A framework for human host immune responses to four types of parasitic infections

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Abstract

Human host immune responses to parasitic infections are complex. They can be categorized into four immunological pathways against four types of parasitic infections. For intracellular protozoa, the eradicable host immunological pathway is TH1 immunity involving macrophages, interferon gamma (IFNg) CD4 T cells, innate lymphoid cells 1 (ILC1), CD8 T cells, invariant natural killer T cells 1 (iNKT1) cells, and immunoglobulin G3 (IgG3) B cells. For free-living extracellular protozoa, the eradicable host immunological pathway is TH22 immunity involving neutrophils, interleukin (IL)-22/IL-17 CD4 T cells, innate lymphoid cells 3 (ILC3), iNKT17 cells, and IgG2 B cells. For endoparasites (helminths), the eradicable host immunological pathway is TH2a immunity with inflammatory eosinophils (iEOS), IL-5/IL-4 CD4 T cells, IL-25 inducing inflammatory innate lymphoid cells 2 (iILC2), mast cells-tryptase (MCt), iNKT2 cells, and IgG4 B cells. For ectoparasites (parasitic insects and arachnids), the eradicable host immunological pathway is TH2b immunity with inflammatory basophils, mast cells-tryptase/chymase (MCtc), IL-3/IL-4 CD4 T cells, IL-33 inducing nature innate lymphoid cells 2 (nILC2), iNKT2 cells, and immunoglobulin E (IgE) B cells. The tolerable host immunity against ectoparasites and endoparasites is TH9 immunity with regulatory eosinophils, regulatory basophils, IL-9 mast cells (MMC9), thymic stromal lymphopoietin inducing innate lymphoid cells 2, IL-9 CD4 T cells, iNKT2 cells, and IgA2 B cells. This categorization provides a complete framework of immunological pathways against four types of parasitic infections.

1 Introduction

Host immune responses to parasitic infections are complex. Parasites include protozoa, helminths, and insects. Previously, I proposed a framework for all the known host immunological pathways and their roles in the immune responses against four specific types of pathogens and the corresponding four specific types of hypersensitivities (1). Here, I extend the framework and propose a new framework of host immunological pathways for four types of parasitic infection. Host immunological pathways against parasites are determined primarily by the location of the infection. After identifying

the location of the parasitic infection, the host immune system can attack these parasites with different effector cells and using different strategies.

2 Host immunological pathways for different types of parasitic infections

2.1 Intracellular protozoa and TH1/TH1-like immunity

For intracellular protozoa, the host immunological pathway is a TH1 immune response involving macrophages (M1), interferon gamma (IFNg) CD4 T cells, CD8 T cells (CD28+, CD27−, Tc1, EM4), invariant natural killer T1 (iNKT1 cells), and IgG3 B cells. Innate lymphoid cells 1 (ILC1) is the immune cells helping to initiate TH1 immune reaction. CCR5 is the chemokine receptor used by TH1 immune cells. The ligands of CCR5 include C-C motif chemokine ligand (CCL) 3 and CCL4 [also known as macrophage inflammatory protein (MIP) 1α and 1β, respectively](2). TH1 immunity is the host immune response to intracellular pathogens. The intracellular location is more important than the pathogen type. Thus, TH1 immunity can be triggered to defend against intracellular bacteria, fungi, and protozoa. Activated macrophages are the key effector cells that digest intracellular bacteria, fungi, and protozoa. Intracellular protozoa are categorized into the parasite groups. Intracellular protozoa, including *Plasmodium*, *Leishmania*, *Toxoplasma*, *Babesia*, and *Cryptosporidium*, can all trigger a TH1 host immune response (3-7). Intracellular bacteria such as *Chlamydia* and intracellular fungi such as *Histoplasma* can also trigger TH1 immunity. This is the intracellular protozoa-eradicable host immune response.

For immune tolerance to intracellular protozoa, the host mounts a TH1-like immune response. The effector cells for TH1-like immunity are macrophages (M2), IFNg/transforming growth factor beta CD4 T cells, CD8 T cells (CD28- CD27- EM3), iNKT1 cells, and IgA1 B cells. CCR2 is the chemokine receptor used by TH1-like immune cells(8). The ligand for CCR2 is monocyte chemoattractant protein-1 (CCL2). TH1-like immunity is a chronic immune tolerance to intracellular pathogens, including intracellular bacteria, protozoa, and fungi. Alternative activated macrophages M2 are the principal cells mediating the TH1-like immunity to intracellular pathogens. Chronic infections with intracellular protozoa usually trigger the TH1-like immunological pathway.

2.2 Extracellular protozoa and TH22/TH17 immunity

For free-living extracellular protozoa, the eradicable host immunological pathway is TH22 immunity with neutrophils (N1), IL-22 CD4 T cells, iNKT17 cells, and IgG2 B cells. Innate lymphoid cells 3 (ILC3) helps to initiate the TH22/TH17 immunity. Neutrophils are the major effector cells of the TH22 host immunological pathway. The chemokine receptor used by TH22 immune cells is CCR10(9). CCR10 ligands include CCL27 (CTACK) and CCL28 (MEC). TH22 immunity is the host immune response to extracellular protozoa, bacteria, and fungi. It is worth noting that extracellular location determines the host immunological pathway, which is more important than whether the pathogen is bacteria, fungi, or protozoa. Neutrophils can use neutrophil extracellular traps and kill these extracellular free-living pathogens. These extracellular free-living protozoa include *Trypanosoma*, ameba, *Giardia*, and *Trichomonas* (10-14). These pathogens can induce TH22 host immunity. Extracellular bacteria, such as *Escherichia coli* and extracellular fungi such as *Aspergillus* can also trigger TH22 host immune reactions.

The immune tolerance pathway against extracellular protozoa, fungi, and bacteria is TH17 immunity. The effector cells of TH17 immunity include neutrophils (N2), IL-17 CD4 T cells, iNKT17 cells, and IgA2 B cells. The chemokine receptor used by TH17 immune cells is CCR6(15). The ligand of

CCR6 is CCL20 (MIP-3α). The TH17 immune reaction is a chronic immune tolerance to extracellular free-living protozoa.

2.3 Helminths (endoparasites) and eradicable TH2a immunity

For helminths (endoparasites), the eradicable host immunological pathway is TH2a immunity with inflammatory eosinophils, IL-5/IL-4 CD4 T cells, mast cells-tryptase (MCt), iNKT2 cells, and IgG4 B cells. Endoparasites means the parasites are located in our bodies. Inflammatory innate lymphoid cells 2 (IL-25 induced iILC2) help to initiate TH2a immune response(16, 17). Eosinophils are the major effector cells that use IgG4-mediated antibody-dependent cellular toxicity to attack the helminth tegument. Mast cells-tryptase are the mast cell subtypes in TH2a immunity. The chemokine receptor used by TH2a immunity is CCR4(18). The ligands of CCR4 are CCL17 (thymus and activation-regulated chemokine) and CCL22 (monocyte-derived dendritic cell). This TH2a pathway belongs to the TH2 immunity and is a subtype. The letter "a" means "acid" which is derived from the name of eosinophils. Helminths (endoparasites) that can induce TH2a immunity with eosinophilia include *Ascaris*, hookworms, tapeworms, pinworms, filarial worms, *Toxocara*, and *Strongyloides* (19-24). However, several helminths can also induce IgE antibodies, so this immune response is a subtype of the TH2 immune response.

2.4 Parasitic insects and arachnids (ectoparasites) and eradicable TH2b immunity

For insects (ectoparasites), the eradicable host immunological pathway is TH2b immunity with inflammatory basophils, mast cells-tryptase/chymase (MCtc), IL-3/IL-4 CD4 T cells, iNKT2 cells, and IgE B cells. Ectoparasites means these insects are located in our bodies' outer skin surface. Nature innate lymphoid cells 2 (IL-33 induced nILC2) help to initiate TH2b immune reaction(25, 26). The major effector cells of TH2b immunity are basophils and mast cells-tryptase/chymase (MCtc). Circulating basophils and resident mast cells have the same characteristics. The chemokine receptor used in the TH2b immune response is CCR1(27). CCR1 is expressed on basophils. Resident mast cells can also serve as antigen-presenting cells. The letter "b" means "base" which is derived from the name of basophils. IgE can cause the physical expelling of insects (ectoparasites) via skin itchiness, skin wheal with toxin dilution, rhinorrhea, mucus formation and secretion, nausea/ vomiting, bronchoconstriction, and increased bowel movement. Basophil accumulation is usually noted at the site of insect bites or dwelling. However, these IgE-mediated mechanisms can also expel helminths in the lung or intestine. Thus, this immune response (TH2b) is a subtype of the TH2 immune response. The bites of parasitic arachnids and insects, including those of ticks, fleas, and mosquitos, can induce a TH2b immune reaction (28-32). The stings of non-parasitic insects such as bees and wasps also induce a TH2b immune reaction.

2.5 Parasites and tolerable TH9 immunity

The TH9 host immunological pathway is a chronic immune tolerance response to parasites (endoparasites and ectoparasites). The main effector cells of the TH9 immunological pathway include regulatory eosinophils, regulatory basophils, mast cells (MMC9), IL-9 CD4 T cells, and IgA2 B cells(33). Thymic stromal lymphopoietin (TSLP) induced innate lymphoid cells 2 help to initiate TH9 immunity(25, 34). IL-9 producing mast cells (MMC9) are the mast cell subtype responsible for TH9 immunity. The chemokine receptor functioning in TH9 immunity is CCR3(35, 36). The ligands of CCR3 are eotaxin-1 (CCL11) and eotaxin-3 (CCL26).

3 Conclusion

This framework describes the immunological pathways of the human host response to four types of parasitic infections. Intracellular protozoa induce TH1/TH1-like immunity; extracellular protozoa induce TH22/TH17 immunity; endoparasites (helminths) induce TH2a eradicable immunity; and ectoparasites (parasitic insects and arachnids) induce TH2b eradicable immunity. TH9 immunity is a tolerable immue response to endoparasites and ectoparasites.

4 Conflict of Interest

The author declares that the manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5 Author Contributions

WCH conceived and wrote the manuscript and agrees to be accountable for the content of the work,

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9 Data Availability Statement

Not applicable.