The Understanding of the Immune Response for Controlling Parasitic Diseases of Animals

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Abstract

Published manuscripts, although updated, are not providing an exclusive review of the large amount of information that currently exists regarding the immune response of various hosts against different parasites and how are they controlled. In fact, a single chapter would be required to bring together the studies related to the immune response of a single host species (as for example, *Bos taurus*) against a particular parasite (*Babesia bigemina*). For this reason, this text aims to summarize the main and most recent aspects of this area of knowledge with the intention of making it useful for the reader. It is also true that, for the designing of an integral control of parasites, it is mandatory to understand other biologic systems, which interact with the immune system as well the strategies used by parasites to evade the effects of the immune system. This chapter is focused on comprehensive strategies of host to control the parasitism.

Keywords: Immune response, Innate immunity, Adaptive immunity, Parasites, Control

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Introduction

The purpose of this manuscript is to provide current information on the innate immune response, which is very scarce and essential for the development of a good acquired immune response. When it was thought that the basic principles of the diversification of the receptors of T and B lymphocytes for antigen (adaptive immune response) had been resolved, researchers began to realize the complexity of the innate immune response and its importance in the protective immune response (Lynn et al., 2008; Cooper & Herrin, 2010; Buchmann, 2014). In this order of ideas, this document deals, with the most recent aspects of the innate immune response.

The immune system is made up of a repertoire of cells, tissues, molecules and mechanisms that protect the animal organism from numerous pathogenic microorganisms (microbes) and toxins found in the environment. Using molecular tools, it is estimated that this system, in general, began to evolve 1000 million years ago (Buchmann, 2014) developing a wide variety of solutions to resolve similar conditions in host protection (Litman et al., 2005). The immune response has also been divided into two types for ease of study: innate immune response and acquired immune response. Innate and adaptive immune responses are part of the whole immune system. Each of these differs in relation to how quickly and for how long it responds to pathogens, its main types of effector cells, and its specificity for different classes of microbes. As its name implies, the innate immune system consists of cells and proteins that are always present and ready to mobilize and fight microbes at the site of infection. The main components of the innate immune system are 1) physical epithelial barriers (skin, mucosa), 2) phagocytic leukocytes (neutrophils, monocytes, macrophages), 3) dendritic cells, 4) innate lymphoid cells (ILC1, ILC2, and ILC3) including natural killer cells (NK) and lymphoid tissue inducer (LTi) (Geuking et al., 2014; Mjösberg, 2015), 5) gamma-delta T cells (Bautista, 2011), and 6) circulating plasma proteins. On the other hand, the adaptive immune system acts against pathogens that are able to evade or overcome innate immune defenses. The components of the adaptive immune system are normally at rest; however, when activated, these components react to the presence of infectious organisms by activating, proliferating, and creating powerful components, which neutralize or eliminate pathogens. The adaptive immune responses are divided into humoral immunity, mediated by antibodies produced by B lymphocytes, and cellular immunity, mediated by T lymphocytes.

The immune system evolved millions of years ago to protect the host against foreign invaders, such as parasites. This system is complex and at present, we do not know it completely. It is also true that the immune system y interconnected with other biological systems and we need to understand them as a whole to prevent or control pathogens. In this review relevant topics about this premise. In this respect, It is important to point out the interaction between the vertebrate immune system and their microbiota too (Yoo et al., 2020, Zheng et al., 2020, Donald & Finlay, 2023, Ullah et al., 2024). In addition, it must bear in mind that nutrition (Munteanu & Schwartz, 2022) and animal welfare (Düpjan & Dawkins, 2022) have a basic influence on the whole immune responses. In This order of ideas, it is not surprising that environmental factors influence the immune response too. In This order of ideas, it is not surprising that environmental factors influence the immune response too (Dawkins, 2019; Luo et al., 2020). At present, the function the function of the immune system is far more complex than previously understood (Rankin & Artis, 2018), so each new discovery is of capital importance to plan new strategies for the control of pathogens, which

affect human beings and animals.

At present, the immune system is far more complex than we though few years ago. Immunologists were focused on the adaptive immune response during many years when new discoveries showed the importance of the innate immune response; then they realized that both arms of the immunity (adaptive and innate) must be considered when designing methods for combating effectively parasites, which affect farm animals and the human being.

Immune System

Vertebrate immunity evolved during millions of years (Boehm, 2012). It is estimated that the adaptive immune system in mammals arose 500 millions of years ago (Flajnik & Kasahara, 2013). However, the innate immunity evolved around one billion of years ago (Martins et al., 2023). In this context and in terms of number of studies, the adaptive immune response historically has more studies than the innate immune response (Figure 1).

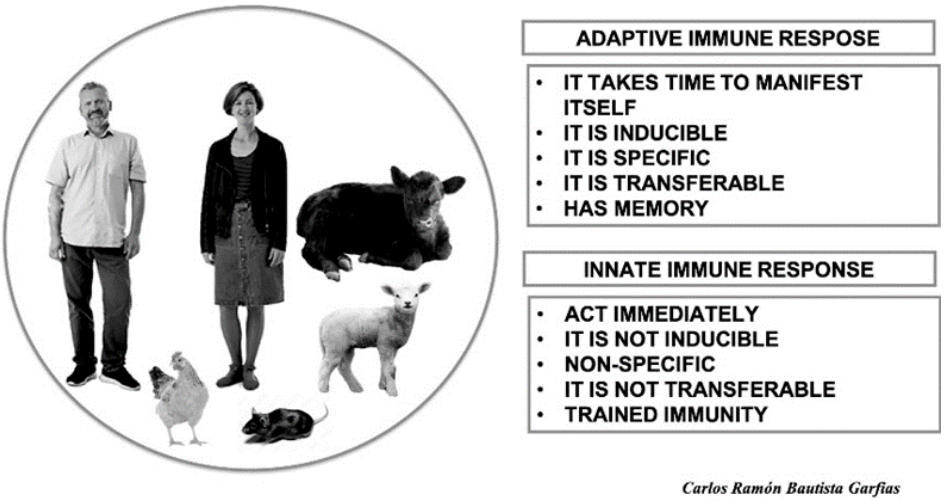

Fig. 1: Characteristics of the immune response of vertebrates. The adaptive immune response has been studied much more than the innate immune response. For this reason, the former appears on top of the innate immune response. The design of the figure based on Silverstein (1979), Zinkernagel et al. (1996), Langman (2000), Janeway & Medzhitov (2002), Cooper & Herrin (2010), Iwasaki & Medzhitov (2015), Netea et al. (2016), Graham et al. (2022), Geckin et al. 2022, Dagenais et al. (2023), Chaves Martens et al., 2023, Vuscan et al. (2024).

Interactions with other Biological Systems

The immune system has links with other biologic systems (Dhillon et al., 2020) such as nervous system (Zefferino et al., 2020) the microbiota (Zheng et al., 2020), endocrine system (Wensveen et al., 2019). Taking these as a whole may provide us an insight in how to implement new approaches for the control of parasites, which affect farm animals and man.

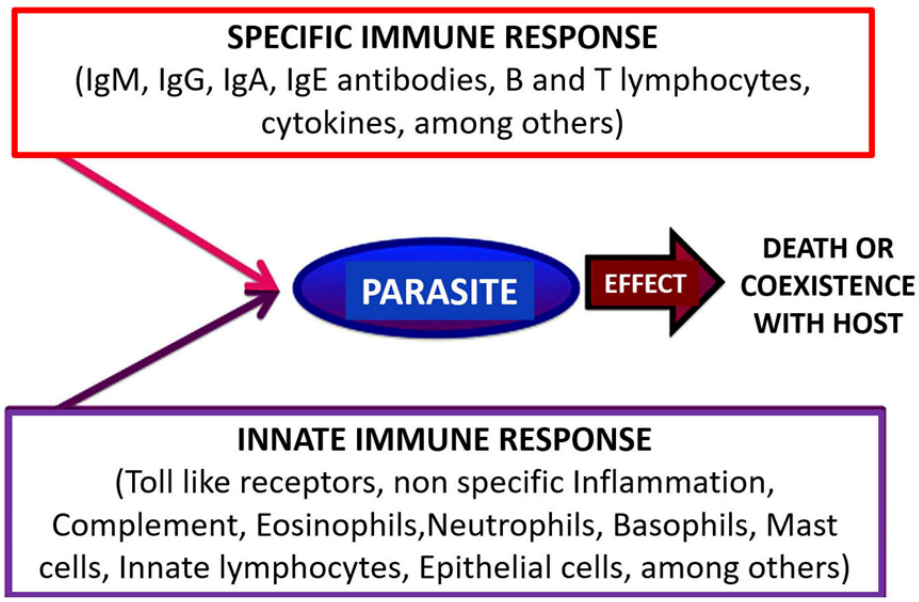

Fig. 2: Immune response against parasites.

Immune Response against Parasites

When the host immune system confronts a parasite, it uses all available means to eliminate it. These include the mechanisms of the innate immune response and later on, those of the acquired immune response, all of which are closely related. Figure 2 summarizes the interactions of various molecules (antibodies, complement, cell receptors) and cells of the host immune system that play a role in protecting the host from

parasites (Lekki-Józwiak & Baska, 2024).

In accordance with Iwasaki & Medzhitov (2015), the immune responses type Th1 act against intracellular pathogens such as protozoan parasites, while the immunity type Th2 act against extracellular pathogens such as helminth parasites. These authors, propose the following series of events: In type 1 responses, the macrophages or dendritic cells stimulated by pathogens produce level 1 cytokines (IL-1beta, IL-12, IL-23, IL-6), which act on different lymphocytes (ILC1, ILC3, TH1, TH17, CTL, NK, NKT, gamma delta-T, TFH1) to produce level 2 cytokines (IFN-gamma, IL-17,IL-21, IL-22) that act on effector cells (macrophage, Neutrophil, epithelium, B lymphocytes) which, then have an adverse effects on protozoan parasites (for example, lysis of pathogens). In type 2 responses, the epithelium stimulated by pathogens produce level 1 cytokines (IL-1alpha, TSLP, IL-25, IL-33), than act on different lymphocytes (ILC2, TH2, TH9, NKT, TFH2) to produce level 2 cytokines (IL-4, IL-5, IL-13.IL-9, IL-21) which act on effector cells (Basophil, Eosinophil, Macrophage, Epithelium, B lymphocytes) than then have an adverse effects on helminth parasites (for example, expulsion of worms).

The host immune response against various parasites involves interrelated specific and non-specific components that aim to eliminate the parasite. It should be noted that although the induction of an acquired immune response against a particular parasite is specific, its effect is non-specific. In this regard, most of the studies carried out over many years have focused primarily on the study of the mechanisms of the acquired immune response of hosts against various parasites. Only in recent years, the capital importance of the innate immune response in the control of parasitic diseases has been re-evaluated.

Evasion of Immune Response by Parasites

Many parasites have evolved a variety of mechanisms to avoid the damaging (survival) effects of the host immune response. A single parasite may display more than one such mechanism. Some of these include:

1. Intracellular localization, for example *Plasmodium* (Moll et al. 2015), *Toxoplasma gondii* (Lima & Lodoen, 2019), *Babesia* (Djokic et al., 2021), *Trichinella spiralis* (Wu et al., 2008).
2. Molecular mimicry (the parasites, for example *Schistosoma* spp., cover themselves with host like molecules so the will not be recognized as foreign substances by the host immune system (Deng et al., 2003; 2007).
3. Evasion of complement effect by parasites such as *Plasmodium, Trypanosoma* and *Leishmania* (Rashidi et al., 2022).
4. Antigenic variation (for example, *Trypanosoma brucei* (Pays et al., 2004), *Giardia lamblia* (Tenaglia et al., 2023).
5. Rapid turnover of surface antigens (for example, *Fasciola hepatica* (Hanna, 1980)
6. Survival in the phagolysosome of macrophages (for example, *Toxoplasma gondii*, (Portes et al., 2020)
7. Inhibition of dendritic cell differentiation, maturation, and function (for example, *Plasmodium falciparum* (Elliott et al., 2007).
8. Inhibition of releasing neutrophil extracellular traps (for example, *Trichinella spiralis*, (Wang et al., 2023).
9. Escape from an stablished immune response (stage-specific antigens) (for example, schistosomes (Wiedemann & Voehringer, 2020).
10. Nonspecific mitogenic activity (for example, *Dirofilaria immitis* (Tezuka et al., 2002).
11. Immunosuppression (for example *Plasmodium*, *Schistosome* (Nussenzweig, 19782).
12. Inhibition of the inflammatory response (for example, parasites such *as Brugia malayi, Schistosoma mansoni, Ancylostoma caninum, Trichinella spiralis* (Alghanmi et al., 2024)
13. Induction of apoptosis in NK cells (for example, filarial parasites (Babu et al., 2007).
14. Uncontrolled proliferation of infected T cells (for example, *Theileria parva* (Dobbelaere et al., 2000)
15. Inhibition of lymphocyte proliferation (Cathepsin L from *Fasciola hepatica* (Prowse et al. 2002)), extracts of salivary glands from *Culicoides sonorensis* (Bishop et al., 2006) which inhibit lymphocyte proliferation and nitric oxide by macrophages.
16. Inhibition of monocyte locomotion. A pentapeptide called Monocyte Locomotion Inhibitory Factor (MIF) has been described in *Entamoeba hystolitica* that has the following activities: inhibition of monocyte locomotion and the respiratory burst of monocytes and neutrophils, inhibition of delayed hypersensitivity (Rico et al., 2003).
17. Resistance to digestion in the phagolysosome. Parasites of the *Leishmania* genus have a molecule on the cell surface called lipophosphoglycan (LPG) that allows them to resist the effect of oxidizing substances and hydrolytic enzymes found in the phagolysosome of infected macrophages (Lewis and Peters, 1977).
18. Inhibition of dendritic cell production. For example, *Brugia malayi* (Semnani et al., 2001) and *Plasmodium* (Wykes et al., 2007)

The Stimulation of the Innate Immunity on Prevention of Diseases Caused by Pathogens

It has been proposed that proper manipulation of innate immunity may be beneficial for performance of vaccines in man and animals (Netea et al., 2018; Ziogas & Netea, 2022).

Conclusions

If we want control parasitic diseases of animals and man we must aware that the understanding of the immune response must include the comprehension of other biologic systems such as the endocrine and nerve, as well factors of the environment (for example, climatic change). It is also true that we should incorporate the new findings on the role of the innate immunity using nonspecific stimulants such as *Lactobacillus casei* to generate a protective immune response to diverse parasites in the host, as for example to *Babesia microti* in mice *Eimeria* spp. in chicken *Trichinella spiralis* in mice and to *Babesia bovis* and *B. bigemina* when the lactobacilli is incorporated in the mixed vaccine against bovine babesiosis. In this connection, the recent findings on the non-specific stimulation of immune cells may be useful for designing new strategies for the control of parasites in animals. Finally, the adverse effect of microplastics, generated by disposable plastic products, on the immune system and the impact of climate change on parasites are factors that should be taken into account when we plan strategies in controlling parasites.

References

Alghanmi, M., Minshawi, F., Altorki, T. A., Zawawi, A., Alsaady, I., Naser, A. Y., & Alhabbab, R. (2024). Helminth-derived proteins as immune system regulators: a systematic review of their promise in alleviating colitis. *BMC Immunology*, *25*(1), 21. doi.org/10.1186/s12865-024-00614-2

Babu, S., Blauvelt, C. P., & Nutman, T. B. (2007). Filarial parasites induce NK cell activation, type 1 and type 2 cytokine secretion, and subsequent apoptotic cell death. *The Journal of Immunology*, *179*(4), 2445-2456.

Bautista-Garfias, C. R., Ixta, O., Orduña, M., Martínez, F., Aguilar, B., & Cortés, A. (1999). Enhancement of resistance in mice treated with Lactobacillus casei: effect on Trichinella spiralis infection. *Veterinary Parasitology*, *80*(3), 251-260.

Bautista-Garfias, C. R., Ixta-Rodríguez, O., Martínez-Gómez, F., López, M. G., & Aguilar-Figueroa, B. R. (2001). Effect of viable or dead Lactobacillus casei organisms administered orally to mice on resistance against Trichinella spiralis infection. *Parasite*, *8*, S226-S228.

Garfias, C. R. B., González, M. T. A., Castro, L. T., Rodríguez, O. I., & Ramírez, E. R. (2003). Comparación entre el efecto de Lactobacillus casei y el de una vacuna comercial en pollos contra la coccidiosis. *Técnica Pecuaria en México*, *41*(3), 317-327.

Bautista-Garfias, C. R., Gomez, M. B., Aguilar, B. R., Ixta, O., Martínez, F., & Mosqueda, J. (2005). The treatment of mice with Lactobacillus casei induces protection against Babesia microti infection. *Parasitology Research*, *97*, 472-477.

Bautista, C. R., Alvarez, J. A., Mosqueda, J. J., Falcon, A., Ramos, J. A., Rojas, C., & Ku, M. (2008). Enhancement of the mexican bovine babesiosis vaccine efficacy by using Lactobacillus casei. *Annals of the New York Academy of Sciences*, *1149*(1), 126-130.

Bautista Garfias, C.R. (2011). Importancia de los linfocitos TCD en la respuesta inmunitaria de los bovinos. *Veterinaria México, 42,* 65-75.

Bautista-Garfias, C. R., Lozano, A. R., Martínez, C. R., Martínez, J. A. Á., Millán, J. V. F., García, G. R. R., & Aguilar-Figueroa, B. R. (2015). Co-immunization of cattle with a vaccine against babesiosis and Lactobacillus casei increases specific IgG1 levels to Babesia bovis and B. bigemina. *Parasitology International*, *64*(5), 319-323.

Bautista-Garfias, C. R., & Rodríguez-Lozano, A. Lactobacillus casei Stimulates in vitro Production of CCL2, Interleukin-12 and Gamma Interferon in Bovine Monocytes. *Complementary and Alternative Medicine: Non–Conventional*, 52-58. https://doi.org/10.47278/book.CAM/2024.158

Bishop, J. V., Mejia, J. S., De Leon, A. A. P., Tabachnick, W. J., & Titus, R. G. (2006). Salivary gland extracts of Culicoides sonorensis inhibit murine lymphocyte proliferation and no production by macrophages. *The American Journal of Tropical Medicine and Hygiene*, *75*(3), 532.

Bautista-Garfias, C. R., Castañeda-Ramírez, G. S., Estrada-Reyes, Z. M., Soares, F. E. D. F., Ventura-Cordero, J., González-Pech, P. G., ... & Aguilar-Marcelino, L. (2022). A review of the impact of climate change on the epidemiology of gastrointestinal nematode infections in small ruminants and wildlife in tropical conditions. *Pathogens*, *11*(2), 148.

Boehm, T. (2012). Evolution of vertebrate immunity. *Current Biology*, *22*(17), R722-R732.

Buchmann, K. (2014). Evolution of innate immunity: clues from invertebrates via fish to mammals. *Frontiers in Immunology*, *5*, 459.

Martins, Y. C., Ribeiro-Gomes, F. L., & Daniel-Ribeiro, C. T. (2023). A short history of innate immunity. *Memórias do Instituto Oswaldo Cruz*, *118*, e230023.

Chulanetra, M., & Chaicumpa, W. (2021). Revisiting the mechanisms of immune evasion employed by human parasites. *Frontiers in Cellular and Infection Microbiology*, *11*, 702125. DOI: 10.3389/fcimb.2021.702125

Cooper, M. D., & Herrin, B. R. (2010). How did our complex immune system evolve?. *Nature Reviews Immunology*, *10*(1), 2-3.

Daëron, M. (2022). The immune system as a system of relations. *Frontiers in Immunology*, *13*, 984678. doi 10.3389/fimmu.2022.984678.

Dagenais, A., Villalba-Guerrero, C., & Olivier, M. (2023). Trained immunity: A “new” weapon in the fight against infectious diseases. *Frontiers in Immunology*, *14*, 1147476. DOI 10.3389/fimmu.2023.1147476.

Dawkins, M. S. (2019). Animal welfare as preventative medicine. *Animal Welfare, 28*(2), 137-141.

Deng, J., Gold, D., LoVerde, P. T., & Fishelson, Z. (2003). Inhibition of the complement membrane attack complex by Schistosoma mansoni paramyosin. *Infection and Immunity*, *71*(11), 6402-6410.

Deng, J., Gold, D., LoVerde, P. T., & Fishelson, Z. (2007). Mapping of the complement C9 binding domain in paramyosin of the blood fluke Schistosoma mansoni. *International Journal for Parasitology*, *37*(1), 67-75.

Dhillon, B. K., Smith, M., Baghela, A., Lee, A. H., & Hancock, R. E. (2020). Systems biology approaches to understanding the human immune system. *Frontiers in Immunology*, *11*, 1683. doi: 10.3389/fimmu.2020.01683

Djokic, V., Rocha, S. C., & Parveen, N. (2021). Lessons learned for pathogenesis, immunology, and disease of erythrocytic parasites: Plasmodium and Babesia. *Frontiers in Cellular and Infection Microbiology*, *11*, 685239. https://doi.org/10.3389/fcimb.2021.685239

Dobbelaere, D. A., Fernandez, P. C., & Heussler, V. T. (2000). Theileria parva: Taking control of host cell proliferation and survival mechanisms: Microreview. *Cellular Microbiology*, *2*(2), 91-99.

Donald, K., & Finlay, B. B. (2023). Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease. *Nature Reviews Immunology*, *23*(11), 735-748.

Düpjan, S., & Dawkins, M. S. (2022). Animal welfare and resistance to disease: interaction of affective states and the immune system. *Frontiers in Veterinary Science*, *9*, 929805.doi: 10.3389/fvets.2022.929805

Elliott, S. R., Spurck, T. P., Dodin, J. M., Maier, A. G., Voss, T. S., Yosaatmadja, F., & Brown, G. V. (2007). Inhibition of dendritic cell maturation by malaria is dose dependent and does not require Plasmodium falciparum erythrocyte membrane protein 1. *Infection and Immunity*, *75*(7), 3621-3632.

Flajnik, M. F., & Kasahara, M. (2010). Origin and evolution of the adaptive immune system: genetic events and selective pressures. *Nature Reviews Genetics*, *11*(1), 47-59. doi: 10.1038/nrg2703

Geckin, B., Föhse, F. K., Domínguez-Andrés, J., & Netea, M. G. (2022). Trained immunity: implications for vaccination. *Current Opinion in Immunology*, *77*, 102190. doi.org/10.1016/j.coi.2022.102190.

Geuking, M. B., Köller, Y., Rupp, S., & McCoy, K. D. (2014). The interplay between the gut microbiota and the immune system. *Gut*

Microbes, *5*(3), 411-418.
Graham, A. L., Schrom, E. C., & Metcalf, C. J. E. (2022). The evolution of powerful yet perilous immune systems. *Trends in Immunology*, *43*(2), 117-131., https://doi.org/10.1016/j.it.2021.12.002
Hanna, R. E. B. (1980). Fasciola hepatica: an immunofluorescent study of antigenic changes in the tegument during development in the rat and the sheep. *Experimental Parasitology*, *50*(2), 155-170. doi.org/10.1016/0014-4894 (80)90017-X
Iwasaki, A., & Medzhitov, R. (2015). Control of adaptive immunity by the innate immune system. *Nature Immunology*, *16*(4), 343-353.
Janeway Jr, C. A., & Medzhitov, R. (2002). Innate immune recognition. *Annual Review of Immunology*, *20*(1), 197-216.
Langman, R. E. (2000). The specificity of immunological reactions. *Molecular Immunology*, *37*(10), 555-561.
Lekki-Jóźwiak, J., & Bąska, P. (2023). The roles of various immune cell populations in immune response against helminths. *International Journal of Molecular Sciences*, *25*(1), 420. doi.org/10.3390/ijms25010420
Lewis, D. H., & Peters, W. (1977). The resistance of intracellular Leishmania parasites to digestion by lysosomal enzymes. *Annals of Tropical Medicine & Parasitology*, *71*(3), 295-312.
Lima, T. S., & Lodoen, M. B. (2019). Mechanisms of human innate immune evasion by Toxoplasma gondii. *Frontiers in Cellular and Infection Microbiology*, *9*, 103. https://doi.org/10.3389/fcimb.2019.00103
Litman, G. W., Cannon, J. P., & Dishaw, L. J. (2005). Reconstructing immune phylogeny: new perspectives. *Nature Reviews Immunology*, *5*(11), 866-879.
Luo, L., Jansen, C. A., Bolhuis, J. E., Arts, J. A., Kemp, B., & Parmentier, H. K. (2020). Early and later life environmental enrichment affect specific antibody responses and blood leukocyte subpopulations in pigs. *Physiology & Behavior*, *217*, 112799. doi: 10.1016/j.physbeh.2020.112799
Lynn, D. J., Winsor, G. L., Chan, C., Richard, N., Laird, M. R., Barsky, A., & Brinkman, F. S. (2008). InnateDB: facilitating systems-level analyses of the mammalian innate immune response. *Molecular Systems Biology*, *4*(1), 218. doi:10.1038/msb.2008.55
Martins, Y. C., Ribeiro-Gomes, F. L., & Daniel-Ribeiro, C. T. (2023). A short history of innate immunity. *Memórias do Instituto Oswaldo Cruz*, *118*, e230023. doi: 10.1590/0074-02760230023
Peters, C. P., Mjösberg, J. M., Bernink, J. H., & Spits, H. (2016). Innate lymphoid cells in inflammatory bowel diseases. *Immunology Letters*, *172*, 124-131. www.nature.com/posters/ilcs/index.htm
Moll, K., Palmkvist, M., Ch'ng, J., Kiwuwa, M. S., & Wahlgren, M. (2015). Evasion of immunity to Plasmodium falciparum: rosettes of blood group A impair recognition of PfEMP1. *PLoS One*, *10*(12), e0145120.doi: 10.1371/ journal.pone.0149765
Munteanu, C., & Schwartz, B. (2022). The relationship between nutrition and the immune system. *Frontiers in Nutrition*, *9*, 1082500. doi.org/10.3389/fnut.2022.1082500
Netea, M. G., Joosten, L. A., Latz, E., Mills, K. H., Natoli, G., Stunnenberg, H. G., & Xavier, R. J. (2016). Trained immunity: a program of innate immune memory in health and disease. *Science*, *352*(6284), aaf1098. doi. org/10.1126/ science.aaf1098
Netea, M. G., Schlitzer, A., Placek, K., Joosten, L. A., & Schultze, J. L. (2019). Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. *Cell Host & Microbe*, *25*(1), 13-26. doi.org/10.1016/j.chom.2018.12.006
Nussenzweig, R. S. (1982). Parasitic disease as a cause of immunosuppression. *New England Journal of Medicine*, *306*(7), 423-424.
Pays, E., Vanhamme, L., & Pérez-Morga, D. (2004). Antigenic variation in Trypanosoma brucei: facts, challenges and mysteries. *Current Opinion in Microbiology*, *7*(4), 369-374.
Portes, J., Barrias, E., Travassos, R., Attias, M., & de Souza, W. (2020). Toxoplasma gondii mechanisms of entry into host cells. *Frontiers in Cellular and Infection Microbiology*, *10*, 294. doi.org/10.3389/fcimb.2020.00294
Prowse, R. K., Chaplin, P., Robinson, H. C., & Spithill, T. W. (2002). Fasciola hepatica cathepsin L suppresses sheep lymphocyte proliferation in vitro and modulates surface CD4 expression on human and ovine T cells. *Parasite Immunology*, *24*(2), 57-66.
Rankin, L. C., & Artis, D. (2018). Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. *Cell*, *173*(3), 554-567. doi.org/10.1016/j.cell.2018.03.013
Rashidi, S., Mansouri, R., Ali-Hassanzadeh, M., Muro, A., Nguewa, P., & Manzano-Román, R. (2022). The defensive interactions of prominent infectious protozoan parasites: the host's complement system. *Biomolecules*, *12*(11), 1564. doi.org/10.3390/biom12111564
Rico, G., Leandro, E., Rojas, S., Giménez, J. A., & Kretschmer, R. R. (2003). The monocyte locomotion inhibitory factor produced by Entamoeba histolytica inhibits induced nitric oxide production in human leukocytes. *Parasitology Research*, *90*, 264-267.
Semnani, R. T., Sabzevari, H., Iyer, R., & Nutman, T. B. (2001). Filarial antigens impair the function of human dendritic cells during differentiation. *Infection and immunity*, *69*(9), 5813-5822. doi: 10.1128/IAI.69.9.5813-5822.2001
Silverstein, A. M. (1979). History of immunology. *Journal of Cellular Immunology*, *42*, 1-2.
Tenaglia, A. H., Luján, L. A., Ríos, D. N., Molina, C. R., Midlej, V., Iribarren, P. A., & Luján, H. D. (2023). Antibodies to variable surface antigens induce antigenic variation in the intestinal parasite Giardia lamblia. *Nature Communications*, *14*(1), 2537. doi.org/10.1038/s41467-023-38317-8
Tezuka, H., Imai, S., Muto, R., Furuhashi, Y., & Fujita, K. (2002). Recombinant Dirofilaria immitis polyprotein that stimulates murine B cells to produce nonspecific polyclonal immunoglobulin E antibody. *Infection and Immunity*, *70*(3), 1235-1244. doi.org/10.1128/iai.70.3.1235-1244.2002
Ullah, H., Arbab, S., Tian, Y., Chen, Y., Liu, C. Q., Li, Q., & Li, K. (2024). Crosstalk between gut microbiota and host immune system and its response to traumatic injury. *Frontiers in Immunology*, *15*, 1413485. doi.org/10.3389/fimmu.2024.1413485
Vuscan, P., Kischkel, B., Joosten, L. A., & Netea, M. G. (2024). Trained immunity: General and emerging concepts. *Immunological Reviews*, *323*(1), 164-185. doi: 10.1111/imr.13326
Wang, J., Tang, B., You, X., Cai, X., Jia, W., Liu, X., & Ding, J. (2023). Trichinella spiralis excretory/secretory products from adult worms inhibit

NETosis and regulate the production of cytokines from neutrophils. *Parasites & Vectors*, *16*(1), 374. doi.org/10.1186/s13071-023-05979-8

Wensveen, F. M., Šestan, M., Turk Wensveen, T., & Polić, B. (2019). 'Beauty and the beast'in infection: How immune–endocrine interactions regulate systemic metabolism in the context of infection. *European Journal of Immunology*, *49*(7), 982-995.

Wiedemann, M., & Voehringer, D. (2020). Immunomodulation and immune escape strategies of gastrointestinal helminths and schistosomes. *Frontiers in Immunology*, *11*, 572865. doi.org/10.3389/fimmu.2020.572865

Wu, Z., Sofronic-Milosavljevic, L., Nagano, I., & Takahashi, Y. (2008). Trichinella spiralis: nurse cell formation with emphasis on analogy to muscle cell repair. *Parasites & Vectors*, *1*, 1-14. doi: 10.1186/1756-3305-1-27

Wykes, M. N., Liu, X. Q., Beattie, L., Stanisic, D. I., Stacey, K. J., Smyth, M. J., & Good, M. F. (2007). Plasmodium strain determines dendritic cell function essential for survival from malaria. *PLoS Pathogens*, *3*(7), e96. doi: 10.1371/ journal.ppat.0030096

Yang, W., Jannatun, N., Zeng, Y., Liu, T., Zhang, G., Chen, C., & Li, Y. (2022). Impacts of microplastics on immunity. *Frontiers in Toxicology*, *4*, 956885. DOI 10.3389/ftox.2022.956885

YooYoo, J. Y., Groer, M., Dutra, S. V. O., Sarkar, A., & McSkimming, D. I. (2020). Gut microbiota and immune system interactions. *Microorganisms*, *8*(10), 1587. doi:10.3390/microorganisms8101587

Zefferino, R., Di Gioia, S., & Conese, M. (2021). Molecular links between endocrine, nervous and immune system during chronic stress. *Brain and Behavior*, *11*(2), e01960. doi: 10.1002/brb3.1960.

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell Research*, *30*(6), 492-506.

Zinkernagel, R. M., Bachmann, M. F., Kündig, T. M., Oehen, S., Pirchet, H., & Hengartner, H. (1996). On immunological memory. *Annual Review of Immunology*, *14*(1), 333-367.

Ziogas, A., & Netea, M. G. (2022). Trained immunity-related vaccines: innate immune memory and heterologous protection against infections. *Trends in Molecular Medicine*, *28*(6), 497-512.