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# THE GATA-3 TRANSCRIPTION FACTOR IS CRUCIAL FOR THE IMMUNE RESPONSE

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## ABSTRACT

T cell differentiation into subtypes is mediated by GATAs, particularly GATA-binding protein 3 (GATA-3), along with T-bet, ROR $\gamma$ t, FOXP3, and others. GATAs are transcription factors 1 to 6 that bind to GATA-DNA sequences, regulating differentiation, development, and cell identity. GATAs are important for the immune system, tumors, and the differentiation of CD4<sup>+</sup> T cells. GATA-2 and GATA-3 are crucial for the development of neurons in the central nervous system (CNS). GATA-2 and GATA-3 play an important role in embryonic brain development and the formation of GABAergic neurons, and GATA-2 deficiency can lead to neuronal defects. GATA-3 mediates the development of the sympathetic nervous system, the maturation of some sensory neurons, and the differentiation of noradrenergic neurons. Anti-GATA agents such as SB010, a novel DNA enzyme capable of cleaving GATA-3 mRNA, may be useful in the treatment of diseases in which Th2 cells are inactive.

**KEYWORDS:** *GATA-3, GATA-binding protein, T cell, transcription factor, cell differentiation*

## INTRODUCTION

Murine type 1 helper T lymphocytes (Th1) and type 2 helper T lymphocytes (Th2) (derived from Th cells), were discovered in 1986 by Robert Coffman and Timothy Mossman, on the basis of cytokine production (1). Subsequently, T cells underwent further division into Th9, Th17, Th22, Treg, and follicular helper T cells (2). The factor that drives the differentiation of these T cell subtypes is GATA-binding protein 3 (GATA-3), along with T-bet, ROR $\gamma$ t, and FOXP3, amongst others (3).

GATAs are transcription factors ranging from GATA-1 to GATA-6 that bind to GATA DNA sequences, regulating differentiation, development, and cell identity (4). GATA-2 and GATA-3 are primary members of the GATA transcription factor family expressed in the central nervous system (CNS), where they regulate neuronal identity, survival, and differentiation (5). GATA-2 is important in the embryonic development of the CNS, where it is involved in neuronal specification, particularly in the spinal cord and autonomic nervous system, while GATA-3 is crucial for the peripheral CNS, especially for the development of sympathetic and sensory neurons (5).

GATA-3 is involved in embryonic development and the functioning of several tissues (6). For example, it is implicated in the pathophysiology of immune cells, and cells of the breast and urinary tract (7). In breast cancer, GATA-3 is a marker and may have prognostic implications, while in the immune system, it is a transcription factor that is crucial for the development and function of specific cell subtypes, particularly Th2 (8).

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GATA-3 promotes the differentiation of CD4<sup>+</sup> T cells and regulates the expression of several cytokines, such as IL-4, IL-5, and IL-13 (9). These cytokines are produced mainly by Th2 lymphocytes and play a fundamental role in the allergic immune response and the response against extracellular parasites such as helminths (10). IL-4 functions mainly in promoting the differentiation of naïve T lymphocytes into Th2 and stimulating B cells; it is fundamental in the production of immunoglobulins. IL-4 is involved in the expression of major histocompatibility complex II (MHC II) molecules and mediates allergic processes (11). The main function of IL-5 is to participate in the differentiation, activation and survival of eosinophils. It contributes to the defense against helminths and stimulates the production of mucus in allergic diseases (12). IL-13 has an action similar to IL-4, participating in the production of IgE, tissue remodeling, fibrosis, bronchial allergic hyperreactivity, and mucus production. GATA-3 inhibits the development of Th1 cells by suppressing T-bet (by reducing the TBX21 gene), which is the master regulator of Th1 cells responsible for the expression of interferon gamma (IFN- $\gamma$ ) (13). GATA-3 and T-bet can compete for common transcription factors or for DNA binding (14). The balance between GATA-3 and T-bet determines the direction of the immune response. GATA-3 is also expressed in non-T cells, such as some types of epithelial cells, innate lymphoid cells type 2 (ILC2), and the thymus during maturation (15).

## DISCUSSION

GATA-2 and GATA-3 are the most relevant transcription factors for the CNS and play an important role in embryonic brain development and the formation of GABAergic neurons (16). A deficiency in GATA-2 can lead to neuronal defects (17). GATA-3 is important for the development of the sympathetic nervous system, the maturation of some other cells, and the differentiation of noradrenergic neurons (18). Mutated GATA-3 genes can lead to a transcriptional defect in Th2 cells and the development of sensory neurons, resulting in deafness (19). GATA-3 is only expressed intracellularly and can be crucial for generating an effective immune response against microorganisms.

GATA-3 may be a therapeutic target for several diseases, including chronic infectious diseases (20). In infectious processes, such as parasitic diseases, GATA-3-mediated Th2 responses are protective. GATA-3-activated cytokines, including IL-4, IL-5, and IL-13, help recruit eosinophils, stimulate IgE production, and increase mucus secretion and intestinal motility (21). GATA-3 is crucial for an effective response against pathogens. In viral and bacterial infections, a Th1 response occurs first, followed by a Th17 response (22,23). The Th17 immune response is adaptive and is mediated by a subpopulation of CD4<sup>+</sup> Th cells called Th17 (24).

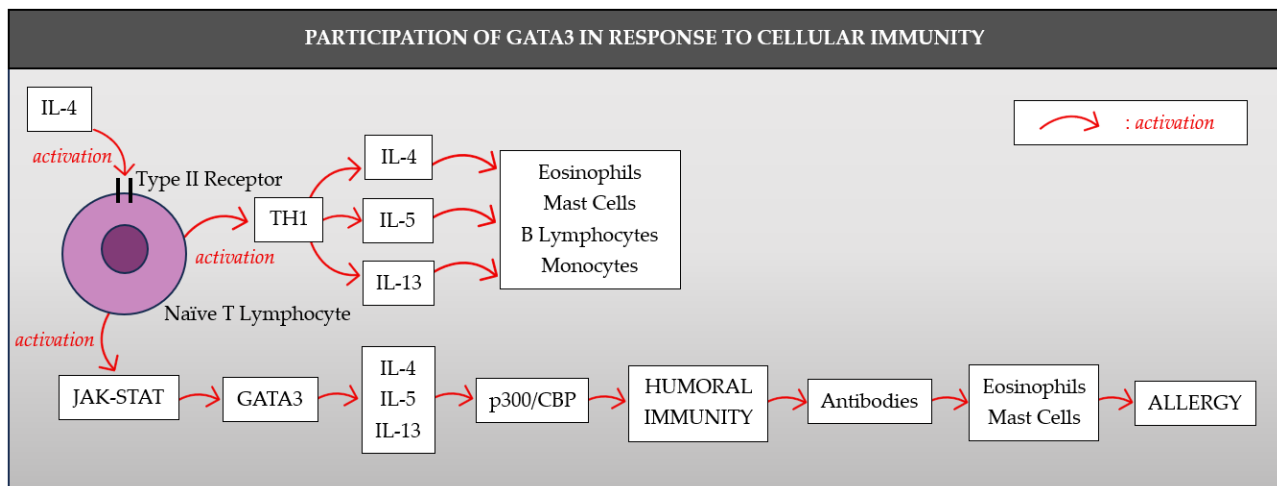
Excessive production of GATA-3 can be harmful, as it suppresses Th1 responses, reducing the production of IFN- $\gamma$ , which is essential for eliminating intracellular viruses and bacteria (25). GATA-3 is also expressed in ILC2s, which are important in viral respiratory infections where they promote tissue repair and mucus production (26). ILC2s can also promote allergic inflammation (27).

Treatment with anti-GATA (such as SB010, a novel DNA enzyme that can cleave GATA-3 mRNA) could be useful in the treatment of diseases where Th2 cells are inactive or involved in an ineffective response (28). GATA-3 is a therapeutic target represented by anti-GATA-3, which may be useful in allergic diseases such as asthma and atopic dermatitis (29).

GATA-3 is important in Th1 cellular immunity and Th2 humoral immunity (30). Th1 immunity involves the activation of macrophages against intracellular pathogens and the activation of IFN- $\gamma$  (31). GATA-3 mediates the Th2 response and therefore, humoral immunity. Th2 immunity involves the activation of antibodies, eosinophils, and mast cells against parasites (32). GATA-3 is involved in the differentiation of Th2 cells, such as naïve CD4<sup>+</sup> lymphocytes, and inhibits the Th1 fate (33). The most representative cytokines induced by GATA-3 are IL-4, IL-5, and IL-13 (34). These cytokines stimulate the production of antibodies, such as IgE and IgG4, in B lymphocytes and plasma cells, and activate mast cells in their involvement in parasitic and allergic diseases.

At the molecular level, GATA-3 begins with the activation of IL-4, which binds to T cells through its type II receptor, consisting of the IL-4R $\alpha$  subunit and the IL-13R $\alpha$ 1 subunit (35). This activates the JAK-STAT pathway and STAT6 enters the nucleus and induces GATA-3 expression through a positive feedback loop; GATA-3 induces an increase in IL-4, which induces an increase in GATA-3.

GATA-3 also acts on DNA, where it binds to GATA sequences in the promoters/enhancers of IL-4, 5, and 13, recruiting transcriptional coactivators, such as p300/CBP (36). Another important effect of GATA-3 is to induce the acetylation of sarcomas, stabilizing the Th2 locus in an active state and making Th2 differentiation irreversible (25). GATA-3 inhibits cellular immunity by repressing T-bet, a crucial factor for Th1 lymphocytes. It also inhibits IFN- $\gamma$  and the Th1 cellular response. It participates in the humoral response through cytokines IL-4 and IL-13, in the production of IgE released by B lymphocytes (Fig.1).



**Fig. 1.** When IL-4 binds its type II receptor, Th1 cells are activated to produce cytokines that activate cells involved in allergic disease. The binding of IL-4 to its type II receptor also activates the JAK-STAT pathway cascade that results in allergy.

## CONCLUSIONS

GATAs are transcription factors that regulate cell differentiation, development, and identity. GATA-2 and GATA-3 are expressed in the CNS, where they regulate neuronal survival and differentiation. GATA-2 is important in embryonic CNS development, where it is involved in neuronal specification, while GATA-3 is crucial for the peripheral CNS and the development of sympathetic and sensory neurons. Recently, anti-GATA (such as SB010, a novel DNA enzyme capable of cleaving GATA-3 mRNA) has been shown to be effective in the treatment of GATA-3-mediated Th2 diseases.

GATA-3 also regulates the expression of cytokines, including IL-4, IL-5, and IL-13, produced mainly by Th2 lymphocytes. These cytokines play a crucial role in the allergic immune response, promoting the differentiation of naïve T lymphocytes into Th2 and stimulating B cells, producing immunoglobulins, expressing MHC II, and participating in differentiation.

### Conflict of interest

The authors declare that they have no conflict of interest.

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# THE POTENTIAL OF STEM CELLS IN THE STUDY AND TREATMENT OF THE CENTRAL NERVOUS SYSTEM

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**KEYWORDS:** *Stem cell, differentiation, therapy, central nervous system, multiple sclerosis*

## INTRODUCTION

Stem cells are self-renewal cells that can divide multiple times and produce other identical stem cells (1). Furthermore, these cells undergo differentiation and can transform into specialized cells, such as neurons, skin cells, muscle cells, and blood cells, amongst others. The most widely studied stem cells are embryonic stem cells, which can give rise to all cell types in the body (2). Adult stem cells are located in the bone marrow, skin, and brain and are used to repair damaged tissue, while induced pluripotent stem cells are adult cells reprogrammed in the laboratory (3). Stem cells serve the body's growth and development and repair damaged tissue and are used in biomedical research and experimental therapies. They play a very interesting and promising role in the study and potential treatment of the central nervous system (CNS) and spinal cord injuries (4). Stem cells are considered promising in the treatment of diseases and injuries of the CNS, brain, and spinal cord, where they can activate molecular and cellular mechanisms.

## DISCUSSION

Stem cells are unspecialized cells capable of renewing themselves while maintaining their characteristics and differentiating into specialized cells, such as neurons or glial cells. The spinal cord transmits nerve impulses between the brain and the rest of the body. After injury, damaged neurons are not easily repaired due to their very limited regeneration capacity (5). In these cases, the use of stem cells has generated considerable therapeutic hope.

Embryonic stem cells are highly plastic and are often used in laboratory research, but not without ethical concerns (6). Significant interest in experimental research has been sparked by the use of healthy adult cells reprogrammed to revert to stem cells. In the spinal cord, stem cells aim to replace damaged neurons and oligodendrocytes, reduce inflammation, promote axon regrowth, and recover motor and sensory functions. This research has proven highly promising in animal models and has raised challenges regarding differentiation, safety, and integration mechanisms.

The damaged CNS is difficult to repair because mature neurons do not divide after an injury, and a glial scar forms with reactive astrocytes and the presence of inhibitory molecules such as Nogo-A that block axonal regrowth (7). Stem cells can differentiate into neurons, oligodendrocytes (to remyelinate axons), and astrocytes, and can be useful therapeutic tools, replacing damaged cells. They can elongate axons and dendrites, form functional synapses, and integrate into existing neuronal circuits. Therefore, stem cells may be important for the functional recovery of the CNS.

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In addition to replacing nonfunctioning cells, mesenchymal stem cells also act by reducing inflammatory dynamics, inhibiting the immune response, and modifying the glial scar. Stem cells generate various molecules such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-line derived neurotrophic factor (GDNF) (8). These proteins promote neuronal survival, increase synaptic plasticity, and stimulate axonal growth. The formation of these molecules involves the Wnt/ $\beta$ -catenin pathway, which is involved in neuronal differentiation; the Notch pathway, which regulates cell proliferation; and the Sonic hedgehog (Shh) pathway, which participates in neural development and regeneration. These molecular pathways regulate the transition between stem cells and nerve cells.

Stem cells can also play a key role in remyelination by activating oligodendrocytes to produce new myelin and reactivate nerve impulses. Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by demyelination and axonal damage. Stem cells hold great promise in MS research (9). MS is an inflammatory disease in which the immune system attacks myelin and it can affect both the brain and spinal cord, causing motor, sensory, and cognitive deficits. Stem cells are useful in MS by modulating the immune system, which is reset by reducing the autoimmune attack on myelin.

## CONCLUSIONS

Stem cells possess two fundamental characteristics: long-term replication and transformation into specialized cells such as neurons, astrocytes, oligodendrocytes, and so on. Treating the CNS with stem cells is one of the most important fields of regenerative medicine, with the goal of using stem cells to replace damaged neurons, repair tissue, and reduce inflammation. The main clinical applications include Parkinson's disease, spinal cord injury, MS, and amyotrophic lateral sclerosis.

### *Conflict of interest*

The author declares that they have no conflict of interest.

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# **DIRECT ACTION OF THE HUMAN JAGN1 GENE ON THE IMMUNE SYSTEM AND INDIRECT ACTION ON THE NERVOUS SYSTEM**

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**KEYWORDS:** *Jagunal homolog 1, JAGN1, gene, neutrophil, immune system, central nervous system*

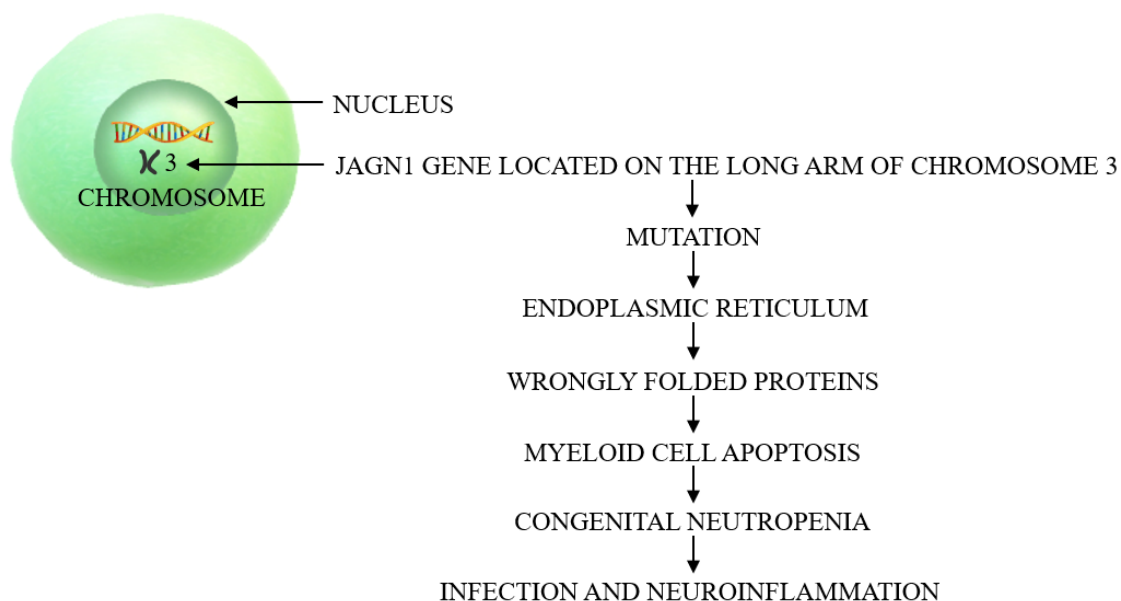
## **INTRODUCTION**

Jagunal homolog 1 (JAGN1) is a crucial gene located in the endoplasmic reticulum (ER) that regulates the function of certain immune cells, such as neutrophils and B cells, and is also important for the proper production and glycosylation of antibodies (1). JAGN1 is active in neutrophil immunity against fungal infections, making it a novel regulator of neutrophils against difficult-to-eradicate pathogenic microbes (2). By affecting glycosylation through modification of the sugar molecule, it is crucial for maintaining humoral immunity which is carried out by IgG antibodies.

## **DISCUSSION**

Although JAGN1 is not a nervous system-specific gene, it has indirect connections in various biological tissues, including the central nervous system (CNS), because it is ubiquitously expressed (3). In the brain, nerve cells depend on a well-functioning ER for the synthesis and proper folding of proteins. Mutations in JAGN1 (SCN6) can cause severe congenital neutropenia with neurological signs described in some patients (4) (Fig.1).

### STEPS FROM MUTATION LEADING TO INFECTION AND NEUROINFLAMMATION



**Fig. 1.** Figure indicating the progressive steps from mutation of the JAGN1 gene located on the long arm of chromosome that leads to infection and neuroinflammation.

At the level of the CNS, the G6PC3 genetic defect can cause delayed psychomotor development, hypotonia, cognitive difficulties, and more rarely, epileptic seizures. This can interfere with neuronal development, synaptic transmission, and neuronal survival. Neutropenia can lead to recurrent infections (particularly of bacterial nature) and chronic inflammation, impacting neurodevelopment, especially in childhood.

SCN type 6 is a severe genetic neutropenic disorder characterized by very low neutrophil counts from birth and an increased risk of serious infections and mental retardation (5). This is considered a primary immunodeficiency caused by mutations in the G6PC3 gene. The disease is inherited in an autosomal recessive manner, and the G6PC3 gene is implicated in glucose metabolism and neutrophil survival. Neutrophil counts often fall below 500/ $\mu$ L due to a maturation defect in the bone marrow. In addition, neutrophils often undergo apoptosis, causing recurrent and severe infections. Neutrophil deficiency can manifest from birth, causing stomatitis, skin infections, and pneumonia. The G6PC3 genetic defect and neutrophil deficiency can cause congenital heart defects, growth retardation, mild facial abnormalities, urogenital abnormalities, and sometimes, pulmonary hypertension. A JAGN1 defect can lead to ER stress and altered glycosylation.

Diagnosis SCN type 6 is made by performing a complete blood count for neutropenia, bone marrow analysis for neutrophil maturation blockade, and genetic testing for the G6PC3 gene mutation (5). Treatment involves administering granulocyte growth factor (G-CSF), antibiotics, and monitoring for infections (6).

### CONCLUSIONS

The human JAGN1 gene, which is not expressed primarily as a neural regulatory gene, directly affects the regulation and functioning of the immune system. JAGN1 influences neutrophil function, protein transport in the ER, and the survival of innate immune cells. Mutations in this gene lead to immunodeficiency with recurrent infections. Therefore, JAGN1 affects the nervous system indirectly, but its effect on the immune system can lead to chronic inflammation, increased susceptibility to infections, and systemic stress responses.

#### *Conflict of interest*

The author declares that they have no conflict of interest.

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# MYD88: AN ADAPTOR OF THE INNATE IMMUNE RESPONSE

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## ABSTRACT

Myeloid Differentiation Primary Response 88 (MyD88) is a key adaptor protein of the innate immune system that acts as a bridge between other proteins, connecting components of a signalling pathway or cellular process that would otherwise not interact directly. MyD88 is an intracellular adaptor of the Toll-like receptors (TLRs) and IL-1 receptor (IL-1R) signaling pathways. In the central nervous system (CNS), MyD88 helps regulate the response of microglia against infections. Microglia express TLRs that recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Toll-like IL-1 receptor (TIR) domain of the TLR recognizes MyD88, triggering a series of reactions that lead to the formation of NF- $\kappa$ B and the production of cytokines (including IL-1 $\beta$ , TNF, and IL-6) and pro-inflammatory chemokines. Activation of these kinases induces AP-1 and the inflammasome, indirectly stimulating the generation of IL-1 $\beta$  and IL-18. The participation of MyD88 in the inflammatory process can exacerbate both infectious diseases and neurodegenerative disorders.

**KEYWORDS:** *Myeloid Differentiation Primary Response 88, MyD88, adaptor protein, Toll-like receptor, IL-1 receptor*

## INTRODUCTION

Myeloid differentiation primary response 88 (MyD88) is a key intracellular adaptor of the Toll-like receptors (TLRs) and IL-1 receptor (IL-1R) signaling pathways (1). The relationship between MyD88 and microglia is very important for regulating the innate immune response in the central nervous system (CNS) (2).

MyD88 is expressed in immune cells such as macrophages, dendritic cells, neutrophils, epithelial cells, and B lymphocytes. TLRs are part of the innate immune system and are important as "sensors" for the presence of microorganisms, to recognize microbial signaling molecules. For example, TLR4 recognizes bacterial lipopolysaccharide (LPS), TLR3 and TLR7 recognize viral RNA, TLR9 recognizes bacterial DNA, and TLR2 recognizes peptide-binding molecules (3). After TLR activation, the receptor's Toll-like IL-1 receptor (TIR) domain binds to the TIR domain of MyD88, which acts as a molecular bridge (4).

MyD88 transmits activation signals from TLRs and IL-1 receptors to the cell nucleus, activating the inflammatory response. The TIR domain is a cytoplasmic protein domain found in TLRs, and in the IL-1 and IL-18 receptors. After ligand-receptor binding, the receptor dimerizes, the cytoplasmic TIR domains approach each other, and a TIR-TIR bond is formed between the receptor and the adaptor (5). The TIR domain is essential for signal transduction. MyD88 is the primary adaptor for IL-1, IL-18, and all TLRs except TLR3 (6). When a TLR recognizes a Pathogen-Associated Molecular Pattern (PAMP), which can be a microorganism or a foreign molecule, MyD88 is recruited, activating IL-1R-

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associated kinase (IRAK) 4 and leading to the formation of IRAK1, Tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF) activation, NF- $\kappa$ B activation, and mitogen-activated protein kinase (MAPK) activation, resulting in the transcription of pro-inflammatory genes (7,8) (Table I).

**Table I.** *MyD88-dependent signaling pathway in microglia.*

i.	TLR: PAMPs and DAMPs
ii.	MyD88
iii.	IRAK4 and IRAK1
iv.	TRAF6
v.	NF- $\kappa$ B and MAPK $\rightarrow$ TNF, IL-1, IL-6

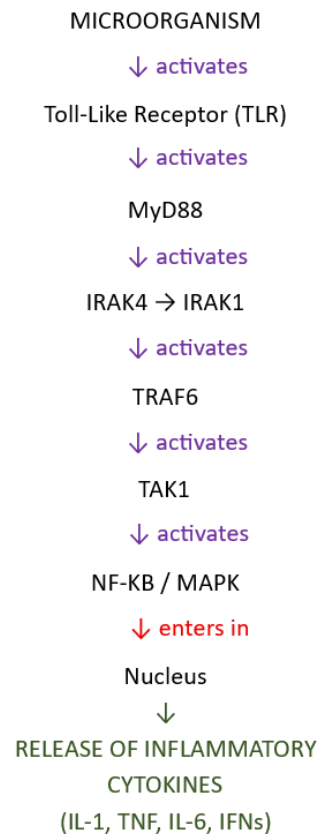
## DISCUSSION

MyD88 is a key adaptor in the signaling pathway of many TLRs and the IL-1 receptor (9). Activation of TLRs and IL-1R leads to the activation of NF- $\kappa$ B and MAPK, resulting in the production of inflammatory cytokines and chemokines (10). The role of MyD88 in neuroinflammation can be both protective and pathological (11). It is protective because it allows for the rapid recognition of pathogens such as viruses, bacteria, etc., and pathological because excessive activation of MyD88 can cause inflammation due to the release of pro-inflammatory cytokines such as IL-1 and TNF (12). These effects can exacerbate the progression of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), by amplifying oxidative stress and the toxic effects of microglial cells (13). Therefore, MyD88 is important for immune defense and brain recovery, but if its activation is continuous (chronic), it can become pathogenic (14). Inactivation of MyD88 in knockout animal models leads to inefficient microglia with reduced neuroinflammation, but also with impaired immune defense (15).

TLRs, with the exception of TLR3, use MyD88 as their primary adaptor. Brain-based microglia immune cells express TLRs that recognize PAMPs and danger-associated molecular patterns (DAMPs). When these receptors are activated, they are able to recruit the adaptor MyD88, and PAMPs and DAMPs bind to TLRs on the membrane of microglia cells. The TIR domain of the TLR recognizes MyD88, which recruits the kinases IRAK4 and IRAK1 (16). A large oligomeric intracellular multiprotein complex called the Myddosome is subsequently formed (17). IRAK phosphorylates and activates TRAF6, an E3 ubiquitin ligase, activating signaling pathways (18). NF- $\kappa$ B translocates to the nucleus and induces pro-inflammatory cytokine genes such as TNF, IL-1 $\beta$ , and IL-6.

The kinases p38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) activate factors such as AP-1, and the inflammasome, which is indirectly stimulated, participates in the maturation of IL-1 $\beta$  and IL-18 (19). Once activated, microglia produce pro-inflammatory cytokines and chemokines, causing increased expression of major histocompatibility complex class II (MHC-II) surface molecules and CD86, which has the ability to present antigen (9).

Viruses are recognized by endosomal TLR7, TLR8, and TLR9, while bacteria use TLR4 for LPS, TLR2 for peptidoglycan, TLR5 for flagellin, and TLR9 for bacterial DNA (20). Beta-glucans and mannans from fungi are recognized by TLR2 and TLR4 in association with Dectin-1 (21). After activation of the TLR or IL-1R, MyD88 is recruited via the TIR, resulting in the formation of the Myddosome signaling complex (22). MyD88 subsequently recruits IRAKs, which leads to the activation of IRAK4 and the phosphorylation of IRAK1/2 (23). After this, TRAF6 and TAK1 are activated, leading to the MAPK cascade (p38, JNK, ERK), the IKK complex, and NF- $\kappa$ B, which translocates to the nucleus, where genes for pro-inflammatory cytokines are activated and cytokines such as IL-1, TNF, and IL-6 are produced (24). AP-1 activated by MAPK leads to further inflammatory gene transcription (25). In viral inflammation, TLR3 activation does not use MyD88, but TRIF, which leads to the production of type I interferon (IFN) (26) (Fig. 1).



**Fig. 1.** Activation of Toll-like receptors (TLRs) by microorganisms leads to a biochemical cascade which ultimately results in the release of inflammatory cytokines.

Viral activation of MyD88 can result in positive, and therefore, protective clinical effects due to the production of IFNs and cytokines that limit viral replication. Activation also promotes the development of the immune adaptive response (27). Furthermore, in early infections, such as with RNA viruses such as influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis C virus (HCV), etc., MyD88 is important for reducing viral load in the initial stages (28). Hyperstimulation of MyD88 can result in a pro-inflammatory cytokine storm with tissue damage and acute respiratory distress syndrome (ARDS) in severe viral infections (29). In chronic infection, MyD88 contributes to the pathogenesis of viral hepatitis or persistent chronic infections, such as those caused by hepatitis B virus (HBV), HCV, or human immunodeficiency virus (HIV) (30). In autoimmune diseases, activation of TLR/MyD88 by viral nucleic acids can promote lupus, rheumatoid arthritis, and Sjögren's disease (31). In virally induced oncogenesis, such as Epstein-Barr virus (EBV)-positive lymphomas, HCV/HBV-induced liver cancer, and so on, chronic MyD88 stimulation can promote cell proliferation and survival (32).

Respiratory infections may cause fever, cough, and severe inflammation, due to activation of MyD88 leading to NF- $\kappa$ B with the release of inflammatory cytokines and chemokines (33). Autosomal recessive MyD88 deficiency is rare but can lead to severe pyogenic bacterial infections (34). However, compared to viruses, it may cause a less severe cytokine storm and therefore, less damage (35).

#### *Role of MyD88 in the central nervous system*

Microglia express TLRs such as TLR4, which recognize pathogenic PAMPs such as LPS, lipoproteins, and viral RNA/DNA. Except for TLR3, all TLRs signal via MyD88. Activation of IRAK, TRAF6, and TAK1 leads to NF- $\kappa$ B and MAPK (AP-1) transcription and signal transduction. In the CNS, MyD88-mediated production of inflammatory cytokines leads to neuroinflammation which can be helpful to fight infections. However, if the response is excessive and chronic, it becomes harmful, as occurs in neurodegenerative diseases. In fact, MyD88 is implicated in AD, MS, PD, and amyotrophic lateral sclerosis (ALS) (13). In these diseases and after trauma and cerebral ischemia, MyD88 can exacerbate the damage through inflammation, but also promote debris removal and repair.

## CONCLUSIONS

MyD88 plays an essential physiological role in the innate immune response and is linked with adaptive immunity. MyD88 functions physiologically in the production of pro-inflammatory cytokines, such as IL-1, TNF, and IL-6. It can also activate various immune cells such as macrophages, neutrophils, and dendritic cells. At the molecular level, MyD88 can stimulate the expression of MHC-II costimulatory molecules for antigen presentation. In the absence of MyD88, the innate immune response can be compromised. MyD88 activation leads to immune response polarization (Th1/Th17) and B cell activation. In macrophages and microglia, MyD88 is important for activating the inflammatory response.

MyD88 activation is essential for innate immunity and the body's immediate defenses. Chronic MyD88 activation can lead to a cytokine storm with clinical consequences from hyperinflammation, or autoimmunity.

An excessive MyD88 response can be harmful in the CNS and mediate neurodegeneration, which has been seen in diseases such as MS, AD, PD, and ALS.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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# INFECTION, IL-1 $\beta$ , TNF, AND ALZHEIMER'S DISEASE

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## ABSTRACT

Interleukin-1 beta (IL-1 $\beta$ ) and tumor necrosis factor (TNF) are two molecules that regulate the immune system, but they are also highly inflammatory cytokines. IL-1 $\beta$  and TNF are produced primarily by monocytic cells and macrophages, but can also be generated by non-immune cells such as fibroblasts, endothelial cells, muscle cells, and others. IL-1 $\beta$  and TNF can be activated by pathogenic microorganisms and can induce systemic inflammation and fever, leading to septic shock. IL-1 $\beta$  and TNF are linked to the nervous system through the neuroimmune axis, a continuous cross-talk between the immune system and the brain. The influence of IL-1 $\beta$  and TNF on the central nervous system (CNS) manifests itself through their action on the hypothalamus, producing fever and neuroinflammation with microglia activation and increased blood-brain barrier (BBB) permeability, effects that can contribute to degenerative diseases such as Alzheimer's disease (AD), multiple sclerosis, and Parkinson's disease. In AD, IL-1 $\beta$  and TNF are produced primarily by activated microglia in response to the accumulation of  $\beta$ -amyloid. Increased IL-1 $\beta$  in affected brain areas stimulates microglial activation, while elevated TNF in the brain and cerebrospinal fluid is protective at low concentrations and neurotoxic at high levels and can induce apoptosis. Therapies that block IL-1 $\beta$  and TNF improve the neuroinflammatory process.

**KEYWORDS:** *Alzheimer's Disease, infection, cytokine, neuroinflammation, immunity*

## INTRODUCTION

Interleukin-1 beta (IL-1 $\beta$ ) and tumor necrosis factor (TNF) are cytokines that regulate the immune system and are produced primarily by macrophages and other immune and non-immune cells such as fibroblasts, endothelial cells, muscle cells, and others (1). IL-1 $\beta$  and TNF are mediators of inflammation and fever and are major activators of endothelial cells. When these cytokines are overproduced, they attract neutrophils to the inflammatory site, increasing local inflammation.

IL-1 $\beta$  and TNF are activated by pathogenic microorganisms and can also induce systemic inflammation, leading to toxic shock syndrome (2). Sepsis and septic shock are primarily mediated by TNF, which induces IL-1 $\beta$ , while acute bacterial infections are mediated by both cytokines (3). Some autoimmune inflammatory diseases, such as rheumatoid arthritis, are mediated primarily by IL-1 $\beta$  and TNF, while in Crohn's disease, the predominant cytokine is TNF (4,5). For Crohn's disease, the anti-TNF drug infliximab is used, while for rheumatoid arthritis, anakinra (anti-IL-1) is used.

Bacteria, viruses, fungi, and parasites can activate cells of the immune system, resulting in the production of pro-inflammatory cytokines such as IL-1 $\beta$  and TNF. Early immune defense cells such as macrophages, neutrophils, and dendritic cells recognize microbes through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs) (6). These receptors are recognized by pathogen-associated molecular patterns (PAMPs), which are microbial components, lipopolysaccharide (LPS) from Gram-negative bacteria, peptidoglycan, and viral RNA,

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among others (7). PRR activation leads to intracellular NF- $\kappa$ B signaling, inflammasome activation, and the production of inflammatory cytokines (8). Among the biological effects of IL-1 $\beta$ , it is worth noting its action on the hypothalamus, producing fever, while on the endothelium, it causes increased vascular permeability (9). Furthermore, IL-1 $\beta$  affects neutrophil recruitment and endothelial cell activation (10). TNF is also a potent pro-inflammatory molecule that promotes vasodilation and blood vessel permeability and helps recruit immune cells, including macrophages and neutrophils (11). IL-1 $\beta$  induces TNF, and vice-versa, creating a synergetic effect that augments inflammation. IL-1 $\beta$  and TNF stimulate the production of arachidonic acid, which in turn generates prostaglandins and leukotrienes, powerful mediators of inflammation and pain (12).

## DISCUSSION

IL-1 $\beta$  and TNF are pro-inflammatory cytokines involved in important immune processes for the body's survival but also contribute to many inflammatory diseases (13). They stimulate each other, and when one is generated and released in response to stimuli, including infections or tissue damage, it can stimulate the other.

IL-1 $\beta$  and TNF have similar redundant effects, as seen in vascular permeability, fever, and macrophage activation (14). The synergistic effect of these two cytokines can worsen the inflammatory state. IL-1 $\beta$  and TNF cause tissue damage primarily through their ability to recruit inflammatory immune cells (15). These two cytokines stimulate various cellular responses involving a variety of cells, such as macrophages, lymphocytes, neutrophils, and mast cells.

IL-1 $\beta$  and TNF act on blood vessels by increasing permeability and activating vascular endothelial growth factor (VEGF). IL-1 $\beta$  and TNF have different receptors and can therefore act synergistically. Bacteria, viruses, fungi, and parasites enter the human body and stimulate innate immune cells, which generate IL-1 $\beta$  and TNF. Innate immune cells are primarily macrophages and dendritic cells, considered sentinel cells, that recognize PAMPs via PRRs, which include TLRs and NOD-like receptor receptors (16). These reactions lead to the intracellular activation of NF- $\kappa$ B and MAPK signalling pathways, resulting in the production of pro-inflammatory cytokines, including IL-1 $\beta$  and TNF (17). However, IL-1 $\beta$  and TNF exhibit different biological effects (18).

IL-1 $\beta$  recognizes PAMPs and damage-associated molecular patterns (DAMPs) and activates the inflammasome, while TNF recognizes microbes and triggers the activation of T and natural killer (NK) cells (19). Furthermore, IL-1 $\beta$  activates the endothelium, causing the expression of adhesion molecules that promote leukocyte recruitment, increases vascular permeability, and activates macrophages and neutrophils (20). TNF acts similarly to IL-1 $\beta$  on the endothelium and vascular permeability, causes strong immune cell recruitment through chemokines, and induces apoptosis in some cells (21). At the systemic level, IL-1 $\beta$  is the endogenous pyrogen that induces fever by acting on the hypothalamus, where it stimulates prostaglandins and increases acute-phase reactants (9). TNF, on the other hand, is less potent in inducing fever, activates lipid and protein metabolism, and at high concentrations causes septic shock with hypotension and disseminated intravascular coagulation. Both cytokines are key acute-phase reactants, but TNF is more closely associated with systemic damage, while IL-1 $\beta$  is more associated with fever and inflammasomes. However, a strong induction of local inflammation leads to systemic inflammation (22).

### *Acute molecular inflammation*

Acute molecular inflammation induced by microorganisms is an immediate defensive response of the human body against infectious agents. It is a complex process involving immune cells, chemical mediators, and recognition receptors. TLRs, NOD-like receptors, and RIG-1 recognize PAMPs, which are characteristic molecules such as LPS from Gram-negative bacteria, peptidoglycans, and viral RNA (23). They also recognize DAMPs released by damaged cells (24). These events are followed by the activation of immune cells such as macrophages, dendritic cells, mast cells, and neutrophils. Macrophages produce cytokines, mast cells release histamine and other chemical mediators, and neutrophils, attracted by chemokines (such as IL-8), migrate to the infection site by chemotaxis (25). Together, these processes fuel inflammation and produce clinical symptoms. Other molecular mediators are the complement system (which helps lyse microorganisms), prostaglandins and leukotrienes which cause vasodilation, and reactive oxygen species which participate with their enzymes in destroying pathogens.

### *Chronic inflammation*

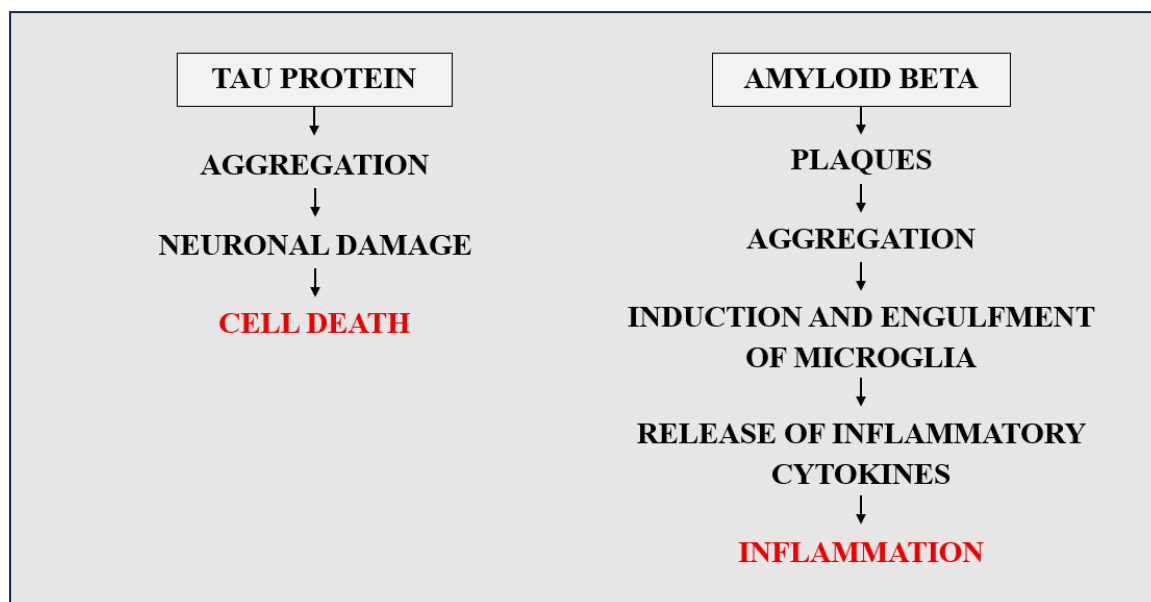
Chronic inflammation differs from acute inflammation because it persists over time. Microorganisms often remain at the inflamed site and infection is difficult to eliminate, continuously stimulating the immune system. Some of the microorganisms that induce chronic inflammation is *Mycobacterium tuberculosis* and *Helicobacter pylori*. Viruses that induce hepatitis (B or C) not only cause chronic inflammation but can also cause liver cancer (26). In the continuous

immune activation exerted by these microorganisms, the adaptive immune response (T and B lymphocyte response) prevails, in addition to the innate immune response (27). Chronic inflammation causes progressive tissue damage, due not only to the pathogen but also to inflammatory molecules produced by host cells. During the recognition phase, PRR stimulation (TLR, NOD-like, and RIG-I) by PAMPs, such as bacterial peptidoglycan or chronic viral RNA, persists (28). In addition, there is activation of PAMPs from damaged cells.

CD4<sup>+</sup> T lymphocytes (Th1 and Th17) produce interferon-gamma (IFN- $\gamma$ ) and IL-17, which stimulate macrophages and attract neutrophils to the inflammatory site (29). In this context, B lymphocytes activated by IL-4 from T cells continuously produce antibodies and can sometimes also produce autoantibodies. Fibroblasts are stimulated by transforming growth factor-beta (TGF- $\beta$ ) and generate collagen, which induces fibrosis (30). Chronically produced cytokines and proteases degrade the extracellular matrix, while TGF- $\beta$  participates in wound healing and fibrosis (31). These events can lead to the formation of granulomas, chronic fibrosis, and a risk of cancer.

### *Alzheimer's Disease*

Much modern research is devoted to the study of Alzheimer's Disease (AD), whose exact cause remains unknown to this day. The difference between a healthy brain and one affected by AD is based on ventricular dilation; the more serious the disease, the more dilation is observed (32). AD is characterized by the formation of tau proteins and  $\beta$ -amyloid (33). The anomaly of tau protein twists to form plaques and tangles which can damage neurons and cause the death of cells (34). However, there are cases in which AD is caused by accumulation of the protein  $\gamma$ -synuclein, which causes vascular damage (35). Tau protein aggregates and damages neurons, while  $\beta$ -amyloid forms plaques that inflame brain tissue and activate and engulf microglia, which subsequently produce inflammatory cytokines (36) (Fig.1).



**Fig. 1.** Steps leading to cell death and inflammation in Alzheimer's disease (AD). Tau protein aggregates and causes neuronal damage resulting in the death of neurons.  $\beta$ -amyloid forms plaques which aggregate and induce and engulf microglia, resulting in the activation and release of inflammatory cytokines.

### CONCLUSIONS

IL-1 $\beta$  and TNF are cytokines produced primarily by macrophages and other innate immune cells in response to pathogenic microorganisms such as viruses, bacteria, fungi, and parasites, but when produced in excess, they are powerful pro-inflammatory molecules. IL-1 $\beta$  and TNF are generated after activation of innate immune receptors, including TLRs. These two cytokines are released when innate immune receptors recognize microbial components such as PAMPs. Among the most important effects of IL-1 $\beta$  and TNF are fever, increased vascular permeability, and leukocyte recruitment.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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# THE RELATIONSHIP BETWEEN INTESTINAL MICROBIOTA AND THE CENTRAL NERVOUS SYSTEM

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## ABSTRACT

There are bidirectional interactions between the intestine and the central nervous system (CNS), both in the case of pathologies and in health. The human intestine hosts many types of microorganisms which can regulate intestinal hemostasis and modulate intestinal pathologies, including inflammatory ones. The CNS regulates various intestinal functions such as blood circulation, motility, and secretion. Psychological stress can aggravate colon diseases, such as ulcerative colitis. The intestine can signal an inflammatory state of the mucosa, pain, and nociceptive responses to the CNS. However, the exact mechanism that regulates the relationship between intestinal microbiota and the brain is still unclear. The pathogenic microorganisms that harbor the intestine engage in crosstalk with the primary afferent neurons of the intestinal tissue. The perception of intestinal stimuli is modulated by the CNS with the involvement of the sympathetic and parasympathetic systems. The microbiota interacts with the intestinal effector mechanisms and with the afferent pathways of the stomach and intestine, creating a bidirectional system that goes from the intestine to the brain and vice-versa. Studying these interactions can better clarify the pathogenic mechanisms that underlie various inflammatory intestinal diseases.

**KEYWORDS:** *Brain, intestine, microbiota, CNS, bidirectional communication, gut-brain axis, immune system*

## INTRODUCTION

The intestine and the central nervous system (CNS) are engaged in bidirectional interaction, both in the case of pathologies and homeostasis. Pathogenic microorganisms that harbor the intestine also participate in this crosstalk with the nervous system and can affect afferent neurons to influence gut motility, secretion, and pain perception.

The gut microbiota plays an important role in the physiology of host organs, including the brain, and communicates with the CNS through molecular and cellular mechanisms (1-4). The gut-brain axis is a bidirectional crosstalk system between the two organs, regulated by the immune system, the central and enteric nervous systems, and the endocrine system (3). Communication occurs through neural, molecular, immune, and metabolic pathways.

## DISCUSSION

The CNS communicates primarily with microbiota through neuronal pathways and the vagus nerve (4). At the cellular level, bacteria produce metabolites such as GABA, which communicate with the CNS (5). The metabolites activate enteric

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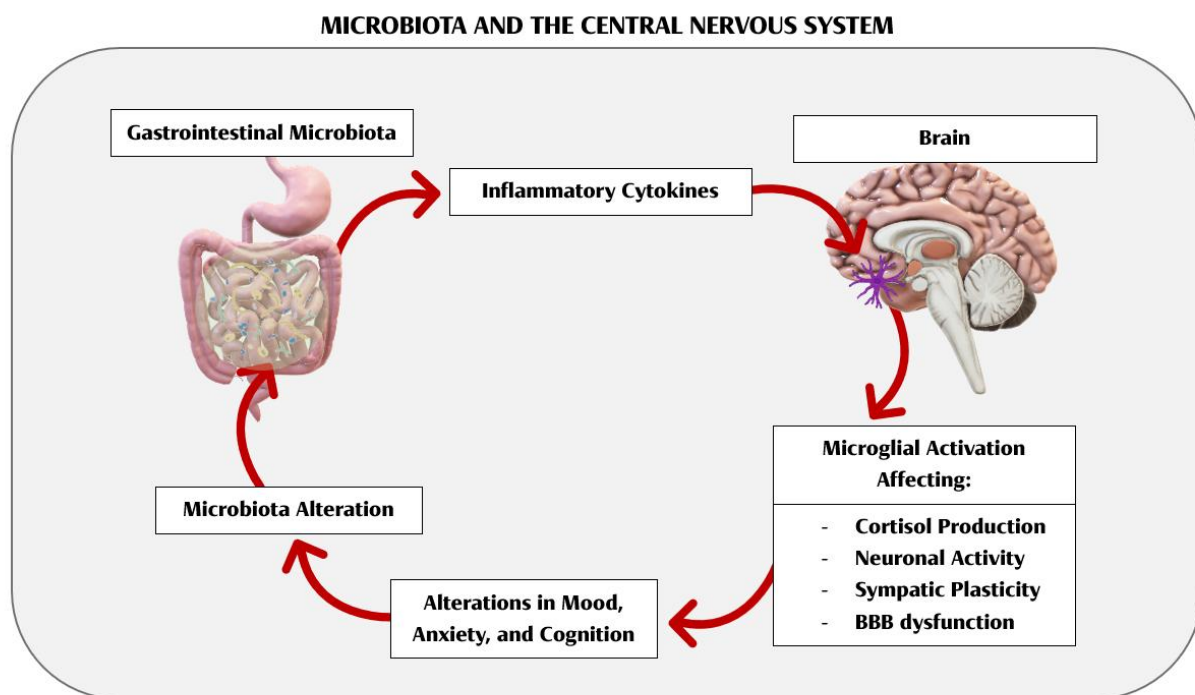
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neurons and enteroendocrine cells, which transmit signals to the CNS through the vagus nerve (4). At the molecular level, communication between the gut and CNS occurs through neurotransmitters such as serotonin produced in the gut, GABA, and dopamine (2). These reactions activate various receptors, such as G protein-coupled receptors and ionotropic receptors, which affect anxiety, mood, and stress (6). The metabolic pathway is activated by microbial metabolites such as short-chain fatty acids, butyrate, propionate, and acetate (7). At the molecular level, these molecules bind to GPR41/GPR43 receptors and inhibit histone deacetylases that modulate epigenetics (6). Microbial metabolites strengthen the blood-brain barrier (BBB) by modulating microglia, neuroinflammation, and neuroplasticity (8).

The main tryptophan metabolites, including serotonin, melatonin, niacin (vitamin B3), and kynurenine derivatives, have effects on the regulation of neurotransmission and modulation of inflammatory tone in the CNS (9). The immune and inflammatory response in the brain is primarily triggered by microglia, with a cellular mechanism of dysbiosis that causes increased intestinal permeability known as leaky gut (8). This allows lipopolysaccharides (LPS) and microbial pathogen-associated molecular patterns (PAMPs) to pass through the tissues, activating a molecular mechanism involving Toll-like receptors (TLRs) and nod-like receptors (NLRs) (10). These latter molecules are important for the production of inflammatory cytokines produced by activated microglia, leading to neuroinflammation (11,12). The endocrine pathway is represented by the hypothalamic-pituitary-adrenal (HPA) axis, which involves a molecular mechanism in which stress plays a role, resulting in increased cortisol (13). The microbiota modulates the expression of glucocorticoid receptors in response to stress, alters neuronal maturation, and modifies behavioral responses (14).

Abnormal functioning of gut microbiota is connected to abnormal immune responses with altered production of inflammatory cytokines and is linked to autoimmune/immune-mediated diseases such as rheumatoid arthritis (15,16) (Fig.1).



**Fig. 1.** Alterations in gastrointestinal microbiota activate inflammatory cytokines which stimulate microglia, causing alterations in mood and cognition with subsequent alterations of the microbiota. These reactions are bidirectional components of the gut-brain axis.

## CONCLUSIONS

At the molecular level, the gut microbiota influences short-chain fatty acids, neurotransmitters, cytokines, and receptors, while at the cellular and systemic level, it is involved in the functions of enteric neurons, microglia, immune cells, the vagus nerve, HPA, and the BBB.

*Conflict of interest*

The author declares that they have no conflict of interest.

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