhance clearance of free virions.
- Resolution via IL-10, TGF-β, and regulatory T cells.

Immune Evasion by Intracellular Pathogens

- Viruses: downregulate MHC I (CMV), inhibit interferon signaling (influenza, SARS-CoV-2).
- Bacteria: inhibit phagosome-lysosome fusion (Mycobacterium), escape into cytoplasm (Listeria).
- Protozoa: antigenic variation (Trypanosomes, Plasmodium).
- Host adapts via cross-presentation and autophagy.

Outcome and Immunopathology

- Effective responses clear infection but can damage tissue.
- Cytokine storms or CTL overactivity → tissue injury.
- Chronic infections arise from immune evasion or T cell exhaustion.
- Balance between pathogen control and host protection is crucial.

Immunity to Fungal Pathogens – Overview

- Most fungi are extracellular, but some (Histoplasma, Candida) survive intracellularly.
- Defense involves barrier integrity, phagocytosis, and Th17-mediated immunity.

Innate Immunity to Fungi

- Recognition by Dectin-1, TLR2/4, mannose receptors.
- Neutrophils and macrophages kill fungi via ROS and NETs.
- Complement opsonization (C3b) enhances fungal clearance.
- Cytokines IL-1, IL-6, TNF-α recruit neutrophils.

Adaptive Immunity to Fungi

- Th1 (IFN-γ) activates macrophages for intracellular fungi.
- Th17 (IL-17) recruits neutrophils for mucosal Candida.
- Antibodies assist opsonization and complement activation.
- Immunodeficiency predisposes to fungal infections.

Immunity to Helminthic Parasites – Overview

- Large multicellular parasites (nematodes, trematodes, cestodes) too big for phagocytosis.
- Main response: Th2-type immunity with IgE, eosinophils, mast cells.
- Goal: expulsion or containment.

Innate Immunity to Helminths

- Epithelial cells release IL-25, IL-33, TSLP → activate ILC2s.
- ILC2s produce IL-5, IL-13 → recruit eosinophils, induce mucus secretion, smooth muscle contraction.
- Mast cell degranulation aids parasite expulsion.

Adaptive Immunity to Helminths

- Th2 cells secrete IL-4, IL-5, IL-13:
  - IL-4 → B cell class switch to IgE.
  - IL-5 → eosinophil activation.
  - IL-13 → mucus production, goblet cell hyperplasia.
- IgE binds FcεRI on mast cells/eosinophils → degranulation.
- Tregs limit inflammation.

Summary Table

Pathogen Type	Dominant T Helper Subset	Key Effectors	Main Cytokines	Outcome
Intracellular (virus/bacteria)	Th1, CTL	Macrophages, CD8+ T cells, IFN-γ	IFN-γ, TNF- α	Infected cell killing
Fungi	Th1/Th17	Neutrophils, macrophages	IFN-γ, IL-17	Fungal clearance
Helminths	Th2	Eosinophils, mast cells, IgE	IL-4, IL-5, IL-13	Parasite expulsion, repair

Key Takeaways

- Intracellular pathogens → cell-mediated (Th1, CTL, IFN-γ).
- Fungi → Th17 and phagocyte responses.
- Helminths → Th2, IgE, eosinophils, mast cells.
- Protection requires balance to avoid immunopathology.