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Review Article

Study the Immune System, Emphasizing Immunological Memory, Neuroimmunology, Immunological Placebo Effect, and Therapeutic Updates of the Immune System

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Abstract

When foreign substances enter our body, such as infectious microorganisms, macromolecules, and others, a collective and organized response from our body occurs to resolve this situation. Many studies of the immune response have already been conducted by scientists, but there are many other mechanisms to be understood due to the complexity of the immune system. Therefore, the great challenge of multidisciplinary studies is to understand and manage the immune system. In this study, a systematic review of the literature was conducted to investigate the neuroimmunology, placebo effect, and emotional illness related to the immunological system. The research included an analysis of experimental studies and reviews that discuss new diagnostic techniques and therapies in the management of these conditions. Recognized databases such as PubMed, Medline, SciELO, and Google Scholar were used for data collection. This methodological approach allowed the compilation and analysis of quality and relevant scientific literature, ensuring a broad and updated view of emerging practices in the immune system.

Keywords: Antibody, Ag, B Lymphocyte, T Lymphocyte, Leukocytes, Lymphatic System.

1. INTRODUCTION

1.1. Immune response

Primary nonspecific defense mechanisms consist of the first, more external line, formed by the skin and mucous membranes of the respiratory, digestive, and urogenital systems, where this line of defense does not distinguish the infectious agent. Suppose the microorganism passes through this first barrier. In that case, it will face the second, more internal, nonspecific line of defense, where chemical substances and cells specialized in removing antigens (Ags) come into action (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024).

The skin, corneas, and mucosa of the respiratory, gastrointestinal, and genitourinary tracts create physical barriers, forming the body's first line of defense (Figure 1) (Lima *et al.,* 2011; Lima, 2013).

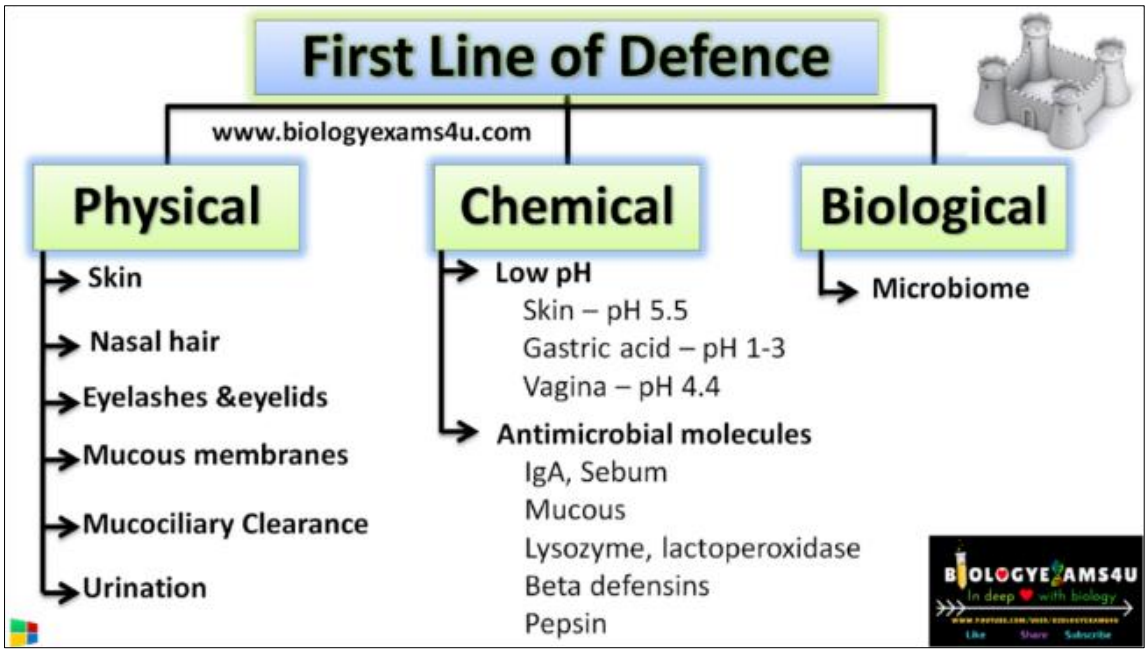


Figure 1: First line defence, physical, chemical, and biological

Sources: Biology Exams 4U and https://www.biologyexams4u.com/2021/06/what-is-first-line-of-defence-in-immune.html

The secondary immune response differs from the primary response due to the production of antibodies with a higher affinity than the antibodies produced in the primary response. The secondary response initially produces antibody (Ac) IgM in small quantities, IgG (Ac) in larger IgA (Ac) and IgE (Ac). These antibodies are produced by memory B cells. The specific defense mechanisms, which constitute the third line of defense, act to provide ideal conditions for the immune response to occur effectively and for the infectious agent to be removed. Lymphoid organs such as the thymus, spleen, tonsils, and lymph nodes that form the well-known immune system are part of this mechanism (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Shan et *al.,* 2018; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

1.2. Breach of anatomical barriers can trigger 2 types of immune response

1. Innate immunity, or adaptive:

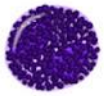
Does not require prior exposure to an Ag, i.e., immunological memory, to be fully effective. Thus, it responds immediately to an Ag. invader. Innate immunity uses Pattern Recognition Receptors (PRRs) to detect foreign Pathogen-Associated Molecular Patterns (PAMPs) and host Damage-Associated Molecular Patterns (PMADs). The anti-infectious response of innate immunity involves elements such as proteins, complement system proteins, and cytokines, monocytes, macrophages, granulocytes, Natural Killer Cells (NK), lymphocytes, and dendritic cells (Shan et *al.,* 2018; Abbas *et al.,* 2023; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

A key component of innate immunity is the complement system, a group of proteins that activate in a cascade to mark pathogens, facilitate their destruction, and promote inflammation. Inflammation, although often associated with pain and redness, is an essential mechanism for recruiting immune cells to the site of infection and isolating the affected area (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Abbas *et al.,* 2023).

2. Acquired immunity, or specific:

Adaptive immunity requires prior exposure to an Ag to be fully effective and takes time to develop after the first contact with a new invader. The response is then rapid. The system remembers previous exposures and is Ag-specific. Specificity is exerted through antibodies humoral immunity) and cells programmed to combat specific Ags, cellular immunity. Components include B and T lymphocytes (Table 1) (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

Table 1: Characteristics and functions of leukocytes

Subtype	Nucleus	Function	Example
Neutrophil	Multi-Lobed	Bacterial or fungal infection. These are the most common first responders to microbial infection.	
Eosinophil	Bi-Lobed	Parasitic infections and allergic reactions (inflammatory).	
Basophil	Bi/Tri-Lobed	Allergic and antigen response (releases histamine causing vasodilation).	
Lymphocyte	Deep Staining, Eccentric	Include B cells, CD4+ helper T cells, and CD8+ cytotoxic T cells. Operate primarily in the lymphatic system.	
Monocyte	Kidney Shaped	Phagocytosis of pathogens. Presentation of antigens to T cells. Eventually, they become tissue macrophages, which remove dead cell debris and attack microorganisms.	

Sources: Simple theme. Theme images by luoman. Powered by Blogger and https://kakistudy.blogspot.com/2018/02/

B and T lymphocytes mature within primary lymphoid tissues. B lymphocytes mature in the bone marrow and T lymphocytes in the thymus. Mature B and T cells subsequently work together to destroy invaders. Tissue Ag-presenting cells present Ag to most types of lymphocytes. B lymphocytes represent 5%-10% of the lymphocytes in the blood and are coated with Ag receptor molecules. When stimulated by an Ag, they differentiate into plasma cells and begin to produce antibodies. In addition to producing antibodies, B cells are also responsible for presenting Ags to T cells. Some activated B lymphocytes do not differentiate into plasma cells, giving rise to immune memory B cells that react rapidly to a second exposure to the same Ag (Figure 2) (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Abbas *et al.,* 2023; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

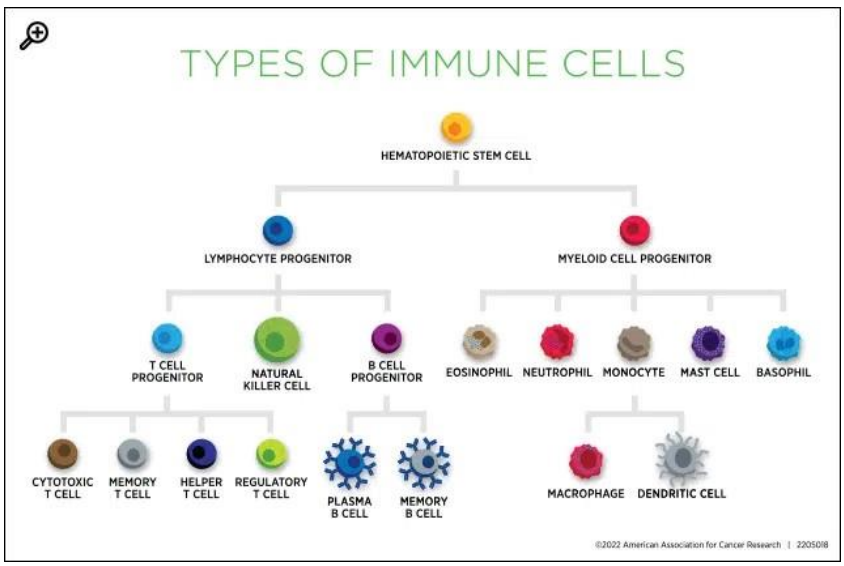


Figure 2: NK cells are lymphocytes, like the B and T cells commonly manipulated by immunotherapy. Unlike B and T cells, which are part of the adaptive immune system, Natural Killer Cells (NK) are part of the innate immune system

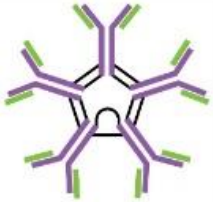
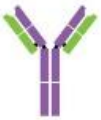
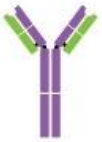
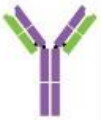
Sources: @2022 American Association for Cancer Research, Annual Meeting 2022: Natural Killer Cells and the Antitumor Immune Response https://www.aacr.org/blog/2022/06/07/annual-meeting-2022-natural-killer-cells-and-the-antitumor-immune-response/

1.3. B lymphocyte

1. Primary immune response

The response is slow and initially provides limited immune protection. The first encounter of mature naïve cells with Ag causes them to transform into lymphoblasts, undergo clonal proliferation, and differentiate into Memory Cells (Th), which will have the capacity to respond to the same Ag or into antibody-secreting plasma cells. After the first exposure, a latent period of days until antibodies are produced. Initially, only IgM is created with the help of T cells; B cells produce IgG, IgA, or IgE (Table 2) (Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Shan *et al.,* 2018; Kierszenbaum, 2019; Abbas *et al.,* 2023; Delves, 2024; Mandell, 2024).

Table 2: The Adaptive Immune Response: B-lymphocytes and Antibodies: Antibody classification, function, and structure

The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

Sources: Mavink.com and https://mavink.com/go.php?id=:fcgguZNyzgu.85564z/fgargabp/xbbo-lzbgnan/zbp.mgnupfyvuc//

2. Secondary immune response

The immune response is faster and more effective. This occurs when memory B and Th cells are re-exposed to the Ag; memory B cells proliferate rapidly and differentiate into mature plasma cells, large amount of antibody. The antibody is released into the blood and other tissues, where it can react with the Ag (Figure 3) (Carvalho and Buzato, 2005; Junqueira and Carneiro, 2023; OpenStax, 2025).

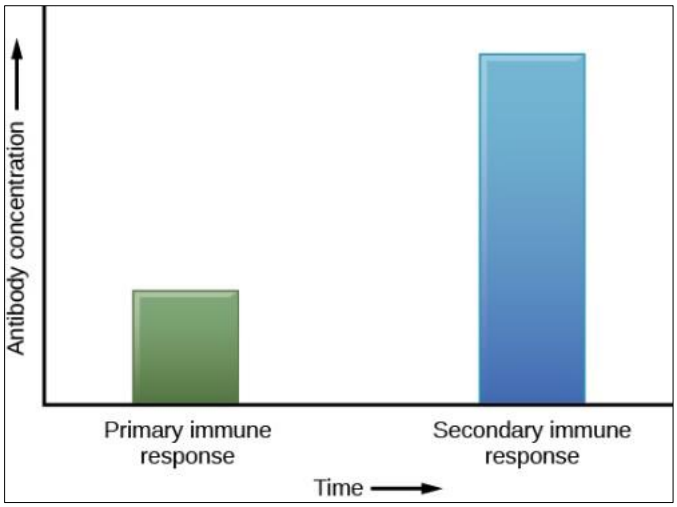


Figure 3: In the primary response to infection, antibodies are first secreted from plasma cells. Upon re-exposure to the same pathogen, memory cells differentiate into antibody-secreting plasma cells that produce increased amounts of antibody for a longer period
Source: OpenStax, 2025 (With permission)

1.4. T lymphocyte

T lymphocytes represent 65%-75% of blood lymphocytes and, like B lymphocytes, also originate from stem cells found in the bone marrow. However, before they migrate to the thymus, they complete their cellular differentiation process. In the thymus, T lymphocytes differentiate into different subpopulations: T-helper, T-suppressor, T-cytotoxic, and NK. T helper lymphocytes stimulate the transformation of B lymphocytes into plasma cells (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

There are two main types of T cells: Cooperating Th and Cytotoxic T Cells (CTLs). T helper lymphocytes function indirectly to inform other immune cells about possible pathogens. Th recognizes specific Major Histocompatibility Complex (MHC) class II Anaphase-Promoting Complex (APC). There are two populations of Th cells: Th1 and Th2. Th1 cells secrete cytokines to enhance the activities of macrophages and other T cells. Th2 cells stimulate B cells without prior treatment with antibodies (OpenStax, 2025). Whether a Th1 or Th2 immune response develops depends on the specific types of cytokines secreted by the cells of the innate immune system, which in turn depends on the nature of the invading pathogen (Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Mandell, 2024).

CTLs are the key component of the cell-mediated part of the adaptive immune system and attack and destroy infected cells. T cells protect against viral infections. This is due to the viruses replicating within cells, where they are protected from extracellular contact with circulating antibodies. Once activated, the T cell creates a large clone of cells with a specific set of cell surface receptors, and the activated B cells. Just like with B cells, the clone includes active T cells and inactive memory T cells. The resulting active T cells then identify infected host cells. Due to the time required to generate a population of clonal T and B cells, there is a delay in the adaptive immune response compared to the innate immune response (Ayres, 2017; Kierszenbaum, 2019; Abbas *et al.,* 2023; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

CTLs attempt to identify and destroy infected cells before the pathogen can replicate and escape, thereby halting the progression of intracellular infections. TC cells also support NK lymphocytes to destroy early cancers. The cytokines secreted by the TH1 response that stimulate macrophages also stimulate CTLs and enhance their ability to identify and destroy infected cells and tumors. B plasma cells and CTLs are collectively called effector cells because they are involved in provoking the immune response to kill pathogens and infected host cells (Figure 4) (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Abbas *et al.,* 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

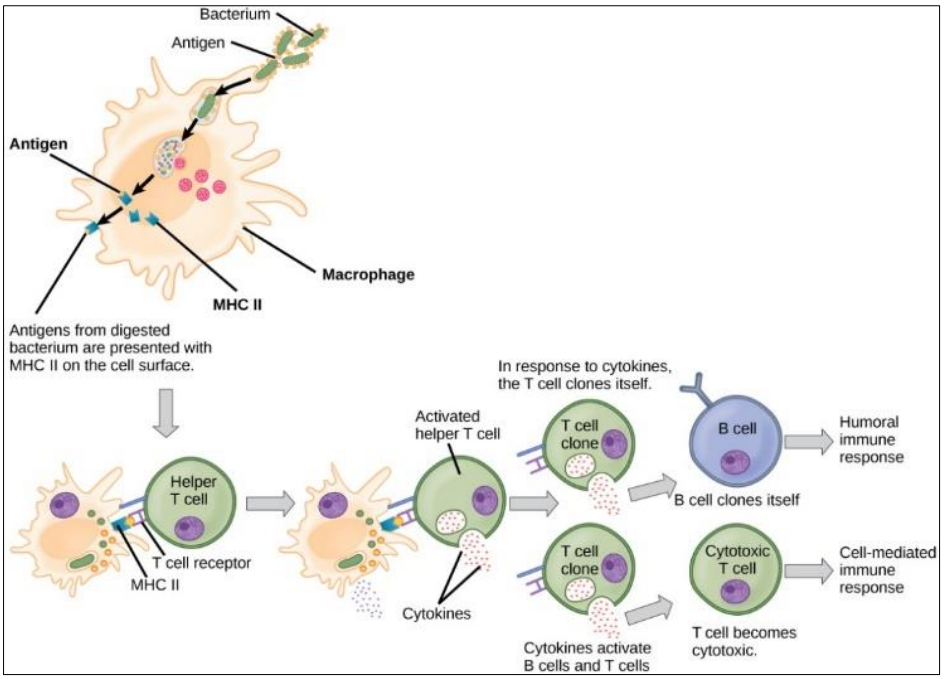


Figure 4: A helper T cell is activated by binding to an Ag presented by an Anaphase-Promoting Complex/Cyclosome (APC/C) through the Major Histocompatibility Complex (MHC) II Ags presented by MHC class II complexes of APC receptor, causing it to release cytokines. Depending on the cytokines released, the humoral or cell-mediated immune response is activated

Source: OpenStax, 2025 (With permission)

1.5. The maturity of a B or T cell

Implies becoming immunocompetent, which means that it can recognize, by union, a molecule or a specific Ag. During the maturation process, B and T cells that bind too tightly to the body's cells are eliminated to minimize an immune response against the body's tissues. Some cells react weakly to the body's cells, but they have receptors on their cell surfaces that allow them to recognize (Abbas *et al.,* 2023; Delves, 2024). This process occurs during fetal development and continues throughout life. Thus, it is genetics and not experience that initially provides a wide range of cells, each capable of uniting with a different specific foreign molecule (Junqueira and Carneiro, 2023; Mandell, 2024).

1.6. They Present Two Types of Responses

1. Humoral immunity: is derived from the responses of B lymphocytes that transform into plasma cells, which secrete specific antibodies against soluble Ags (Figure 5) (Junqueira and Carneiro, 2023; Delves, 2024).

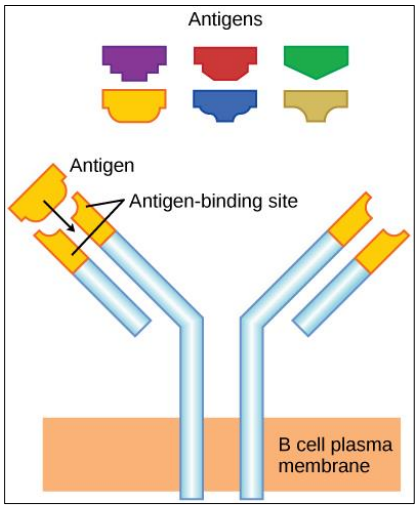


Figure 5: B cell receptors are embedded in the membranes of B cells and bind a variety of Ags through their variable regions

Source: OpenStax, 2025 (With permission)

Each B cell has only one type of Ag receptor, which makes it unique. When a B cell encounters an Ag that binds to its receptor, the Ag molecule is endocytosed on the cell surface bound to a class II MHC molecule. When this process is complete, the B cell is sensitized. In most cases, the sensitized B cell then needs to encounter a specific type of T cell, called a helper T cell or CD4+, before it can be activated (Ayres, 2017; Kierszenbaum, 2019; Mandell, 2024; OpenStax, 2025).

The helper T cell binds to the Ag-MHC class II complex and is induced to release cytokines that prompt the B cell to divide rapidly, producing thousands of identical cells. These daughter cells are plasma cells and memory B cells. Memory B cells remain dormant at this point until a subsequent encounter with an Ag, triggered by reinfection with the same bacteria or virus, results in their division into a new population of plasma cells (Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

Plasma cells, on the other hand, produce and secrete large quantities of antibody molecules. An antibody, also known as an immunoglobulin, is a protein produced by plasma cells after stimulation by an Ag. Antibodies occur in blood, gastric and mucous secretions, and breast milk. Antibodies in these body fluids can bind to pathogens and mark them for destruction by phagocytes before they can infect cells (Ayres, 2017; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

Antibodies coat extracellular pathogens and neutralize them by blocking key sites on the pathogen that enhance their infectivity, such as receptors that attach pathogens to host cells. Neutralizing antibodies can prevent pathogens from entering and infecting host cells. Neutralized pathogens coated with antibodies can be filtered out by the spleen and eliminated in urine or feces. Antibodies also mark pathogens for destruction by phagocytic cells, such as macrophages or neutrophils, in a process called opsonization. In a process called complement fixation, some antibodies provide a site for the binding of complement proteins. The combination of antibodies and complement promotes rapid elimination of the pathogens (Figure 6) (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

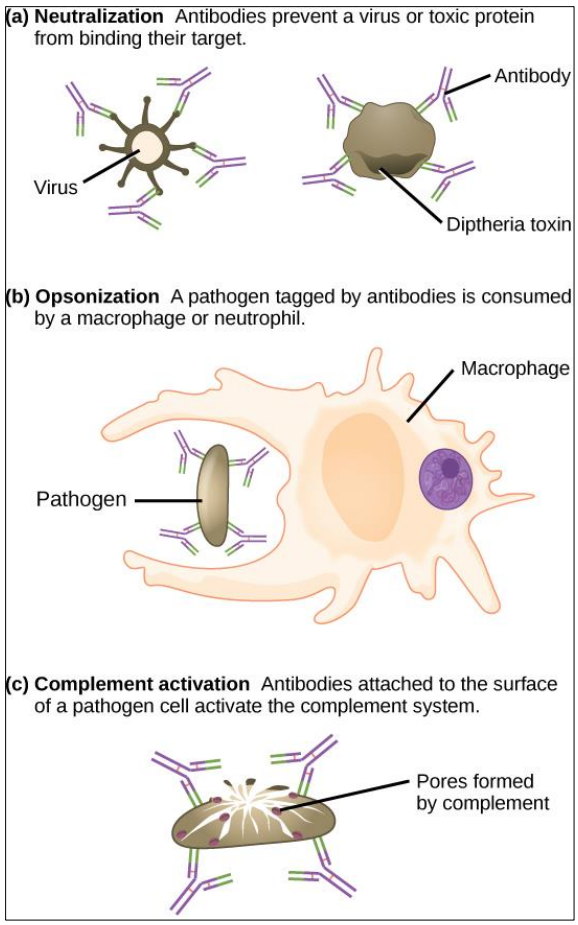


Figure 6: Antibodies can inhibit infection by (a) preventing the Ag from binding to its target, (b) marking a pathogen for destruction by macrophages or neutrophils, or (c) activating the complement cascade
Source: OpenStax, 2025 (With permission)

2. Cell-mediated immunity:

It is derived from certain responses by T lymphocytes**,** neutrophils, monocytes, macrophages, polymorphonuclear leukocytes, eosinophils, basophils, and innate lymphoid cells such as natural killer cells (Delves, 2024; OpenStax, 2025).

Lymphocytes are a type of leukocyte, or white blood cell, responsible for defending the body. In this process, CD8+ T lymphocytes are activated first, followed by the cellular immune response mediated by CD4+ T lymphocytes. This activation stimulates B lymphocytes, leading to the humoral immune response through antibody production. T lymphocytes also help enhance the function of macrophages and neutrophils, enabling them to phagocytize bacteria more effectively. Antibodies serve as a bridge between the Ag and neutrophils or macrophages. Neutrophils complete the immune response by phagocytizing any remaining cells. They have a surface receptor called the T Cell Receptor (TCR) that binds to Ags (Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Abbas *et al.,* 2023; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

Most T cells (alpha-beta TCRs) recognize the peptide of Ags (Ags) displayed together with the MHC of an MCT. T cells with gamma-delta TCRs recognize protein Ags directly or recognize lipid Ags presented by an MHC molecule called CD1 (Carvalho and Buzato, 2005; Delves, 2024; OpenStax, 2025).

Pattern Recognition Receptors (PRRs) recognize common microbial Pathogen-Associated Molecular Patterns (PAMPs) such as Gram-negative lipopolysaccharides, Gram-positive peptidoglycans, bacterial flagellin, unmethylated Cytosine-Guanosine Dinucleotides (CpG motifs), and double-stranded viral RNA. These receptors can also recognize molecules, PMADs, that are produced by stressed or infected human cells. Activation can also occur when Ag-antibody and complement-microbe complexes bind to surface receptors on the Fc or IgG region (Fc-gamma R) and Complement Component (C3b) and Complement Effector Protein (iC3b1) (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

Collaborating T cells cannot respond adequately to an Ag unless it is processed and embedded in an MHC class II molecule. The APC expresses MHC class II on its surfaces, and when it combines with a foreign Ag, it forms a complex to signal an invader (Figure 7) (Abbas *et al.,* 2023; Delves, 2024; Mandell, 2024; OpenStax, 2025).

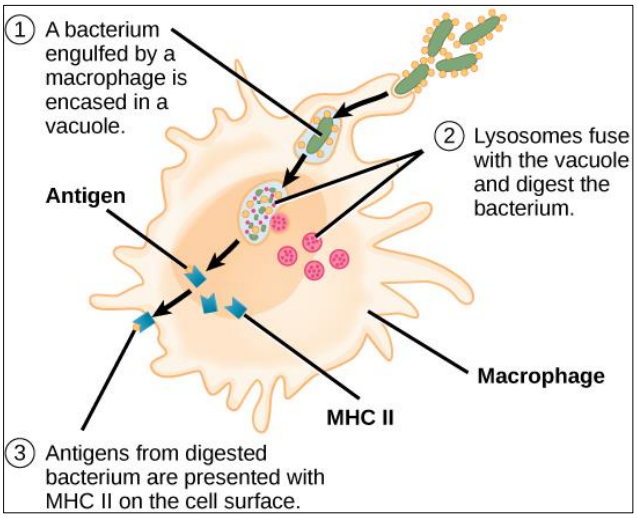


Figure 7: An Ag-Presenting Cell (APC), such as a macrophage, envelops an extraneous Ag, digests it partially in a lysosome, and embeds it in an MHC class II molecule for its presentation on the cell surface. Adaptive immune response lymphocytes must interact with MHC class II molecules embedded in the Ag to mature into functional immune cells

Source: OpenStax, 2025 (With permission)

Unless the Ag is rapidly phagocytosed and entirely degraded, which is an uncommon event, the acquired immune response occurs through recognition of the Ag by receptors on the surface of B and T cells. Our skin is in constant contact with microorganisms commonly present in the environment. When the epithelial tissue or skin is ruptured, these microorganisms, which may be bacteria, can enter deeper tissues and trigger the immune system. These bacteria, which carry various Ags, pass into the internal tissues through the blood fluid and multiply rapidly. Macrophages, which are resident cells of this tissue, begin to phagocytize these bacteria, then perform $CD4^{+}$, which is the exposure of the Ags that were present in the bacteria to the external membrane of the macrophage (Lima *et al.,* 2011; Ayres, 2017; Kierszenbaum, 2019;

Abbas *et al.,* 2023; Junqueira and Carneiro, 2023; Mandell, 2024; OpenStax, 2025).

Next, neutrophils appear, coming through the bloodstream, and also begin to phagocytize the bacteria, but the neutrophils do not perform Ag presentation. After that, dendritic cells appear, which also phagocytize the bacteria and perform Agic presentation. Soon after, they fall into a lymphatic vessel and are carried to an organ associated with the immune system, the lymph nodes. In this organ, T lymphocytes are activated upon contact with Ags that come with dendritic cells and enter into successive mitoses (Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; OpenStax, 2025).

T lymphocytes are specific cells, so there is a type for each bacterial Ag, remembering that we do not have T lymphocytes that respond to all Ags. Activated and multiplying, T lymphocytes help activate B lymphocytes, releasing cytokines and binding to membrane receptors. After being activated by cytokines, binding to receptors, and by contact with an Ag, B lymphocytes release antibodies, each of which is specific to an Ag (Figure 8) (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Delves, 2024; OpenStax, 2025).

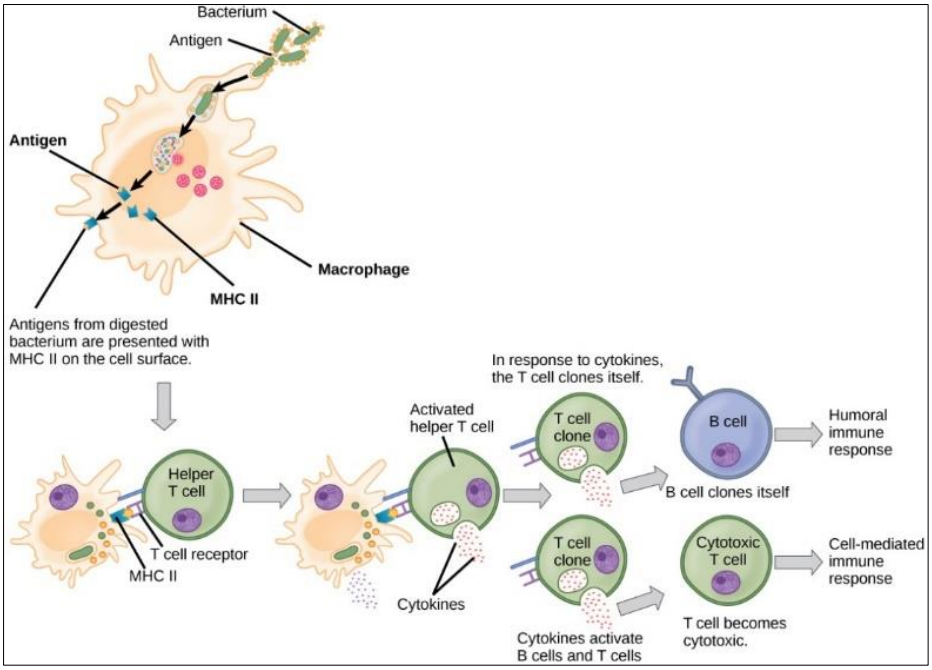


Figure 8: A helper T cell is activated by binding to an Ag presented by an Ag-Presenting Cell (APC) via the Major Histocompatibility Complex (MHC II receptor), causing it to release cytokines. Depending on the cytokines released, this activates either a humoral or cell-mediated immune response
Source: OpenStax, 2025 (With permission)

The proliferating and differentiating into plasma cells, B cells can also differentiate into memory B cells, which are characterized by long life spans. Memory cells circulate in the blood, lymphatic vessels, and tissues and probably do not produce antibodies. However, when exposed to the same Agic stimulus, they begin to differentiate into plasma cells capable of producing antibodies preselected by the specific Ag that stimulated the primary response (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Mandell, 2024).

The developing potentially self-reactive lymphocytes are removed from the repertoire before they mature. Clonal selection occurs in both B lymphocytes and T cells. T cells do not secrete antibodies, but they regulate the B cell response, being preeminent in cell-mediated immune responses (Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024).

1.7. ARTICLES

Article 1: Complement Component (C3) protein: A key component of immunological memory

One of the most important proteins in this team is called C3. When C3 is activated, it splits into two parts: component 3C3a and C3b. C3b has a job; it marks harmful invaders for removal, while C3a helps to stir up the body's inflammatory responses. In infections, C3 levels increase. The body uses C3 to boost its defenses. It's especially important in the lungs, where C3 is low under normal conditions but increases during infections. This local production of C3 helps the body respond to the problem (Earhart *et al.*, 2024).

The scientists performed the experiment using two types of mice: One group had C3 and the other did not. They introduced heat-killed bacteria to both groups to train their immune cells, then challenged them with an immune challenge using a component of *Escherichia coli* (Escherich, 1885) (Enterobacteriales:

Enterobacteriaceae). Then they checked the lungs for markers of inflammation and other signs of immune activity. The mice with C3 showed a stronger immune response compared to those without. Levels of certain signaling molecules, which indicate inflammation, were significantly higher in the C3 group. This suggests that C3 is crucial for an effective immune memory response (Earhart *et al.*, 2024).

The researchers found that macrophages from mice lacking C3 exhibited a weaker response compared to their normal counterparts. This indicates a consistent pattern: C3 appears to play a significant role in enhancing immune training in these cells. When C3 is activated, it produces C3a, which binds to specific receptors known as C3a receptors on immune cells (Earhart *et al.*, 2024).

The researchers successfully blocked these receptors and observed a decrease in the immune response in both normal and C3-deficient cells. This demonstrates the importance of the C3a receptor in the process. The scientists investigated changes in gene expression, specifically what occurs inside cells during immune training. They identified differences in genes related to metabolism in the C3-deficient cells, which are crucial because they affect how these cells produce energy (Earhart *et al.*, 2024).

2. Article on innate immune memory, the missing part of the immunological response

For Pérez-Vázquez *et al.* (2018), the innate and adaptive immune systems can induce subsets of memory cells after immunization; there are certain differences between them:

1. One of the most crucial is that the protection of memory in innate cells does not last as long as that of adaptive cells.
2. The difference is that T and B cells undergo permanent genetic changes by recombination and somatic hypermutation to produce receptors. The adaptations of innate cells depend on epigenetic modifications that are labeled and reversible by cellular mechanisms, such as cell division.
3. Although both adaptive and innate memory cells have an increased response to a secondary challenge, adaptive immune memory cells will only be activated if the same Ag is encountered. In contrast, innate memory cells are capable of responding to diverse Ags after they have been primed.

Pérez-Vázquez *et al.* (2018) concluded in their article that innate immune cells have the unexpected ability to increase their response to immunological re-exposure. This ability is known as trained immunity and resembles adaptive immunological memory; however, it lacks the Ag recognition specificity of lymphocytes.

Trained memory relies on pattern recognition receptors and metabolic changes that lead to long-term modifications predisposing chromatin to express inflammatory cytokines after pathogen re-exposure. This recent evidence highlights a better understanding of the biology of the immune system and how its initial classification of innate and adaptive responses seems simplified and misleading (Pérez-Vázquez *et al.,* 2018)

1.8. NOVAS TERAPIAS

1. Scientists discovered a cell that can treat several types of cancer. Ag experience history directs distinct functional states of CD8+ Terapia cell Car-T cells during the antileukemia response

Scientists from Cardiff University (Wales) have developed a new receptor for a type of immune system cell, called CAR-T. Although it has not been tested in patients, the discovery could be used for universal cancer treatment, revolutionizing current treatments [Research published in the journal Nature Immunology - Doi: doi.org/10.1038/s41590-024-02034-1] (Jornal USP, 2020; DeGolier *et al.,* 2025).

"The discovery of a new receptor for T cells, lymphocytes that attack cancer cells or infections, could increase the chances of immunotherapies that can fight cancer. What is impressive is that it is not just one cancer, but all its forms", [Vanderson Rocha - Hematology and Cell Therapy at the Hospital das Clínicas of the USP School of Medicine, in an interview with Jornal da USP no Ar] (Jornal USP, 2020).

This discovery is due to the fact that this new receptor functions as a separator of cancer cells from normal cells and can probably be used in immunotherapies to attack only cancer cells, sparing normal cells [Vanderson Rocha]. Rocha points out that this discovery is still experimental and that there is still a big step to go before treatment can begin with patients, requiring several studies to conclude that this new receptor can be used in various types of cancer (Jornal USP, 2020).

CAR cells emerged with the idea of "arming" T lymphocytes with receptors to fight cancer. Today, immunotherapies have been tested with CAR cells to treat lymphomas, leukemias, lymphoblastomas, and myelomas, and each has a specific receptor. Studies involving these cells are being carried out at the HC of the USP School of Medicine in São Paulo and Ribeirão Preto. In 2019, a man was treated at USP in Ribeirão Preto and was cured of lymphoma through a therapy that was unprecedented in Latin America (Jornal USP, 2020).

1.9. Future Developments in Immunotherapy

1.9.1. New research in immunotherapy

1. **Combination immunotherapy**: Immunotherapies with other forms of treatment, such as chemotherapy, radiotherapy, and even other immunotherapies, are showing promising results.

These combinations can help overcome resistance to treatment and improve efficacy.

2. **CAR-T cell therapy**: CAR-T cell therapy, which involves genetically modifying a patient's T cells to attack cancer cells, is effective for leukemia and lymphoma.
3. **New cancer vaccines:** Immunotherapy vaccines aim to train the immune system to recognize and attack cancer cells specifically.
4. **Checkpoint inhibitors**: Checkpoint inhibitors are drugs that help the immune system recognize and attack cancer cells.

1.9.2. Promising treatments in development. Emerging immunotherapy treatments are being developed to be even more effective, less invasive, and more affordable:

1. **Immunomodulators:** Substances that alter the body's immune response, potentially making the body's environment less hospitable to cancer.
2. **Oncolytic viral therapy:** Uses modified viruses to infect and destroy cancer cells, while also stimulating an immune response against the cancer.
3. **Biomarkers for immunotherapy:** The development of biomarkers that can predict a patient's response to immunotherapy [Dr. Marcelo Cruz is a physician from UNICAMP, clinical oncologist a clinical oncologist at Grupo Orizonti, a fellow of the Developmental Therapeutics Program, Master in Clinical Research from the Feinberg School of Medicine, Northwestern University, Chicago – USA] (Cruz, 2024).

1.9.3. HIV: The 3 advances that bring more hope for carriers of the virus

HIV attacks the immune system and weakens the defenses against many infections and certain types of cancer that people with stronger immune systems can fight off more easily (Ventas, 2022).

1. More effective and convenient antiretrovirals

This can be combated with Antiretroviral Therapy (ART). This combination of drugs does not cure the infection, but it inhibits the replication of the virus in the body and allows the immune system to strengthen. "What's more, what we've learned in recent years is that effective treatment reduces the risk of transmission by 100%" [BBC News Mund: Ayako Miyashita, California HIV/AIDS Policy Research Centers (CHPRC)] (Ventas, 2022).

2. Successful preventive drugs

Pre-exposure Prophylaxis, better known as PrEP. If the pill is taken daily, PrEP therapy can reduce the chances of contracting the virus that causes AIDS through sex by more than 90% and 70% through the use of unsterilized or shared needles [U.S. Centers for Disease Control and Prevention (CDC)] [Miyashita, co-director of the CHPRC Southern California Center]. Recently, the long-acting injectable PrEP was also approved [Goodman-Meza-American pharmaceutical Gilead Sciences] (Ventas, 2022).

The clinical trial of a prolonged-release injection conducted in South Africa proved to be a great success: it almost eliminated the risk of participants contracting HIV, and it was 88%. Injectable PrEP is the first drug with the new technology that bodes well for HIV prevention in a long time (Ventas, 2022).

3. Research for a vaccine

A clinical trial of three experimental vaccines based on synthetic messenger RNA (mRNA) technology, already used in some vaccines against COVID-19 [Conducted by the US National Institute of Allergy and Infectious Diseases (NIAID)], the clinical trial is still in the first phase [Miyashita] (Ventas, 2022).

4. Immunological therapies in the treatment of inflammatory bowel diseases: Impact of new biological agents in patients with Crohn's disease and ulcerative colitis

In the summary of the vision article by Linhares *et al.,* (2024) on Inflammatory Bowel Diseases (IBD), such as Crohn's Disease (CD) and Ulcerative Colitis (UC), the authors found that these diseases result from an inadequate immune response to microorganisms in the gut microbiota in genetically predisposed individuals. Chronic inflammation is regulated by cytokines, such as Interleukin-23 (IL-23), which activate Th17 helper T cells. Biological therapies, including Tumor Necrosis Factor (TNF) and IL-23 inhibitors, have revolutionized treatment, but many patients still face inadequate responses (Linhares *et al.,* 2024).

Furthermore, emerging approaches, such as extracellular vesicles, demonstrate potential for regulating immunity and the gut microbiota, highlighting new therapeutic avenues. IBDs are characterized by chronic inflammation of the gastrointestinal tract, driven by a dysregulated immune response. Traditional treatments, including corticosteroids and immunosuppressants, have limited long-term efficacy and are associated with significant adverse effects. Newer immune therapies, such as IL-23 and Janus kinase (JAK) inhibitors, display greater efficacy in refractory patients, with fewer side effects (Linhares *et al.,* 2024).

According to the authors, IL-23 plays a crucial role in activating Th17 cells and perpetuating intestinal inflammation. These new therapeutic approaches also have favorable safety profiles compared to traditional therapies (Linhares *et al.,* 2024).

5. Lymphatic System

The lymphatic system is a network of organs, tissues, and lymphoid vessels that are spread throughout the human body, in addition to being part of the immune system. Its main functions are to help defend the body and to filter and remove excess fluids and impurities.

Some diseases can affect this system, most of which are benign, but when a malignant mutation occurs, it is possible for cancers, such as lymphomas, to develop (Figure 9) (OpenStax, 2025).

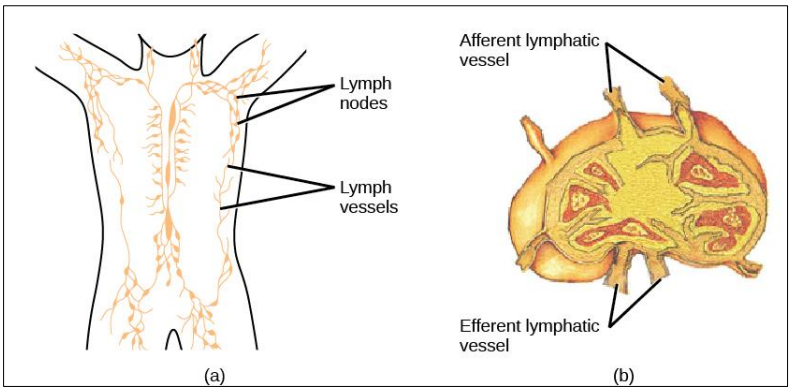


Figure 9: (a) Lymphatic vessels carry a clear fluid called lymph throughout the body. The fluid passes through (b) lymph nodes, which filter the lymph entering the node through afferent vessels and exiting through efferent vessels; the lymph nodes fill with lymphocytes that purge infectious cells
Sources: Credit a: Modification of work by NIH; credit b: Modification of work by NCI, NIH

The immune system is characterized by the circulation of cells throughout the body, and the regulation, maturation, and interaction of immune factors occur at specific sites. The blood circulates immune cells, proteins, and other factors throughout the body. About 0.1% of all blood cells are leukocytes, which include monocytes, the precursors of macrophages, and lymphocytes. The majority of blood cells are red blood cells. Immune system cells can travel between the blood and lymphatic systems, which are separated by the interstitial space, by a process called extravasation through the surrounding tissue, the lymph (Figure 10) (OpenStax, 2025).

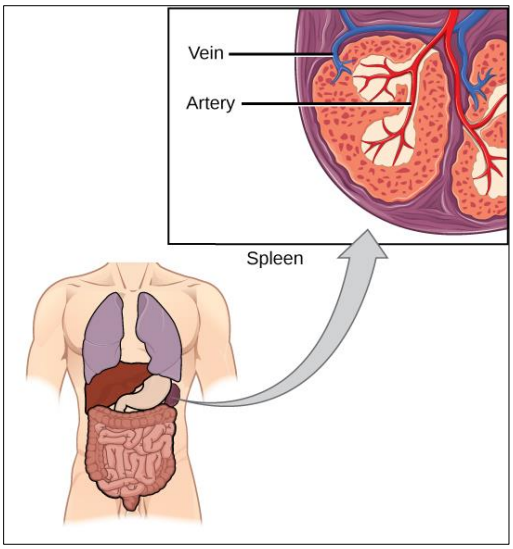


Figure 10: The chest functions to immunologically filter blood and allow communication between cells, corresponding to innate and adaptive immune responses
Source: Credit: modification of work by NCI, NIH

The spleen houses B and T cells, macrophages, dendritic cells, and NK cells. The base is the site of the APC that contains foreign particles trapped in the blood and can communicate with lymphocytes. Antibodies are synthesized and secreted by activated plasma cells. The spleen lymphocytes filter foreign substances and pathogens supplemented with antibodies, from the blood (OpenStax, 2025).

2.0. MUCOSAL-ASSOCIATED IMMUNE TISSUE (MALT)

These are lymphoid tissues associated with the mucosal surfaces of the gastrointestinal tract, respiratory tract, and urogenital tract. They provide an innate immune response: complement, acute phase proteins, phagocytic and NK cells, type II interferons (α and β) with the function of neutralizing agents, destroying cells, cytotoxicity, and protection against viral infections. They

provide a primary defense to the host on the mucosal surface (Figure 11) (Freihorst and Ogra, 2001; Parslow *et al.,* 2001; Immunology Discipline-MED-194, 2018).

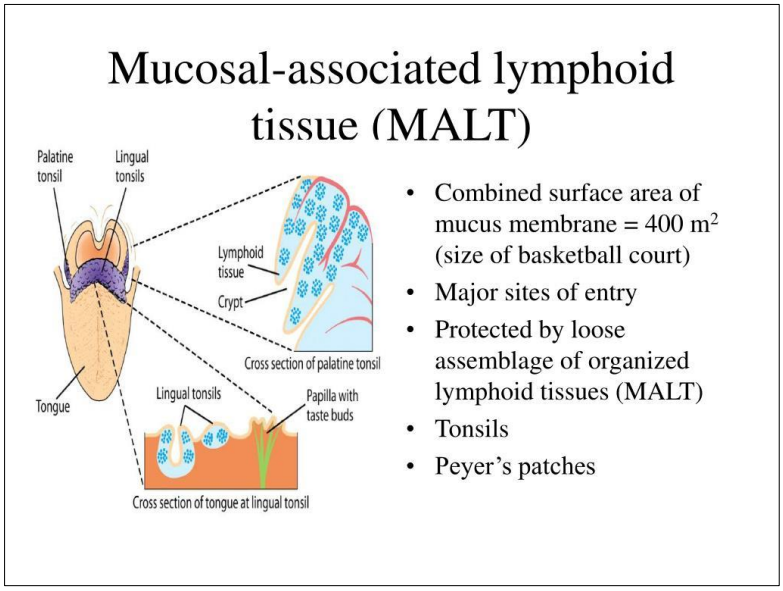


Figure 11: Mucosal-Associated Lymphoid Tissue (MALT) is a crucial component of a functional immune system because mucosal surfaces, such as the nasal fossa, are the first tissue on which inhaled or ingested pathogens are deposited

Source: quizsoethoms.z21.web.core.windows.net

2.1. Types of Tissues

2.1.1. Organized lymphoid tissue/cell types

A. M cells perform transcytosis, transporting materials from the lumen without degrading them to the follicle. They have a certain degree of selectivity and are capable of transporting soluble proteins, inert particles, and various microorganisms (Freihorst and Ogra, 2001; Parslow *et al.,* 2001; Immunology Discipline-MED-194, 2018):

B. Dome Cells are located just below the epithelium. They have MHC class II. They function as APCs, and when they mature, they interact with T cells.

C. Follicular T cells. CD8+ cells are only found in the interfollicular areas. They often display activation markers such as IL-2Rα (CD25).

D. Follicular B cells are abundantly present in follicles, mainly in germinal centers. They mostly present IgA, unlike systemic B cells present IgM and IgD as the primary surface Ig (Freihorst and Ogra, 2001; Parslow *et al.,* 2001; Immunology Discipline-MED-194, 2018).

2.1.2. Diffuse lymphoid tissue

A. **Includes dendritic cells (**APCs), NK cells, and mast cells.

B. **T lymphocytes are of two types**: They contain a T receptor, CD4 or CD8, CD4+ and CD45RO, a memory marker, in response to foreign Ags. A second type of lymphocytes presents unusual, atypical markers such as TCR γ and d and CD8 α, TCR α and β. The receptors of this second class of lymphocytes do not bind to MHC-peptide (class I and II). T cells γ:d have a receptor, NKG2D, that has the function of destroying cells with an abnormal phenotype. MHC molecules bind to two molecules in response to intestinal tissue damage.

C. **lymphocytes** are highly differentiated, existing almost entirely as IgA-secreting plasma cells (IgA1 and IgA2). Functions: Resistance to proteolysis, anti-inflammatory properties, and pro-inflammatory properties (Freihorst and Ogra, 2001; Parslow *et al.,* 2001; Immunology Discipline-MED-194, 2018).

2.2. OBJECTIVE

This manuscript aims to study the immune system, emphasizing immunological memory, neuroimmunology, immunological placebo effect, and therapeutic updates of the immune system.

3.0. METHODS

In this study, a systematic review of the literature was conducted to investigate the neuroimmunology, placebo effect, and emotional illness related to the immunological system. The research included an analysis of experimental studies and reviews that discuss new diagnostic techniques and therapies in the management of these conditions.. The research included an analysis of experimental studies and reviews that discuss new diagnostic techniques and therapies in the management of these conditions. The recognized databases PubMed, Medline, SciELO, and Google Scholar were used for data collection. The descriptors selected in the search engine were used with the use of

Boolean operators AND, OR, and NOT to optimize online searches. This methodological approach allowed the compilation and analysis of quality and relevant scientific literature, ensuring a broad and updated view searches. This methodological approach allowed the compilation and analysis of quality and relevant scientific literature, ensuring a broad and updated view of emerging practices in the immune system. The selection strategy was planned to ensure the inclusion of fundamental studies to evaluate the effectiveness of the new modalities.

4.0. SELECTED STUDIES

4.1. Immunological Memory

The cells responsible for attacking the Ag are specific to each Ag and play an essential role in the presence of the Ag. However, at the end of the response, when the Ag has already been eliminated, the number of specific cells does not need to be eliminated to cause damage to the host's energy expenditure. Many of these cells, which are no longer necessary, die, but those that do not die are called memory cells (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; OpenStax, 2025).

Immunological memory is the ability of the immune system to respond quickly and effectively to previously encountered pathogens, reflecting the persistence of clonal populations of Ag-specific lymphocytes. It refers to the ability of the immune system to recognize an Ag again and react against it by producing antibodies specifically to it. This rapid and effective response is long-lived Ag-specific lymphocytes, which have been induced to remain at rest but still release small amounts of antibodies upon new contact with the Ag (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; OpenStax, 2025).

Immunological memory occurs when an individual, upon the same Ag, quickly recognizes it and divides, making the response on the second contact even faster than on the first. This process occurs every time the organism comes into contact with the Ag, making the response more efficient (Figure 12) (Junqueira and Carneiro, 2023; Delves, 2024; OpenStax, 2025).

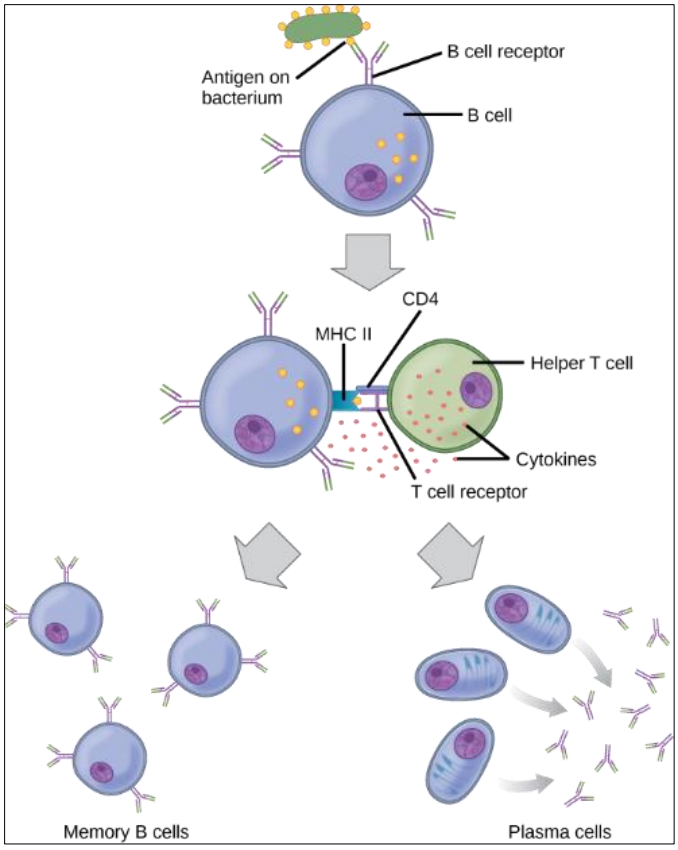


Figure 12: After initially binding an Ag to the B cell receptor, a B cell internalizes the Ag and presents it to the Major Histocompatibility Complex (MHC class II). A helper T cell recognizes the MHC class II-Ag complex and activates the B cell. As a result, memory B cells and plasma cells are produced
Source: OpenStax, 2025 (With permission)

The alpha (α) and beta (β) chains of the TCR bind to the Ag-MHC complex on an Ag-presenting cell (APC), and either CD4 or CD8 interacts with the MHC. Both actions stimulate the T cell (signal 1) via the

accessory CD3 chains. However, without a second signal coactivation, the T cell is anergic or tolerant (Ayres, 2017; Kierszenbaum, 2019; Junqueira and Carneiro, 2023; Delves, 2024; OpenStax, 2025).

The immune response must be regulated to avoid devastating damage to the host. Regulatory T cells express the Foxp3 transcription factor and do not control the immunological response by the secretion of immunosuppressive cytokines, such as IL-10 and the Beta-Transforming Growth Factor (TGF-beta), or by mechanisms dependent on cell contact. These regulatory cells assist in the prevention of autoimmune responses (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; Tanaka *et al.,* 2023; Delves, 2024).

Cytokines are polypeptides secreted by cells of the immune system and others when the cell interacts with a specific Ag, with molecules associated with pathogens such as endotoxins, or with other cytokines:

1. Chemokines induce chemotaxis and leukocyte migration.
2. Interferons are a family of proteins that have antiviral activity and also act as immunomodulators.
3. Interleukins (IL-1 to IL-38) are produced collectively by a wide variety of cells and have multiple effects on cellular development and regulation of immune responses to Interleukins (Carvalho and Buzato, 2005; Lima *et al.,* 2011; Lima, 2013; Ayres, 2017; Kierszenbaum, 2019; *Tanaka et al.,* 2023).

When the body comes into contact with an Ag, immunoglobulin IgM is produced to fight the aggressor, and IgG is also produced to form a memory against it. In the event of a second contact, the body will be able to generate a faster and more intense response, as a result of the stored memory and the immediate activation of the immune system (Stites and Terra, 1992; Zago *et al.,* 2013; Ayres, 2017; Silva Junior, 2019).

Upon contact with the Ag for the second time, there is already a population of B lymphocytes capable of recognizing this Ag, due to the memory cells generated in the primary response. In both the first and second infections, IgM and IgG antibodies are produced; however, in the primary response, IgM is the main immunoglobulin, and IgG production is lower and later (Stites and Terra, 1992; Zago *et al.,* 2013; Ayres, 2017; Silva Junior, 2019).

In the secondary response, IgG is predominant in both responses; the concentration of IgM in the plasma decreases rapidly, so that after one or two weeks, a sharp drop is observed, while IgG production is persistent. In this second contact with the Ag, antibody production is faster, and higher levels are reached (Stites and Terra, 1992; Zago *et al.,* 2013; Ayres, 2017; Silva Junior, 2019).

4.2. Clonal selection and immunological memory

The immune system's ability to respond to an Ag exists before you encounter that Ag. The immune system is based on the previous formation of an incredibly diverse population of:

1. B lymphocytes, each with their surface covered with thousands of identical copies of a receptor for Ag, the B cell receptor for Ag = BCR.
2. T cells (T lymphocytes) each have a surface covered with thousands of identical copies of a TCR (Kimball, 2025).

The activation of a B cell in a group of B cells whose BCR is specific to an epitope, a small dark sphere, not an Ag. This phenomenon is called clonal selection because it is an Ag that selects particular lymphocytes for clonal expansion. Clonal selection leads to the eventual production of:

1. A set of antibody-secreting plasma cells. Plasma cells are B cells that are shaped, for example, forming a large endoplasmic reticulum to synthesize and secrete an antibody.
2. The antibody is the secret version of the BCR. BCR only IgM, and each item has 10 identical union locations.
3. A group of memory cells that are B lymphocytes with receptors of the same specificity as those of the original activated B cell group (Kimball, 2025).

4.3. What is immunosuppression?

The immune system, tissues, and organs help the body fend off infections. Immunosuppression is a condition in which the immune system does not function as well as it should. Without a fully intact immune system, infections that the body might otherwise control on its own can become serious and even fatal. Suppression can result from a disease that affects the body's defense system, such as Human Immunodeficiency Syndrome (AIDS), caused by the human immunodeficiency virus (HIV), chronic kidney disease, or cancer, or from pharmaceutical agents used to combat certain conditions, such as cancer. In some cases, immunosuppression can be intentionally induced. This induction may be necessary for therapeutic interventions, such as tissue and organ transplantation, to reduce the risk of rejection (Harpaz *et al.,* 2016; Sattui *et al.,* 2021; Lombardi *et al.,* 2022).

4.4. What are the symptoms of immunodepression?

Immunocompromised patients are often vulnerable to infections from everyday microorganisms that do not affect healthy individuals. These microbes can cause opportunistic infections caused by bacteria, viruses, parasites, and fungi, which often impact those with weakened immune systems because they spread easily through body fluids, air, or contaminated food,

water, animals, and objects. Immunocompromised individuals experience more frequent and harder-to-treat infections, especially in the respiratory and gastrointestinal tracts, as well as in other internal organs and systems, including those affected by corticosteroids and medications used for autoimmune diseases (Harpaz et al., 2016; Sattui et al., 2021; Lombardi et al., 2022).

Once they are immunocompetent, T and B cells will migrate to the bloodstream and lymph nodes, where they will remain until they are called during an infection. B cells are involved in the humoral immune response, which targets pathogens released in the blood and lymph, and T cells are involved in the cell-mediated immune response, which targets infected cells (OpenStax, 2025).

4.5. Precautions for people with immunosuppression

However, the period of transmissibility of an infectious disease can often begin before the first symptoms appear. This means that, before any symptoms appear, the infectious agent can already be transmitted by the individual who has not yet become ill. Therefore, other forms of care are necessary, in addition to avoiding contact at the time of infection (Harpaz *et al.,* 2016; Sattui *et al.,* 2021; Lombardi *et al.,* 2022).

For individuals living with immunocompromised patients, the same recommendations for vaccination against the flu and chickenpox apply. Additionally, children who live with immunocompromised patients should not receive the oral polio vaccine, as it contains live viruses that are later eliminated in the vaccinated child's feces and can cause serious illness if the immunocompromised patient becomes accidentally infected (Harpaz *et al.,* 2016; Sattui *et al.,* 2021; Lombardi *et al.,* 2022).

Immunocompromised patients need to adopt a healthy lifestyle. This includes a balanced diet rich in nutrients, regular exercise, and adequate sleep. In addition, avoid alcohol and tobacco consumption, as these habits can further compromise the immune system. By taking care of your body in a comprehensive way, you will be contributing significantly to protecting your health (Harpaz *et al.,* 2016; Sattui *et al.,* 2021; Lombardi *et al.,* 2022).

Strengthen your immunity with healthy habits and a balanced diet. Eat foods rich in vitamins and minerals, such as fruits, vegetables, and lean proteins. Exercise regularly to strengthen your body and mind and ensure a good night's sleep to recharge your batteries. Remember to stay hydrated and avoid stress, as these factors can compromise the effectiveness of your immune system. Don't forget to take care of your mental health. Practicing relaxation techniques, such as meditation and deep breathing, can help reduce anxiety and strengthen (Harpaz *et al.,* 2016; Sattui *et al.,* 2021; Lombardi *et al.,* 2022).

4.6. Neuroimmunology

Neuroimmunology is a branch of neuroscience that combines two specialties of Immunology and Neurology. It addresses only the immunological phenomena that occur in the Nervous System (SNC), in the function of the immune system. The Neuroimmunology diagnoses and treats cerebral inflammatory diseases, such as autoimmune encephalitis, demyelinating diseases, and SNC infections, as well as rare immunological disorders. To understand neuroimmunology diseases, we present new data that expand our understanding of new treatment concepts for a large number of diseases, especially regarding their link with inflammatory markers (Graves *et al.,* 2022; Lambris *et al.,* 2022; Eva *et al.,* 2023).

There are three types of therapies for diseases that have been used both in animal models and in human clinical trials. These therapies include the use of DNA methylation inhibitors, Histone Deacetylase (HDAC) inhibitors, and RNA-based approaches. New high-performance technologies, when combined with advances in imaging modalities, such as in vivo optical nanotechnologies, can lead to an understanding of the nuclear organization and the interaction between the immune and nervous systems (Graves *et al.,* 2022; Lambris *et al.,* 2022; Eva *et al.,* 2023).

4.6.1. Neuroimmunological Treatments and Multiple Sclerosis (MS)

As neuroimmunological techniques have only been known for, their interpretation, diagnosis, and treatment remain. In recent years, there has been a significant development in a generation of discoveries that mark a new path in the diagnosis and treatment of patients with these conditions (QMH, 2025). The group of neuroimmunological diseases covers a wide range of pathologies, including:

1. Immune-mediated neuropathies.
2. Myasthenia gravis**.**
3. Polymyositis.
4. Lupus and rheumatoid arthritis.
5. Paraneoplastic syndromes.

In neuroimmunology, the teachings based on immunological disorders constitute a fundamental basis for the difficulties of being diagnosed with disabilities and affecting younger groups of patients, with personal and environmental repercussions. MS is a condition of the central nervous system that affects the myelin of the brain, brain stem, and spinal cord. Myelin, the substance that covers the neurons, is damaged, resulting in the conduction of two nerve signals in the brain. It is the most common chronic disease in young adults in Europe and the second most common cause of disability in this population group, after trauma (QMH, 2025).

4.6.2. Neuroimmunomodulation in neurodegenerative diseases: New scientific evidence

Microglia cells play a role in the brain's immune system. The healthy and adequately regulated functioning of these cells is essential for the homeostasis of the CNS, whether in normal conditions or the presence of nutrients. Numerous synais for CNS homeostasis, such as structures and/or residues of bacteria, viruses, fungi, abnormal endogenous proteins, complement factors, antibodies, cytokines, chemokines, among others, bind to certain microglial receptors, including Toll-Like Receptors (TLRs) and Advanced Glycation Products (RAGE) receptors, which induce their activation (McGeer *et al.,* 1996; Meda *et al.,* 2001; McGeer *et al.,* 2006; Streit *et al.,* 2008; Schmid *et al.,* 2009; Venneti *et al.,* 2009; Colton and Wilcock, 2010).

The activation of these cells regulates the expression of different surface markers, such as the molecular PPRs of the MHC-II, also producing pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12, IFN-γ and TNF-α, and also synthesize and release short-term cytotoxic factors, such as Superoxide Radicals (O2-), Nitric Oxide (NO) and Oxygen-Reactive Species (ROS) (Streit *et al.,* 2008; Schmid *et al.,* 2009; Venneti *et al.,* 2009; Colton and Wilcock, 2010; Town, 2010; Morales *et al.,* 2015).

The system regulates Reactive Oxygen Species (ROS) levels and preserves redox balance in both organelles and the cytoplasm, extending into the interstitial fluid and blood to eliminate extracellular ROS. There are three primary antioxidant strategies for cellular protection against ROS damage:

1. ROS scavenging by low-molecular-weight molecules in intracellular and extracellular spaces.
2. Conversion of ROS into less reactive compounds by enzymatic antioxidants, thus reducing oxidation.
3. Sequestration of pro-oxidant transition metals, such as iron and copper, by chelating proteins, preventing their participation in ROS generation (Santana *et al.,* 2024)

Microglial activation influences responses to pathological events, depending on the cellular context, and adapts to changes in the microenvironment. Important evidence for the critical role of neuroinflammation in neurodegenerative diseases in various types of experimental results:

1. Epidemiology shows a marked improvement in the cognitive capacity of patients with Alzheimer's Disease (AD) exposed to anti-inflammatory treatments. This epidemiological evidence comes from studies with patients receiving chronic treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), sometimes for long periods. The results will show a decrease in the incidence of AD, suggesting that the attenuation of the inflammatory response would help prevent or reduce the probability of development of the disease (McGeer *et al.,* 1996; Meda *et al.,* 2001; Streit *et al.,* 2008; Schmid *et al.,* 2009; Venneti *et al.,* 2009; Morales *et al.,* 2015).
2. Studies in transgenic animals demonstrate the neuroprotective effect of two inhibitors of the enzyme Cyclooxygenase (COX-1), which inhibit these factors. The process of microglial activation is phenotypically and functionally diverse; the response depends on the type, intensity, and context of the stimulus, on the factors that can generate a neuroprotective effect or a possible pro-inflammatory effect. It is precisely the delicate balance between neurotoxic and neuroprotective effects, as well as pro-inflammatory and anti-inflammatory actions, that determines microglial activity in a neurological or specific condition (Venneti *et al.,* 2009; Colton and Wilcock, 2010; Town, 2010; Morales *et al.,* 2015).

Morales *et al.* (2015) proposed their neuroimmunomodulators theory, external or internal damage activates microglial cells, promoting the production of cytotoxic factors that induce neuronal degeneration. These factors, which activate protein kinases, require aggregates of tau released in extracellular cells to activate microglia cells, triggering a positive feedback mechanism that promotes neurodegeneration. Natural compounds with strong anti-inflammatory activity, capable of crossing the blood-brain barrier, emerge as candidates for the prevention and treatment of neurodegenerative diseases, such as AD (Colton and Wilcock, 2010; Town, 2010; Morales *et al.,* 2015).

There are therapeutic approaches based on the use of antioxidants, which have been shown to contribute to improved health and quality of life in patients with AD. It is important to search for natural antioxidant compounds with strong anti-inflammatory activity that can cross the blood-brain barrier. An essential strategy for preventing brain damage involves nutritional changes, nutritional supplements, functional foods, and nutraceuticals, among many other factors, including exercise, an active social life, and sustained intellectual activity (Morales *et al.,* 2015).

4.6.3. The Neuroimmune connection of alcoholism

Chronic alcohol consumption compromises the tight junctions of the intestinal epithelium, allowing Lipopolysaccharide (LPS), a gram-negative bacterial endotoxin normally confined to the intestine, to enter the bloodstream. Once it does not bleed, LPS binds and activates the TLRs expressed in Kupffer cells, which are not found in other tissues. This initiates a signaling cascade that culminates in the release of pro-inflammatory cytokines into the bloodstream. These cytokines can cross the blood-brain barrier and interact

with the brain, also affecting behavior (Ineurociencias.org, 2019).

Research has shown that alcohol increases the expression of TLRs in the brain and its sensitivity to LPS. To test how peripheral administration of LPS affects drinking behavior, field studies show that a single injection of LPS produces long-term increases in alcohol consumption, consistent with neuroimmune signaling mediating alcohol-reinforcing properties (Figure 13) (Erickson *et al.,* 2019; Ineurociencias.org, 2019).

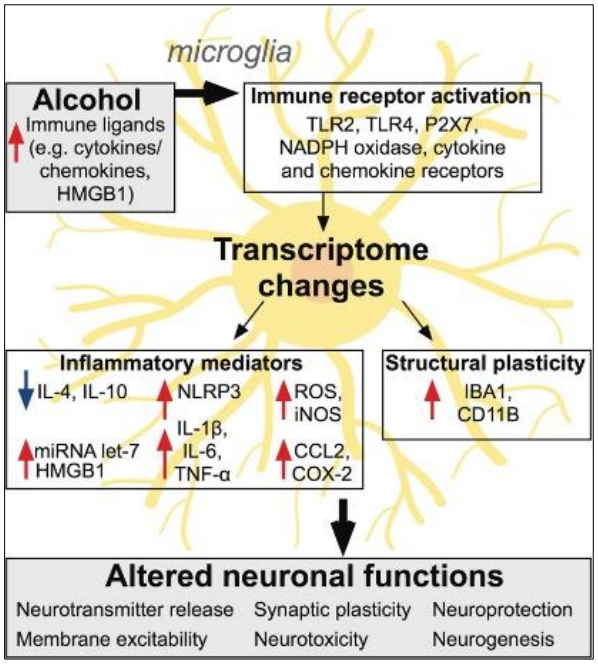


Figure 13: Microglia-specific consequences of alcohol-induced neuroinflammation. Alcohol exposure proinflammatory environment in the brain, resulting in upregulation of immune ligands such as cytokines and chemokines. This results in activation of immune receptors on microglia, persistent transcriptome changes, structural plasticity, and the production of several inflammatory mediators that can alter neuronal functions
Sources: Doi: 10.1016/j.pbb.2018.12.007. EPUB 2018 Dec 24. PMID: 30590091; PMCID: PMC6946054

This single injection of LPS also increases the rate of firing of two dopaminergic neurons in the ventral tegmental area, providing an example of how neuroimmune activation after peripheral administration of LPS modulates the brain's reward circuit. It is important to highlight that peripheral immunological function has also been shown to be relevant for other mental disorders, such as schizophrenia, depression, and autism. the exact mechanism by which peripheral immunological activation exerts its effects in the brain remains unexplored (Ineurociencias.org, 2019).

The use of peroxisome Proliferator-Activated Receptor (PPAR) gamma agonists, such as pioglitazone and rosiglitazone:

1. They have anti-inflammatory properties mediated by their ability to inhibit the transcription factor NFκB and thereby decrease the production of pro-inflammatory cytokines.
2. Pioglitazone has been shown to reduce alcohol consumption, abrogate reinstatement of alcohol seeking, reduce alcohol self-administration, and decrease the severity of physical withdrawal symptoms in rats.

These findings suggest that PPAR agonists may be viable options for the treatment of neuroimmune pathologies in alcoholism and other forms of addiction (Ineurociencias.org, 2019).

4.7. Immunological Placebo Effect

The placebo effect occurs when a person experiences health benefits after receiving a treatment that, in theory, has no active therapeutic properties. Common examples include sugar pills, saline injections, or even sham surgeries. Although these treatments do not contain pharmacological substances, they can produce real improvements in conditions such as pain, insomnia, anxiety, depression, and even physical symptoms of chronic diseases. Science has shown that the placebo effect is not only psychological, but also physiological, involving complex interactions between the brain, nervous system, and immune system. Studies have shown that belief in a treatment can stimulate the brain to release chemicals such as endorphins, dopamine, and serotonin. These molecules are associated with pain relief, feelings of well-being, and mood regulation (Figure 14) (Abarca *et al.,* 2005; Celedón, 2008; Finnissa *et al.,* 2010; Meissner, 2011; Benedetti, 2012; Colloca *et al.,* 2013; Díaz *et al.,* 2014).

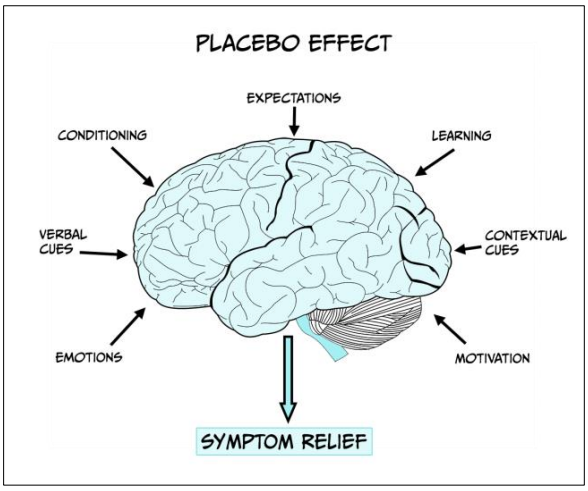


Figure 14: Psychological influences on the ability of a placebo to produce symptom relief

Sources: https://doi.org/10.20919/ZDGF9829/20, Introduction to Biological Psychology Copyright © 2023 by Catherine N. and https://openpress.sussex.ac.uk/introductiontobiologicalpsychology/chapter/title-placebos-a-psychological-and-biological-perspective/

Neuroimaging studies have shown that the placebo effect affects pain perception and emotions, the prefrontal cortex, and the amygdala. This helps explain why placebos can improve both physical and emotional symptoms. Research suggests that the placebo effect may influence the immune system, reducing inflammation and strengthening the body's response to infection. The placebo effect has been observed in settings, from clinical trials to everyday medical practice (Finnissa *et al.,* 2010; Díaz *et al.,* 2014).

Here are a few notable examples:

1. **Pain Relief:** Patients who believe they are receiving painkillers report significant pain reductions, even when the "drug" is inert.
2. **Mental Health:** In studies of depression, placebos often have efficacy rates comparable to antidepressants, especially in mild to moderate cases.
3. **Sham Surgeries:** Patients who undergo sham surgeries report improvements similar to those who undergo real medical procedures.

The placebo effect is the change, often physiologically demonstrable, that occurs in the body as a result of the psychological stimulus induced by administering an inert substance, a drug, or a treatment. It is the reduction of symptoms triggered by the patient's perception of receiving a therapeutic intervention. This phenomenon is not limited to medications but is also observed in medical physiotherapy (Abarca *et al.,* 2005; Celedón, 2008; Finnissa *et al.,* 2010; Díaz *et al.,* 2014).

Due to the placebo effect, changes can occur in objective variables such as blood pressure, cholesterol, body temperature, and heart rate. The administration of a placebo can produce beneficial effects, but it may also lead to negative consequences, such as adverse reactions. When this happens, we refer to the nocebo effect, which arises when people hold negative expectations about the effects of a therapy or medication, potentially worsening the disease and hindering recovery (Table 3) (Meissner, 2011; Benedetti, 2012; Colloca *et al.,* 2013; Díaz *et al.,* 2014).

Table 3: The Patient's Decision Problem

	Active Agent	Placebo
Alleviation	Correct Positive	*False Positive*
No effect	*False Rejection*	Correct Rejection

Sources: https://doi.org/10.20919/ZDGF9829/20, Introduction to Biological Psychology Copyright © 2023 by Catherine N. and https://openpress.sussex.ac.uk/introductiontobiologicalpsychology/chapter/title-placebos-a-psychological-and-biological-perspective/

Studies corroborate the nature of the placebo effect as a learning phenomenon in which humans learn to produce a benefit through verbally induced expectations and conditioning or learning. Specific expectations related to knowledge of the therapeutic agent, the circumstances of its administration, and the

condition to be treated are directly linked to the placebo effect (Silva, 2008; Lazovski, 2010; Pharmacodynamics, 2013; Díaz *et al.,* 2014).

Expectancy theory postulates that suggestive actions, such as words of encouragement, associated with the administration of a placebo, can trigger a physiological response. Verbally induced expectations can activate different neurotransmitters, as occurs in pain, where opiates, cannabinoids, dopamine, and cholecystokinin modulate their perception to varying degrees of intensity (Sobrino and Alonso, 2006; Haga *et al.,* 2009; Díaz *et al.,* 2014).

On the other hand, the analgesic effects of a placebo can be triggered by verbal instructions that anticipate a benefit, which creates expectations of analgesia and recalls previous experiences with pain relief. Expectations can also be influenced by the therapeutic act, health professionals, medical instruments, and the hospital environment. It has been suggested that medications are less effective without therapy (Lazovski, 2010; Pharmacodynamics, 2013; Díaz *et al.,* 2014).

Covert drug administration, in which a patient is treated with a pharmacologic agent without their knowledge, may be less effective than overt drug administration, in the patient's view; this is because, in the covert condition, the patient does not acquire expectations of improvement, thus reducing the overall effect of the medication. Patient expectations may potentiate the pharmacodynamic effect of medications (Haga *et al.,* 2009; Díaz *et al.,* 2014).

Research has shown that the placebo effect can influence immune response. The expectation of receiving a treatment can modulate immune system activity, reducing inflammation and improving symptoms in inflammatory conditions. The mind-body connection in this context underscores the brain's ability to influence physiological processes through psychological mechanisms (Haga *et al.,* 2009; Díaz *et al.,* 2014).

4.8. Neurobiological Mechanisms of the Placebo Effect

4.8.1. Activation of brain areas

1. **Prefrontal and Anterior Cingulate Cortex**: The prefrontal cortex and anterior cingulate cortex are key areas involved in experiencing the placebo effect. These regions are associated with anticipation, attention, and emotional evaluation.
2. **Insular Cortex:** The insular cortex, or insula, is involved in the perception and processing of emotions and bodily sensations and also plays a crucial role in the placebo effect. Activation of the insular cortex can modulate pain perception and contribute to the subjective sense of well-being experienced by patients (De Hower, 2018; Kim *et al.*, 2021; Prados and Gibson, 2023; Rey, 2024).

4.8.2. Neurotransmitters and neuromodulators

1. **Endorphins:** One of the most studied explanations for the placebo effect is the release of endorphins, which are endogenous peptides that act as natural analgesics. The administration of placebos can induce the release of endorphins, resulting in a reduction in pain.
2. **Dopamine:** A neurotransmitter associated with pleasure and reward, is also involved in the placebo effect.
3. **Serotonin:** Another crucial neurotransmitter has been linked to mood modulation and pain perception. The placebo effect may influence serotonergic activity, thus contributing to symptom improvement in depressive and anxiety disorders (Rey, 2024).

4.8.3. Conditioning and expectation

1. **Classical conditioning:** Classical conditioning plays a significant role in the placebo effect.
2. **Expectation:** The patient's positive expectation about the efficacy of a treatment is also a critical component of the placebo effect. The anticipation of reward and pain relief, resulting in actual symptom improvement, is also a critical component of the placebo effect (Rey, 2024).

4.8.4. Clinical applications of the placebo effect. The main clinical applications of the placebo effect are highlighted below:

1. Immunological.
2. Pain Management.
3. Psychiatric Disorders.
4. Somatoform Disorders.
5. Neurological Diseases.
6. Cardiovascular Conditions.
7. Oncology.
8. Gastrointestinal Disorders (Rey, 2024).

4.8.5. Ethical considerations in the clinical application of the placebo effect

1. Informed Consent.
2. Transparency and Honesty.
3. Beneficence and Nonmaleficence.
4. Effective Communication.
5. Personalization of Treatment.
6. Training in Medical Ethics (Rey, 2024).

4.8.6. Psycho-neuro-endocrine-immune mechanisms of the placebo effect - Endocannabinoid

During recent years, it has been discovered that the placebo response not only has neurobiological functions on analgesia, but that it is also capable of generating effects on the immune and endocrine systems. Beyond studies about its mechanism of action, the placebo effect has proved to be useful in the clinical setting with promising results in the management of

neurological, psychiatric, and immunologic disorders (Figure 15) (Ortega *et al.,* 2022).

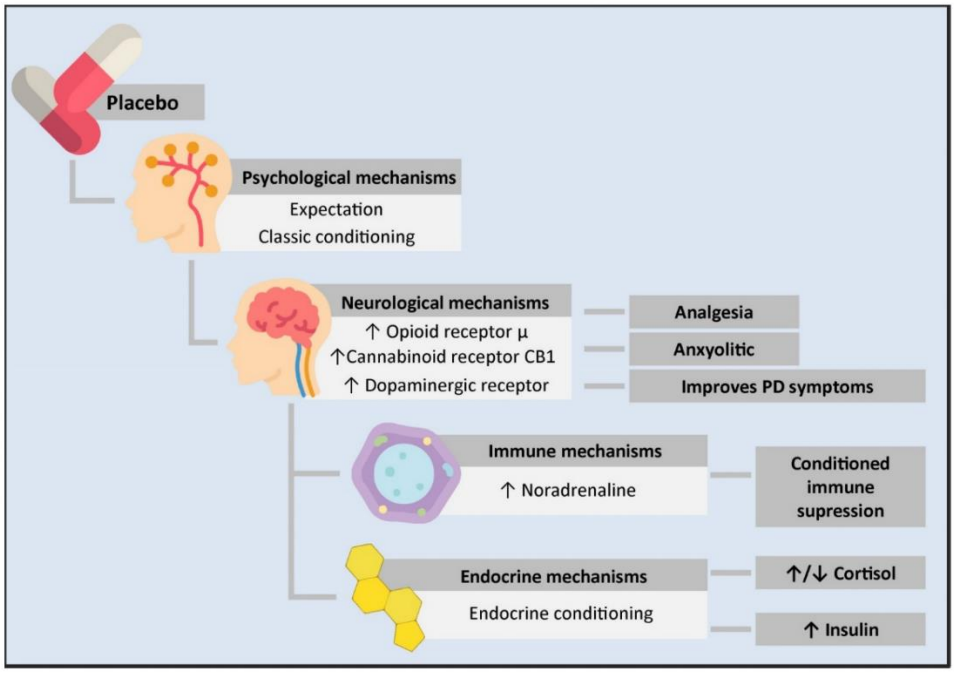


Figure 15: From a psychological can cause expectations or function as a conditioned stimulus. This is transmitted at the neurological level through an increase in the neurotransmission of μ-opioid receptors in the rostral anterior cingulate cortex, a mechanism involved in placebo-mediated analgesia and anxiolytic responses. There is an increase in cannabinoid receptor 1 (CB1) receptor transmission in placebo-conditioned analgesia with non-opioid mechanisms and an increase in dopaminergic transmission in patients treated with placebos, leading to clinical improvement

Source: Doi: 10.3390/ijms23084196

4.8.7. Alternative treatments

A. The Endocannabinoid System

Comprises the receptors, endogenous agonists, and the related biochemical apparatus responsible for synthesizing these substances and terminating their actions. The receptors have been named cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). The receptors are G-protein coupled. Within the central nervous system, CB1 is primarily located in presynaptic nerve terminals and is responsible for most of the neurobehavioral effects of cannabinoids. CB2, on the other hand, is the main cannabinoid receptor in the immune system, but can also be expressed in neurons. The main endogenous agonists of CB1 and CB2 are derivatives of arachidonic acid (Boczek and Zylinska, 2021; Lu and Mackie, 2021; Dantas, 2022; Briques *et al.,* 2023; Bufaiçal Filho *et al.,* 2024; WeCann Team, 2024).

Endogenous cannabinoids also act in response to cellular damage, modulating the functions of neuronal, glial, and endothelial cells and providing anti-inflammatory effects. Furthermore, because their receptors are present in cells of the immune system, the inhibitory action of the protein (Gi/o) modulates the production of pro-inflammatory cytokines and blocks microglial activation (Boczek and Zylinska, 2021; Lu and Mackie, 2021; Dantas, 2022; Briques *et al.,* 2023; Bufaiçal Filho *et al.,* 2024; WeCann Team, 2024).

B. Relationship between ozone therapy and immunity

The relationship between ozone therapy and immunity is very close. Widely recognized in developed countries as a form of treatment for various diseases, ozone therapy can also be used to strengthen the immune system. Research suggests that this therapy has antioxidant and anti-inflammatory properties, which can help reduce inflammation and oxidative stress, both of which are related to many chronic diseases and health problems. In addition, ozone therapy has the potential to improve blood circulation and tissue oxygenation, thus strengthening the body's immune function (Elvis and Ekta, 2011; Smith *et al.,* 2017).

Ozone therapy is an alternative treatment that uses ozone (O_3), a highly reactive form of oxygen, to promote therapeutic benefits. Antioxidant properties may contribute to a better immune response and help protect healthy cells from damage caused by conventional treatments. The relationship between ozone therapy and immunity is very close. Widely recognized in developed countries as a form of treatment for various diseases, ozone therapy can also be used to strengthen

the immune system. Research suggests that this therapy has antioxidant and anti-inflammatory properties, which can help reduce inflammation and oxidative stress, both of which are related to many chronic diseases and health problems. In addition, ozone therapy has the potential to improve blood circulation and tissue oxygenation, thus strengthening the body's immune function (Elvis and Ekta, 2011; Smith *et al.,* 2017).

Antioxidant properties: May contribute to a better immune response and help protect healthy cells from damage caused by conventional treatments, and antimicrobial action helps prevent or treat infections, which are a common concern in cancer patients, especially those who have a compromised immune system (Elvis and Ekta, 2011; Smith *et al.,* 2017).

When addressing immunostimulants, it is common to observe low concentrations of O3, which suggests inhibition of prostaglandin synthesis, as well as the release of bradykinin and increased secretions of macrophages and leukocytes. ozone administered in concentrations between 30 and 55 mcg/cc causes the greatest increase in interferon production, in addition to the elevated production of tumor necrosis factor and IL-2. The latter hormone triggers a whole series of subsequent immunological reactions, corroborating the results found in the study mentioned above (Elvis and Ekta, 2011; Smith *et al.,* 2017).

4.8.8. Emotional autoimmune response

Autoimmune diseases result from the body's antibodies attacking itself. The immune system makes its defenses for invaders and attacks itself. This results in an inversion and a failure to recognize the Ags that need to be fought. Autoimmune disease triggers a self-destruction mechanism. It is the body itself that cannot recognize the Ags and begins to attack itself. The immune system becomes incapable of recognizing the difference between viruses, bacteria, and other pathogens and attacks its tissues and organs. From a biological and psychosomatic perspective, autoimmune diseases can be interpreted as a response to unresolved internal conflicts (Brod *et al.,* 2014; GreenMe.com.br, 2023; Shimo *et al.,* 2023).

4.8.8.1. For example:

1. **Lupus:** It can be related to a feeling of self-destruction or an internal struggle for not meeting the expectations of others.
2. **Hashimoto's thyroiditis:** This could be linked to not feeling able to express yourself or "swallow" certain situations.
3. **Rheumatoid Arthritis:** It is associated with a deep feeling of rigidity in the face of responsibilities or repressed resentment.
4. **Celiac disease:** Related to a conflict of rejection or difficulty in assimilating a life situation.
5. **Multiple Sclerosis:** The perception of not being able to advance or being paralyzed in an emotional situation.
6. **Chronic Fatigue Syndrome**: You can reflect on a conflict of extreme emotional exhaustion, feeling like you are laughing at the demands of life (GreenMe.com.br, 2023; Health Union LLC, 2024).
7. **Crohn and Colitis:** Linked to territorial problems or the inability to "let go" of painful situations (GreenMe.com.br, 2023; Health Union LLC, 2024).

The body, without finding a way to process these emotions, somatizes them, sending signals through the immune system to call for attention, resulting in emotional imbalance:

1. **Type 1 diabetes:** A conflict related to feeling lost.
2. **Psoriasis:** A conflict of separation, like feeling that what you are isolated from does not belong to you.
3. **Myasthenia gravis**: Related to the perception of being unable to act or move until it has slowed down.
4. **Stress:** Chronic stress can trigger abnormal immune responses and contribute to the development of autoimmune diseases.
5. **Nutrient deficiencies:** A diet deficient in essential nutrients can weaken the immune system and make it more prone to autoimmune attacks.
6. **Genetic predisposition:** Some individuals may have a genetic predisposition to developing autoimmune diseases, making monitoring and preventative care crucial.
7. **Gut problems:** Gut health is closely linked to the immune system. Problems such as leaky gut syndrome can contribute to immune dysfunction (GreenMe.com.br, 2023; Health Union LLC, 2024).

Patients who have been diagnosed with autoimmune disorders report adverse emotional effects due to these conditions for the following reasons:

1. **Unpredictability**: The very nature of these conditions, which is characterized by unpredictability, means that people feel insecure all the time.
2. **Feeling of loss:** Not being able to have control over your own body can be extremely frustrating.
3. **Feeling of loneliness:** Chronic fatigue and breakouts can restrict people from socializing or working, which leads to loneliness and depression.
4. **Fear of the unknown:** Problems related to the progression of the disease and its possible complications ensure a constant level of anxiety (GreenMe.com.br, 2023; Health Union LLC, 2024).

4.8.9. When faced with emotions, it is possible to apply different strategies to improve emotional well-being:

Recognizing emotions:

1. The initial step consists of recognizing and naming emotions that are experienced, without censorship.
2. Communication: Talk about feelings with trusted people such as friends, family, or even a therapist.
3. Self-care. Rest: This should be considered the most critical factor to improve both physical and mental recovery.
4. Food: It is important to highlight that with an adequate diet, you can have the available energy necessary to combat the disease.
5. Exercise: Exercising regularly helps in managing stress, vulnerability, and spirit. Relaxation: While the regular practice of relaxation is largely meditative, it encompasses techniques such as yoga and deep breathing.
6. Establishing limits: Learning to use the word and taking care of your own needs is fundamental.
7. Professional support: A therapist can help in specific moments and provide tools for managing changes in spirit.
8. Connection with nature: It is important to spend time in natural environments, as this can contribute to your rest, disconnection, and relaxation.
9. Celebration of achievements (Figure 16) (D'Acquisto, 2017; Health Union LLC, 2024).

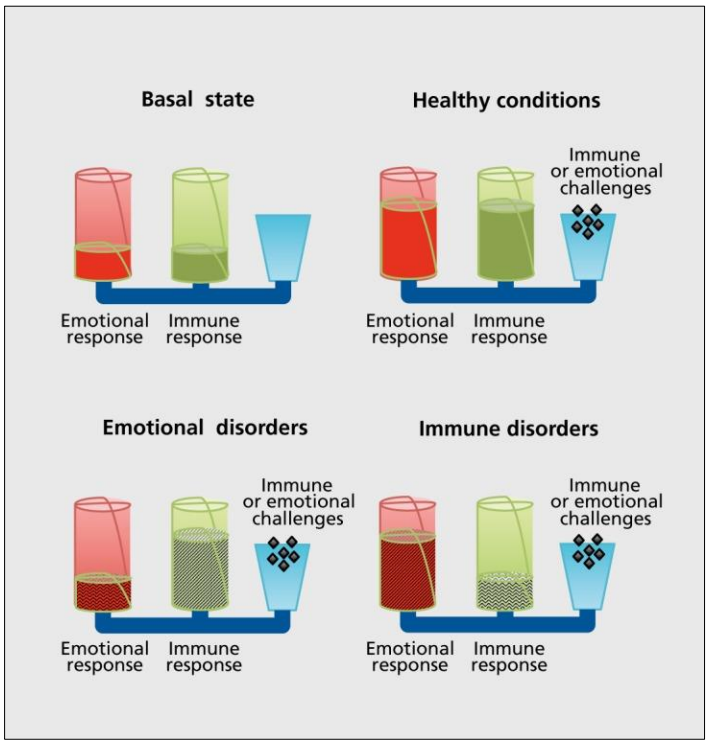


Figure 16: Scheme of the link between the emotional and immunological systems in healthy and human conditions. In a normal basal state, emotional and immunological responses are interlinked in balance. In healthy pathogenic conditions of different natures, changes in environmental conditions and significant life events stimulate an adaptive response that helps the host cope with these challenges. In patients suffering from emotional or immunological disturbances, the same challenges cause an exacerbated or dysfunctional compensatory immunological or emotional response

Sources: Doi: 10.31887/DCNS.2017.19.1/fdacquisto. PMID: 28566943; PMCID: PMC5442367

4.8.10. The development of alopecia in patients with attention deficit disorder (ADD)

A. LITERATURE REVIEW:

B. Main findings:

The review revealed a potential association between attention deficit disorder and hair loss, with evidence suggesting that stress associated with Attention-Deficit/Hyperactivity Disorder (ADHD) may contribute to the development of hair loss. Studies show that chronic stress elevates cortisol levels, which can negatively affect the hair growth cycle. Gaps Identified: Although preliminary evidence was found regarding the relationship between ADHD stress and hair loss, gaps in the research were identified, particularly the lack of direct studies on the autoimmune response in patients with ADHD (Pelleja *et al.,* 2024).

C. Case Study:

Participant Profile: Patients with ADHD who are presented with hair loss showed elevated stress levels and symptoms related to anxiety and depression.

Clinical Data: The data indicated a significant prevalence of alopecia areata in this group, with a common pattern of hair loss onset coinciding with stressful events or exacerbation of ADHD symptoms.

D. Assessment of Biological Mechanisms:

Cortisol Levels: Patients with ADHD and alopecia showed significantly higher cortisol levels compared to healthy controls, supporting the hypothesis that chronic stress contributes to alopecia Health Union (LLC, 2024; Pelleja *et al.,* 2024; BBC News World, 2025).

Autoimmune Responses: An increased incidence of autoimmune markers was observed in some patients with alopecia areata, suggesting a possible connection between ADHD and a stress-induced autoimmune response (LLC, 2024; Pelleja *et al.,* 2024).

E. Study of psychosocial factors:

1. **Emotional impact:** Questionnaires and interviews revealed that patients with ADHD and alopecia experienced a greater decrease in self-esteem and an increase in emotional problems compared to patients with alopecia without ADHD.
2. **Vicious cycle:** A vicious cycle was identified where alopecia aggravated self-esteem and stress problems in patients with ADHD, exacerbating their emotional and social difficulties. Development of management strategies:
3. **Effective interventions:** Management strategies that combine alopecia treatments, such as topical and systemic therapies, with stress-reducing interventions, such as cognitive-behavioral therapy, showed improvements in patients' hair health and emotional well-being.
4. **Clinical recommendations:** Guidelines were proposed for a comprehensive approach that includes emotional support, stress management, and dermatological treatment, tailored to the specific needs of patients with ADHD.
5. **These results** suggest a significant connection between ADHD and alopecia, with stress and psychosocial factors playing a crucial role in the development of alopecia in these patients. Comprehensive management strategies can improve both hair health and overall well-being (LLC, 2024; Pelleja *et al.,* 2024).

The self-esteem issues and emotional difficulties observed in patients with ADHD and alopecia confirm that psychosocial factors play an important role in the progression of alopecia. Hair loss can exacerbate self-esteem issues and contribute to a vicious cycle of stress and worsening alopecia. This cycle reinforces the need for interventions that not only treat alopecia from a dermatological perspective but also address the patient's emotional well-being (LLC, 2024; Pelleja *et al.,* 2024).

4.8.11. Autoimmune diseases: When there is "friendly fire" in your body

Imagine you're on a battlefield and the soldiers under your command stopped attacking enemy troops and started attacking you, sometimes mercilessly (BBC News Word, 2025).

This is how autoimmune diseases work: the immune system attacks the healthy cells in our body. "Under normal conditions, the body would use its immune system to attack certain harmful environmental factors, such as bacteria and viruses, but what it ends up doing is causing a problem for the body itself," [explains Dr. Mario César Salinas, head of the Immunology Department at the Autonomous University of Nuevo León Hospital in Mexico, to BBC Mundo]. Our body becomes confused (BBC News Word, 2025).

The immune system, which is a network of tissues, organs, and cells, makes a mistake and instead of protecting us from pathogens, infections, and diseases, it identifies healthy cells as enemies and attacks them. This mistake results in an autoimmune disease (BBC News World, 2025).

4.8.11.1. Factors

Some of these are: celiac disease, autoimmune hepatitis, Hashimoto's thyroiditis, rheumatoid arthritis, systemic and discoid lupus erythematosus, psoriasis, and Guillain-Barré syndrome. "Some of these diseases affect a single organ, such as the thyroid gland, and others attack several systems at the same time, such as rheumatoid arthritis or mixed connective tissue disease," [Salinas]. "Genetic background influences these types of diseases. They are present in several members of a family who have suffered from autoimmune diseases," notes the expert [Salinas] (BBC News World, 2025).

4.8.11.2. Factors involved in autoimmune diseases

"The immune response of a genetically predisposed individual to an environmental pathogen, in association with defects in immunoregulatory mechanisms, can lead to the development of an autoimmune disease," the professors stated in their article: "Autoimmune Diseases: Genes, Insects, and Failed Regulation" [Salinas] (BBC News World, 2025).

"The importance of the individual components represented in this diagram may vary between individuals and diseases. However, the onset of an autoimmune disease requires the convergence of all three components," they added [Salinas] (BBC News World, 2025).

4.8.12. Hypothyroidism emotional meaning

4.8.12.1. Causes of Hypothyroidism:

1. **Autoimmune disease:** This is the most common cause of hypothyroidism, known as Hashimoto's Thyroiditis. The immune system mistakenly attacks the thyroid, decreasing its ability to produce hormones.
2. **Medical treatments:** Radiation therapy or surgery to treat conditions such as thyroid cancer can damage the thyroid and lead to hypothyroidism.

3. **Medications:** Some medications, such as lithium, can cause hypothyroidism.
4. **Iodine deficiency:** Iodine is essential for the production of thyroid hormones. A lack of iodine in the diet can cause hypothyroidism.
5. **Pituitary disease:** Although uncommon, hypothyroidism can sometimes be the result of problems with the pituitary gland (SignificadoEmocional.com, 2025).

There are many factors to consider when discussing the emotional meaning of hypothyroidism. Whether you're a man or a woman, the emotional impact of this condition can be intense and varied (SignificadoEmocional.com, 2025).

4.8.12.2. Hypothyroidism in women

1. Hypothyroidism can lead to a feeling of emotional disconnection. Your body moves more slowly, your mind feels dull, and it can be difficult to connect with your emotions.
2. Hypothyroidism can also mean a sense of lack of control. When our bodies don't respond as we expect, it can be incredibly frustrating and can lead to a feeling of helplessness.
3. It can also represent a fear of change. The thyroid regulates our energy and metabolism, two things that are constantly in flux. Hypothyroidism can mean that we're struggling with the changes and flow of life (SignificadoEmocional.com, 2025).

4.8.12.3. Hypothyroidism in men

1. Hypothyroidism can manifest as a loss of vigor and vitality.
2. Many men are reluctant to take care of themselves the way they need to, and hypothyroidism can be a sign that they need some time to themselves.
3. It may indicate a disconnect from emotions. Men may feel disconnected from their emotions when they have hypothyroidism, which may be a sign that they need to pay more attention to their emotional needs (SignificadoEmocional.com, 2025).

4.8.12.4. Strategies to alleviate pain and promote emotional well-being:

1. Self-care. This includes healthy nutrition, regular physical activity, and adequate rest.
2. Emotional support can be vital. Talking to friends, family, or a therapist can be of great help in managing the emotional impact.
3. Stress can be a critical aspect, such as meditation, yoga, or cognitive-behavioral therapy (SignificadoEmocional.com, 2025).

4.9. Articles

4. 9.1. New drugs for autoimmune diseases

The mechanism of action of new drugs for autoimmune diseases varies according to the type of disease and the specific target of the treatment. In general, these drugs act by modulating the immune system, seeking to control the autoimmune response that leads to inflammation and damage. Some drugs can act by blocking pro-inflammatory cytokines, such as TNF-α, while others can interfere with specific pathways of the immune system (CliniPam Saúde Curitiba, 2025; Medical Academy, 2025).

The efficacy and safety of new drugs for autoimmune diseases are being evaluated in treatment. Clinical trials have shown promising results in reducing the symptoms and improving the quality of life of patients. However, it is emphasized that each patient may react differently to the treatment, and doctors must closely monitor possible side effects (CliniPam Saúde Curitiba, 2025; Medical Academy, 2025).

4.9.2. New drugs for autoimmune diseases. Breakthrough insight in a Nature article, January 22, 2024 [Nature, 625(7996), 646-648. Doi: 10.1038/d41586-024-00169-7]

"Pioneering use of iron oxide nanoparticles to map immune cells involved in diabetes. These nanoparticles, called navacims, have histocompatibility complexes that mimic Ag-presenting cells, inducing the transformation of T cells into regulatory T cells at the site of inflammation. Shows potential to reverse symptoms in models of type 1 diabetes" [Pere Santamaria, from the University of Calgary] (CliniPam Saúde Curitiba, 2025).

Cellular immunotherapy, strategies based on regulatory T cells, are being explored. "We are investigating the manipulation of peripheral tolerance, in the liver, a key site for the induction of immune tolerance. The technique aims to target Ags to the liver, promoting immune tolerance in animal models of diseases similar to multiple sclerosis." According to the article, researchers such as Jeffrey Hubbell] (CliniPam Saúde Curitiba, 2025; Medical Academy, 2025).

"CAR-T therapies, traditionally used in oncology, are being adapted for autoimmune diseases. These therapies specifically target the immune cells that contribute to the disease, with promising results showing long-lasting remissions in conditions such as lupus [According to the article, researchers, including Jeffrey Hubbell]. Developing CAR-T therapies that target autoreactive B cells in diseases such as pemphigus vulgaris, offering a more targeted and potentially less invasive treatment [Aimee Payne]. While challenges remain, the potential for significant changes in the management of these diseases is clear (CliniPam Saúde Curitiba, 2025; Medical Academy, 2025).

The three main methods by which current research is attempting to establish immune tolerance in autoimmune diseases:

1. **Leveraging the liver:** Demonstrating the strategy of targeting Ags to the liver method, as detailed previously [Jeffrey Hubbell and his team].
2. **Nanoparticle presenters:** Illustrating how nanoparticles can be used to present Ags to T cells

and induce them to become regulatory T cells, a novel technique led by [Pere Santamaria].

3. **B-cell Killing:** Representing CAR-T therapies that direct T cells [Aimee Payne] (CliniPam Saúde Curitiba, 2025).

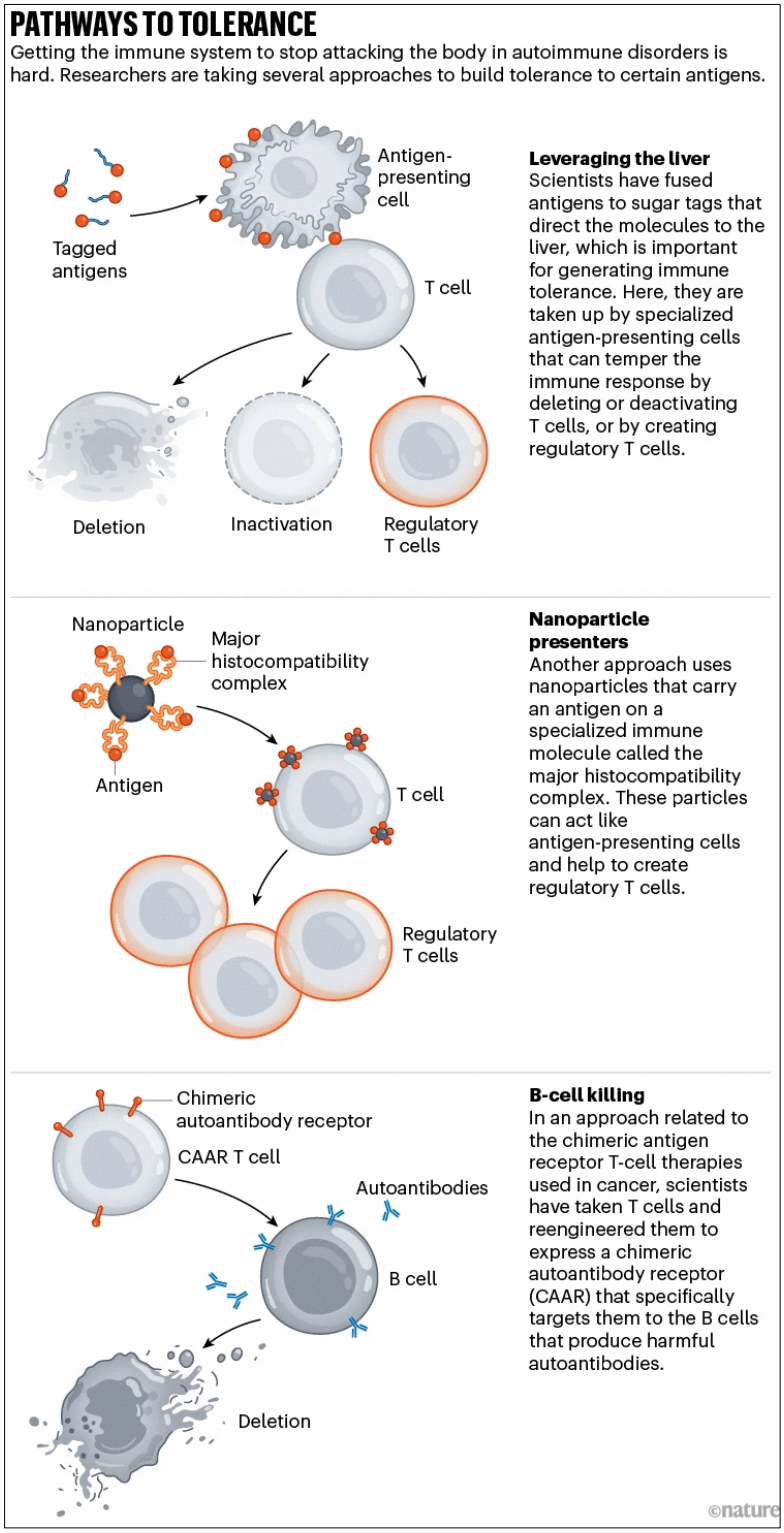


Figure 17: Can autoimmune diseases be cured? Scientists see hope at last
Source: Doi: 10.1038/d41586-024-00169-7

4.9.3. Institute for Research and Innovation in Health, University of Porto (iBS) opens doors to new therapies for inflammatory and autoimmune diseases

It proves that the complex glycan sugars that cover the surface of T lymphocytes are essential for ensuring the proper functioning of the immune system.

Scientists have discovered that the composition of these sugars on the surface of T lymphocytes determines, from childhood, a greater or lesser susceptibility to chronic inflammatory and autoimmune diseases [A research team led by Salomé Pinho, from the i3S, published a pioneering study in the renowned Journal Cellular & Molecular Immunology] (News from the University of Porto, 2024).

"Identification of new mechanisms of regulation of the immune system that can be translated into new targets to create innovative therapeutic strategies for pathologies that develop due to the inability of the immune system to combat them". For example, "if we can glycol-reprogram T cells, we can regulate the immune response" [This study, which was later reviewed and discussed by researchers Manuel Vicente, Eduarda Leite-Gomes and Salomé Pinho in the scientific journal Trends in Immunology, even earning the honors of being featured on the cover of the publication] (News from the University of Porto, 2024).

The researchers began by concluding that "as progenitor T cells develop in the thymus, the composition of these sugars on the surface undergoes changes, from more premature stages to mature/differentiated stages, and this occurs both in humans and in animal models in mice", [Salomé Pinho, leader of the "Immunology, Cancer & GlycoMedicine" (Vicente *et al.,* 2023) group and affiliated professor at the Faculty of Medicine (FMUP) and the Abel Salazar Institute of Biomedical Sciences (ICBAS) at the University of Porto] (News from the University of Porto, 2024).

5. CONCLUSION

The immune system is our body's defense system, which is responsible for protecting us from different agents, such as viruses, bacteria, and even cancer cells. This important system of the human body has two essential characteristics: specificity and memory capacity. This system is composed of various cells, tissues, organs, and molecules. Among the cells that comprise the immune system, leukocytes stand out, particularly B lymphocytes, which are involved in the production of antibodies. Antibodies are proteins that Ags, ensuring that they are destroyed. Many events of the immune response have already been elucidated by science, but there are still many other mechanisms to be understood due to the complexity of the human body. Therefore, the great challenge of immunology is to understand and manipulate the immune system.

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