RESEARCH PAPER

Molecular Interplay Between Gut Barrier Dysfunction and Microglial Activation in Rheumatoid Arthritis: A Comprehensive Review

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder traditionally characterized by synovial inflammation and joint destruction. Emerging evidence highlights the importance of the joint–gut–brain axis, a bidirectional network integrating immune, neural, and microbial pathways. Gut dysbiosis contributes to increased intestinal permeability ("leaky gut"), allowing translocation of microbial products such as lipopolysaccharides (LPS) into systemic circulation. This promotes widespread immune activation and elevated pro-inflammatory cytokines, including TNF-α, IL-6, and IL-17. These circulating mediators disrupt the blood–brain barrier (BBB) and activate microglia, the resident immune cells of the central nervous system, leading to neuroinflammation. Activated microglia further release cytokines and neurotoxic mediators, contributing to central sensitization, fatigue, and cognitive dysfunction observed in RA patients. Additionally, neuroinflammation induces autonomic imbalance, particularly vagal suppression, exacerbating gut barrier dysfunction and perpetuating systemic inflammation. This review summarizes current evidence linking gut dysbiosis, microglial activation, and neuroinflammation in RA pathogenesis and highlights potential therapeutic strategies targeting this integrated axis, including microbiota modulation, cytokine inhibition, and neuroimmune regulation.

Keywords: Rheumatoid arthritis; gut–brain axis; microglia; leaky gut; neuroinflammation; cytokines; dysbiosis; blood–brain barrier.

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Introduction:

Arthritis is an inflammatory disease characterized by inflammation, stiffness, cartilage degeneration, and synovial swelling in the joints, often leading to joint dysfunction and potential disability [1.2]. According to statistics, approximately 23 % of Americans will be diagnosed with arthritis at least once in their lifetime [3]. The aetiology of RA is considered to be multifactorial, involving a complex interaction of genetic predisposition and environmental factors [4-6]. Clinically, anti-inflammatory/anti-rheumatic drugs can be used to alleviate arthritis symptoms, and surgical intervention facilitates the restoration of patients' function. However, they are often accompanied by significant side effects and complications. Despite the research effort, the exact aetiology of RA remains unknown and a complete cure for the condition is absent [7]. Consequently, it is of significant clinical importance to conduct thorough research into the onset and progression of arthritis diseases, as well as to discover new methods for preventing and treating them. In recent years, the roles of the gut-joint axis and brain-joint axis in the diagnosis and treatment of arthritis have garnered increasing attention [1,2]. Research indicates that dysbiosis of the Gut Microbiota (GM) is not only associated but also contributes to the onset of joint diseases like osteoarthritis (OA), rheumatoid arthritis

(RA), and spondyloarthritis (SpA) by disrupting intestinal homeostasis [8,9]. The connection between intestinal lesions and joint disease is believed to be potentially linked to various mechanisms, including the trafficking of GM and their metabolites, the aberrant movement of immune cells, the recognition of arthritogenic peptides, and the clonal expansion of T cells [8]. Although substantial clinical evidence demonstrates a close association between the gut and joint diseases, the precise mechanisms underlying the gut-joint axis remain incompletely understood with the development of gastrointestinal diseases such as inflammatory bowel disease (IBD),

Recent research on the association between brain and joint diseases has introduced the concept of the brain-joint axis. Interestingly, while studying neurodegenerative diseases, researchers discovered a bidirectional communication network between the central nervous system (CNS) and the gastrointestinal tract, leading to the concept of the brain-gut axis [10]. As research deepens, it has been discovered that this axis representing bidirectional information exchange between the brain and gut is not only associated with brain-related and gut-related diseases but is also believed to play a role in the development of arthritis [11,12]. The individual system of defence and biotransformation are intimately related to the brain - gut axis have an impact on how arthritis develops. As a result, the brain, gut and joint interact intricately, leading to the idea of the brain-gut-joint axis. The development and course of arthritis depend heavily on the interaction among the brain, gut, and joint. Thus, the goal of this review is to identify the interactions between the brain, gut and joints and to investigate their impact on the development and course of arthritis. Despite a variety of mechanisms, such as the control of the immunological, biological, hormonal, and cerebral mechanisms, such events may affect the joint milieu. As a result, this study provides a fresh viewpoint on the etiology and prognosis of arthritis, which has important ramifications for enhancing patient quality of life.

The role of the gut-joint axis in arthritis

Intestinalepithelial layer structure:

The intestinal epithelial layer forms the major barrier that separates our body from the external environment. Trillions of commensal bacteria reside in the gastro intestinal tract and have a vital role in digestion and the development of the immune system. However, they pre sent a risk of infection [13]. The maintenance of the intestinal epithelial barrier is the essential function of the intestinal epithelial cells (IECs). The IECs integrate positive and negative interactions from the microbiota living in the gut and signal the immune cells to accommodate the micro biota, thereby perpetuating the normal function of the body [14-16]. An imbalance in the intestinal barrier structure can flare up into an uncontrollable immune reaction in the intestinal microenvironment or allow the unrestrainedgrowth of microbiota, which leads to various diseases, including intestinal inflammatory disorders, extra intestinal autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, and metabolic disorders such as diabetes and obesity [16-18].

Intestinal epithelial Cells Barrier:

The intestinal epithelial barrier is a one-cell-thick internal lining of the gut that contains different types of epithelial cells. Underneath the epithelial layer, there is a thin layer of connective tissue, the laminapropria, which has a crucial role in nurturing healthy communication between the microbiome and the immune cells. The intestinal epithelial system is also home to immune cells, including dendritic cells, T cells, B cells, and macro phages, which function in close relation with the IECs to maintain intestinal homeostasis [15,19].Gut microbiota, consisting of hundreds of trillions of bacteria and viruses, are pivotal for the maintenance of a symbiotic relationship with immune cells.[20] Recent studies have reported compelling evidence for the metabolic, immunological, and physiological roles had by the gut microbiota. However, the first layer of defense in the epithelium of the gut is formed by a layer of mucus, which is critical for the limitation of the exposure of epithelial cells to the microbiome[21]. The absence of mucin, a highly glycosylated polymeric protein in the mucous layer, makes an animal vulnerable to intestinal inflammation.

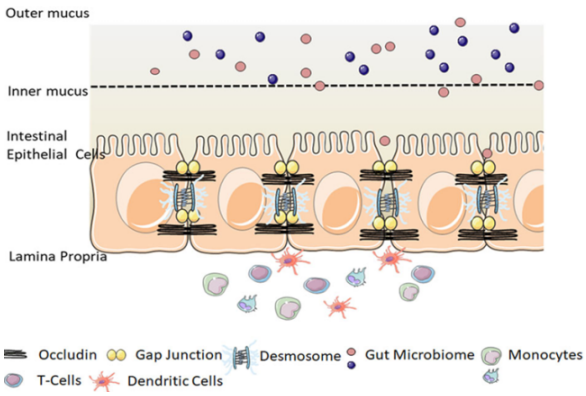

Fig. 1 Intestinal epithelial barrier (IEB)*. Epithelial cells form a layer that functions as a physical barrier facilitated by tight connections between each cell. A number of tight junction protein components seal the*

paracellular pathway and conduct gate and fence functions. The mucosal layer is a chemical barrier that is critical to limit the contact between the microbiome and epithelial cells. Immune cells are also a major participant in the immune response and the tolerance of the host against external substances.

Mechanism of regulation of intestinal epithelial tight junction proteins :

A crucial function of IECs is the maintenance of barrier integrity, which allows the permeability of essential ions, nutrients, and water but restricts the entry of bacterial toxins and pathogens.

The transport of molecules across the epithelial layer occurs through three major pathways: the trans-cellular pathway (passive diffusion across the cell membranes), the carrier-mediated pathway (carrier/ receptor-mediated trans-cellular pathway), and the para cellular pathway (passive diffusion between the spaces through adjacent cells).The epithelial tight junction proteins, is the "gate and fence function," which allows the paracellular transport of some solutes and molecules but prevents the intramembrane transport of proteins, lipids, and microbial-derived peptides[22,23].Any alteration in the tight junction structure can prove to be detrimental to the organism.

The tight junction is composed of several transmem brane and cytosolic proteins, including occludin, claudins, zonula occludens (ZOs), tricellulin, cingulin, and junctional adhesion molecules (JAM), which interact with each other, as well as with the cytoskeleton, and form a complex architecture27. Most of these proteins, except for cingulin and ZO, are integral membrane proteins that extend into the paracellular spaces between the cells. Cingulin and ZOs are cytoskeletal linker proteins, which interact with the cytoplasmic peripheral membrane pro teins, occludin, claudin, and JAM to form strong cross links and interact with the membrane cytoskeleton com posed of F-actin and myosin. Together with intracellular signaling proteins, tight junction proteins activate a plethora of cellular processes to maintain barrier integrity [24].

The expression level of occludin was found to be closely correlated with the barrier properties in vitro and in vivo [25]. Interestingly, occludin knockout mice had morphologically intact tight junctions but displayed complex histological phenotypes, with chronic inflammation and a defective epithelial barrier, which implicated that its crucial role was in tight junction stability rather than tight junction assembly. In contrast, certain other studies reported normal barrier function in occludin deficient mice but showed chronic inflammation and hyperplasia in the gastric epithelium and testicular atrophy [26]. Severely compromised occludin expression has been observed in disease models of intestinal inflamma tory diseases, which suggests it has a critical role in the maintenance of barrier integrity [27].

Tight junction proteins are closely regulated, which is imperative for the maintenance of normal barrier integrity. IECs proliferate rapidly and renew quickly, and it is essential that the tight junction proteins are also strictly regulated to avoid any detrimental effect on membrane integrity [28]. They are also capable of efficiently adapting to the different demands of the cell by sealing, opening, and maintaining paracellular transport under various physio logical and pathological conditions [29]

The mechanism of the regulation of tight junction proteins is intricate and somewhat obscure. The tight junction proteins are regulated by multiple signaling proteins and signaling molecules. Several molecules involved in the signal transduction processes, including small GTP-binding proteins and tyrosine kinases, have been found to be localized at these tight junctions, presumably indicating their pivotal role in the maintenance of tight junction integrity [30,31]. A significant body of evidence has highlighted the role of cytokines in the regulation of various tight junction proteins in a multitude of pathological conditions. Tumor necrosis factor-α (TNFα), interferon-γ (IFN-γ), and interleukins all are well-known for their indisputable role in the regulation of tight junction integrity [32]. TNFα is a key player in the caveolin-1-mediated internalization of occludin, which elevates gut permeability; further, the overexpression of occludin alleviates the cytokine induced increase in gut permeability [33]

Intestinal Dysbiosis, Tight Junction Proteins, and Inflammation in Rheumatoid Arthritis:

Intestinal permeability, a crucial aspect of gastrointestinal physiology, has gained attention for its potential implications in various systemic inflammatory conditions, including autoimmune disorders such as RA [34-36]. Although RA patients are likely to present with a higher intestinal permeability, only a few studies have succeeded in making conclusions about intestinal permeability [37]. Thus, elevated intestinal permeability in RA patients remains to be further investigated. Among the various players responsible for intestinal permeability, the tight junctions (TJs) stand out,

whose function is regulated by several factors of two routes [38]. TJs are composed of a complex network of proteins. In terms of their function in the TJs, the transmembrane proteins occludin and claudin-1 are structural components of the TJs, while zonulin, a protein secreted by epithelial cells, is a potent regulator of the TJs. Therefore, these proteins play pivotal roles in maintaining the integrity of the intestinal barrier. Fig 1 resumes the role terms of their function in the TJs, the transmembrane proteins occludin and claudin-1 are structural components of the TJs, while zonulin, a protein secreted by epithelial cells, is a potent regulator of the TJs. [39, 40] Therefore, these proteins play pivotal roles in maintaining the integrity of the intestinal barrier. Figure:1 resumes the role and the existing interrelation of the three proteins. Investigating the relationship between these proteins and RA may provide insights into the underlying mechanisms linking the gut and systemic inflammation.

Despite the growing interest in the potential link between intestinal permeability and RA, the existing literature lacks conclusive evidence. Previous studies have described that increased epithelial permeability in RA patients is likely to lead to oral and intestinal microbiota products influencing the pathogenesis and disease activity [41,42].

Another modifying factor of intestinal permeability is the gut microbiota. The relationship between intestinal barrier function and gut microbiota has been communicated [35]. Previous studies have established that RA patients present dysbiosis in different grades and a lower microbiota diversity compared to healthy individuals [43-45]. Furthermore, it is thought that intestinal dysbiosis associated with clinical characteristics of RA, such as immunoglobulin.

The gut-brain-immune system's mechanisms for communication:

The two-way communication between the gut microbiota, immune system, and CNS establishes the foundation of the gut–brain–immune axis. This interactive triad engages through various interconnected pathways, including neural pathways (via the vagus nerve and the enteric nervous system (ENS)), endocrine signals (hormones secreted by entero-endocrine cells), immune responses (cytokine signaling), and metabolic processes (microbial metabolites such as short-chain fatty acids (SCFAs)).[46, 47] Gut microbes can affect brain activity, immune function, and neuroinflammation through these routes. Dysregulations in this system have increasingly been associated with the onset of NDs, emphasizing the microbiome as an essential and modifiable factor in the progression of these diseases.[48,49] The subsequent sections will delve into these mechanisms in greater depth.

Gut–CNS communication

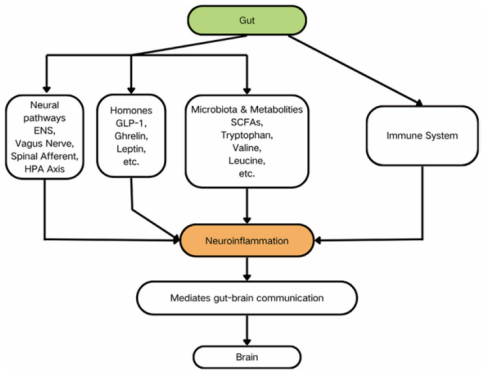

Fig:2 *The gut–brain–immune Systems: A key component in the pathogenesis of neuroinflammation. This schematic illustrates the central role of the gut–brain–immune axis in the pathogenesis of neuroinflammation leads to neurodegenerative diseases (NDs), the gut (green) as the origin of various signaling cascades that influence immune responses and brain function. Gut dysbiosis, characterized by a reduction in short-chain fatty acid (SCFA)-producing bacteria and an increase in pro-inflammatory components such as lipopolysaccharide (LPS), disrupts neural (enteric nervous system, vagus nerve, spinal afferents, hypothalamic–pituitary–adrenal axis), hormonal (glucagon-like peptide-1, ghrelin, leptin), and microbial metabolic pathways (SCFAs, tryptophan, valine, leucine), all of which are shown in white boxes. These interconnected signals converge on neuroinflammation (yellow), depicted as the central integrative hub linking peripheral disturbances to central nervous system (CNS) dysfunction. Dysbiosis-induced immune activation promotes systemic inflammation, T cell imbalance, and the infiltration of immune cells into the CNS, resulting in microglial activation, cytokine release, synaptic disruption, and neuronal injury. While not explicitly illustrated, neural cells such as neurons, astrocytes, and oligodendrocytes are primary targets of this inflammatory cascade. Additionally, vagal transmission of microbial cues and SCFA-mediated epigenetic modifications in both immune and neural cells contribute to sustained neuroinflammation. The communication is bidirectional, with CNS pathology feeding back to alter gut physiology and microbiota composition, forming a self-perpetuating pathological loop. The brain (white) represents the final recipient of these signals.*

The gastrointestinal (GI) system communicates with the CNS through various pathways of neural transmission, microbial by products, immune signals like cytokines, and hormonal channels.[50,51] Central to this complex system is the vagus nerve, which serves as the primary two-way pathway, transmitting sensory information from the stomach and intestines to the brain stem while also regulating GI functions and systemic inflammation via the cholinergic anti-inflammatory reflex.[52,53] The ENS, often referred to as the "second brain", is made up of a vast network of intrinsic neurons that independently manage GI motility, secretion, and the integrity of the intestinal barrier.[54,55] The ENS is also linked to the CNS through sympathetic and parasympathetic fibers. Gut microbiota influence neurocircuitry through the production of bioactive metabolites such as SCFAs, with particular emphasis on butyrate.

Specific bacterial species can produce neurotransmitter precursors such as gamma aminobutyric acid, serotonin, and dopamine, which may interact with enteric neurons and vagal afferent fibers, thereby altering neuronal excitability and neurobehavioral characteristics.[56] Intestinal epithelial enteroendocrine cells also function as sensors for luminal substances and microbial signals. They release systemic hormones like glucagon-like peptide (GLP)-1, peptide YY, cholecystokinin, and ghrelin, which can reach the brain or connect to hypothalamic and limbic systems through vagal af ferents, transmitting signals related to metabolism, stress, and cognition.[57] Collectively, these interconnected pathways form a dynamic interface between the gut and the brain, known as the gut–brain axis (GBA), where microbial, neuronal, and hormonal signals interplay to influence CNS activity, neuroinflammation, and, subsequently, the likelihood of NDs.

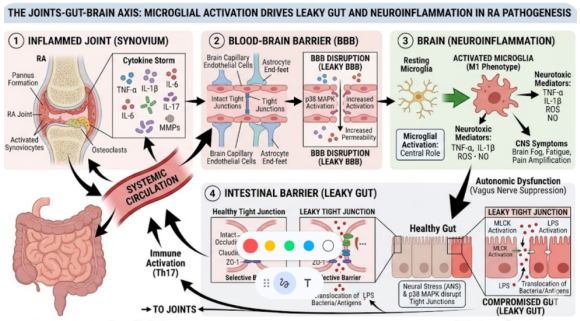

Fig:3**. Inflamed Joint (Synovium) Pannus formation, elease of inflammatory mediators: Cytokines: **TNF-α, IL-1β, IL-6, IL-17,** Matrix metalloproteinases (MMPs)- Results in a **cytokine storm**, which enters systemic circulation. 2. **Systemic inflammation** Activation of immune cells (especially **Th17 cells**) - Acts as a connecting link between: Joints → Brain → Gut 3. Cytokines activate pathways (e.g., **p38 MAPK**) Leads to: **Breakdown of tight junctions**, Increased permeability ("leaky BBB") Allows inflammatory mediators enter to CNS Brain (Neuroinflammation). Entry of cytokines activates **microglia**, Microglial transformation: From resting state → **Activated (M1 phenotype)**, Activated microglia release: TNF-α, IL-1β, Reactive oxygen species (ROS), Nitric oxide (NO). 3. Neuroinflammation affects autonomic regulation Leads to: **Vagus nerve suppression.** Intestinal Barrier (Leaky Gut)- Disruption of tight junctions → **increased permeability.

Immune system-gut interaction:

The gut microbiota is essential for the immune system's development and regulation, significantly influencing NDs. Host–microbe interactions initiate when pattern recognition receptors pre sent on intestinal epithelial cells and innate immune cells detect microbial-associated molecular patterns like lipopolysaccharides (LPS) and peptidoglycans.[58] This interaction helps maintain immune balance by harmonizing pro-inflammatory signals with regulatory pathways. Changes in microbial composition, referred to as dysbiosis, can undermine the structural integrity of the gut epithelium by modifying the expression of tight junction pro teins.[59,60] This change results in increased intestinal permeability, often termed "leaky gut". Consequently, microbial antigens and metabolites can infiltrate the lamina propria and enter systemic circulation, initiating antigen presentation, T cell polarization, and widespread inflammatory responses that can influence the CNS.[61,62] At the core of mucosal defense is the gut-associated lymphoid tissue, which oversees immunological surveillance and tolerance through pattern recognition receptor signaling and the activation of nuclear factor kappa-B (NF-κB).[63] Simultane ously, microbial metabolites, particularly SCFAs and compounds derived from tryptophan, serve immunoregulatory functions, affecting dendritic cell maturation, regulatory T cell (Treg) in duction, and T helper 17 (Th17) cell differentiation. These mechanisms adjust key cytokines such as IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α), influencing peripheral immune responses and neuroimmune interactions, including microglial activation within the

brain.[64,65]Furthermore, this immunological network is intricately connected to the hypothalamic–pituitary adrenal axis, which acts as the body's primary stress response mechanism.77 Signals derived from the microbiota, transmitted via vagal afferents or immune pathways, can stimulate the hy pothalamus to release corticotropin-releasing hormone.[66,67] This, in turn, causes the pituitary gland to release adrenocorticotropic hormone, prompting the adrenal glands to produce glucocorti coids such as cortisol. These hormones create feedback loops that influence immune activity and microbial ecology, establishing a reciprocal neuroimmune feedback system.[68] Long-term disrup tions in this loop, such as consistently elevated cortisol levels, may heighten blood–brain barrier (BBB) permeability, maintain neuroinflammation, and hasten the progression of NDs.[69,70]

A significant aspect of the gut-brain-immune trio

In the gut–brain–immune triad, the reciprocal communication between the immune system and the CNS is essential for pre serving brain equilibrium and influencing vulnerability to NDs. This communication occurs through a complex network of sign aling molecules, immune cells, and microbial metabolites that together influence neural functions, glial activities, and neuro inflammation.[71] Cytokine signaling serves as a primary means of immune interaction with the CNS. Proinflammatory cytokines such as IL-6, TNF-α, and IL-1 can penetrate the BBB or act on certain areas of the CNS that have a more permeable barrier.[72,73] For example, pro-inflammatory cytokines like IL-1 are particu larly effective in perturbing CNS homeostasis. They affect BBB permeability by compromising the structure of capillary endothe lial tight junctions and stimulate downstream pro-inflammatory pathways while simultaneously reducing the protective role of astrocytes by limiting their production of sonic hedgehog, anoth er crucial factor for maintaining BBB homeostasis. Further more, IL-1 prompts astrocytes to secrete potentially neurotoxic substances that enhance localized inflammation, foster angio genesis, and elevate vascular permeability.[74] Together, these processes trigger and maintain BBB dysfunction, fostering a pro inflammatory environment within the CNS that may further lead to neurodegeneration. Additionally, the movement of immune cells through a disrupted BBB exacerbates neural damage. Peripheral immune cells, including activated monocytes and T lymphocytes—often primed by microbial antigens and cytokine-rich environments in the gut—can migrate into the CNS. Once they enter the CNS, these peripheral immune cells may interact with resident glial cells, leading to chronic inflammation and neuronal impairment.[75] Microglia, the inherent immune guardians of the CNS, serve as another crucial point of interaction within this triad.[76] Microglia play a vital role in immune monitoring, synaptic pruning, and injury response.[77,78] Notably, germ-free (GF) mice exhibit significant pathological issues in microglia, including un usual shapes, hindered maturation, and metabolic disorders.[79] The abnormalities in microglia found in GF animals are mainly linked to the lack of SCFAs, especially acetate, which is crucial. Acetate reprograms microglia during resting metabolic phases, and it has been demonstrated to restore normal maturation and functional responses in GF models, further supporting the idea that metabolites derived from the gut are integral in regulating the immune tone of the CNS.[80-82]-

The role of the brain gut-joint axis in arthritis

Interestingly, while studying neurodegenerative diseases, researchers discovered a bidirectional communication network between the central nervous system (CNS) and the gastrointestinal tract, leading to the concept of the brain-gut axis [10]. A link has been identified between gut and joint disorders, as they share aspects of pathogenesis, such as identified genetic risk factors and the role of pro-inflammatory cytokines, and often occur concurrently [83]. Based on this, it is believed that there is a special connection between the gut and the joints, and the concept of the gut-joint axis has been proposed.

Based on the gut-joint axis theory, intestinal dysbiosis may contribute to the progression of RA through multiple pathways. Research has found that intestinal dysbiosis can regulate the ratio of Th17/Treg cells and Tfh/Tfr cells, which plays a crucial role in the early development of RA [84,85]. Additionally, some pathogenic GM and host molecules share similar structures or sequences, often triggering cross-reactive immune responses that that contribute to the onset of RA through molecular mimicry [86].

Core Concept

Joint inflammation → systemic cytokines → BBB disruption → microglial activation → neuroinflammation → autonomic dysfunction → leaky gut → systemic inflammation → worsened RA

Conclusion

The interaction between the immune system and the CNS is crucial and dynamic in the context of the gut

brain–immune triad. Proinflammatory substances, such as IL-1, can disrupt the BBB and worsen glial dysfunction and neuronal susceptibility. At the same time, microbial metabolites like ac etate provide immunomodulatory signals that contribute to the maintenance of immune homeostasis in the CNS. Gaining insight into the intricacies of this two-way communication establishes a significant conceptual basis for developing therapeutic approach es aimed at modifying peripheral immunity while safeguarding CNS health in NDs.

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