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Review

The Brain–Immune–Gut Axis: Rethinking Neurodegeneration Through Immunology, Microbiome, and Nutrition

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Abstract

Neurodegenerative diseases, once conceptualized primarily as disorders of protein misfolding and neuronal loss, are increasingly recognized as systemic immunometabolic syndromes. The traditional view of the brain as an immune-privileged organ has been overturned by discoveries of glymphatic clearance, meningeal lymphatics, and direct neuroimmune interfaces, all of which integrate central and peripheral immunity. Within the brain, microglia emerge as both guardians and drivers of pathology, with genetic risk factors such as APOE4 and TREM2 linking innate immune dysfunction to Alzheimer's and related dementias. Beyond the CNS, the gut-associated lymphoid tissue (GALT) and microbiome play pivotal roles in regulating immune tone through microbial metabolites, bile acid transformations, and vagal neurocircuits. Aging further amplifies this vulnerability by accelerating immunosenescence and "inflammaging," compromising synaptic resilience. Diet and nutrition serve as programmable levers within this brain–immune–gut axis: dietary fiber, polyphenols, and omega-3 fatty acids promote immune tolerance and neuroprotection, whereas obesogenic diets exacerbate neuroinflammation. Emerging therapies—ranging from microbiome-targeted interventions and GLP-1 receptor agonists to bioelectronic neuromodulation and immune rejuvenation strategies—underscore the translational potential of this paradigm. This review synthesizes evidence positioning the brain–immune–gut axis as a central determinant of neurodegenerative disease, highlighting how immune regulation, microbial ecology, and dietary inputs can be harnessed for prevention and treatment.

Keywords: neurodegenerative diseases, brain, gut, immunity, microbiome, nutrition.

1. From Immune Privilege to Immune Integration

For most of the twentieth century, the brain was considered immunologically privileged, cordoned off from peripheral immune surveillance by the blood–brain barrier (BBB). Early transplantation studies and clinical observations supported this view: grafts survived longer in the brain than in peripheral tissues, and encephalitis was thought to occur only when this barrier was breached. The CNS was regarded as an island of neural activity, protected from the volatility of the immune system [1-6].

This perspective began to shift with the discovery of immune cells and cytokines in cerebrospinal fluid, followed by the identification of meningeal lymphatic vessels and direct bone marrow channels linking skull and dura. These findings demonstrated that the brain is not immunologically insulated but instead continuously interacts with the periphery. Immune cells patrol the meninges, dendritic cells present antigens draining from the parenchyma, and microglia act as sentinels within the CNS itself. The BBB, once conceived as a rigid fortress, is now recognized as a dynamic regulatory interface, allowing selective exchange of cytokines, chemokines, and metabolites that influence both brain and immune homeostasis [7-17].

The consequence of this reconceptualization is profound. Rather than being an immunologically

exempt organ, the brain is embedded in a systemic immune network. This shift reframes neurodegenerative diseases: not as isolated neuronal catastrophes, but as disorders shaped by maladaptive immune responses.

2. Microglia: Sentinels and Saboteurs

Microglia, the brain's resident macrophages, exemplify this dual role. In development, they sculpt synaptic connections through pruning and trophic support. In adulthood, they respond to pathogens, injury, and aberrant protein aggregates. Yet with aging and genetic susceptibility, microglia can transition into pathogenic states. Lipid-droplet–accumulating microglia secrete pro-inflammatory cytokines, generate reactive oxygen species, and engulf synapses inappropriately, accelerating cognitive decline [18-24].

Genetic evidence underscores their centrality. Variants in TREM2, APOE, CD33, and other immune-related genes consistently emerge in genome-wide association studies of Alzheimer's disease. The APOE4 allele in particular rewires microglial metabolism, amplifying inflammatory responses to amyloid and tau, and impairing phagocytic clearance. These immune pathways appear not merely correlative but causal, suggesting that modulating microglial activation could alter disease trajectory [25-30].

The broader implication is that microglia are not passive bystanders to proteinopathy but active participants in the progression of neurodegeneration. Understanding the molecular switches that tip them from protective to pathogenic states is now a major frontier in neuroimmunology.

4. The Gut–Brain–Immune Axis

Parallel to advances in CNS immunology has been the recognition of the gut as a central regulator of brain health. The gut-associated lymphoid tissue (GALT) is the largest immune organ in the body, containing Peyer's patches, mesenteric lymph nodes, and lamina propria immune cells. It orchestrates systemic inflammatory tone and shapes the pool of lymphocytes capable of migrating to the brain. The permeability of the intestinal barrier, often disrupted in dysbiosis or systemic disease, influences the degree to which microbial antigens and metabolites enter circulation and reach the CNS [31-38].

The microbiome adds another dimension. Microbes generate short-chain fatty acids (SCFAs), bile acid derivatives, tryptophan metabolites, and lipopolysaccharides, all of which have immunomodulatory effects. SCFAs like butyrate enhance regulatory T cell activity and dampen microglial activation. Conversely, bacterial amyloids and endotoxins can prime microglia toward pro-inflammatory states. Preclinical models show that depletion of gut bacteria alters amyloid deposition, synaptic plasticity, and even motor behaviors. The gut thus functions as both a training ground and amplifier of immune signals that ultimately impact brain physiology [39-47].

5. Neural Circuits and the Inflammatory Reflex

The gut–brain dialogue is not confined to metabolites. Neural circuits, particularly through the vagus nerve, provide a bi-directional channel linking intestinal signals to brainstem nuclei. This "inflammatory reflex" regulates systemic cytokine production, acting as a neural brake on immune overactivation. Stimulation of vagal pathways can suppress tumor necrosis factor release, improve outcomes in inflammatory bowel disease, and modulate microglial activity in the CNS [48-54].

The enteric nervous system (ENS), sometimes called the "second brain," also mediates local integration of dietary and microbial inputs. Enteroendocrine cells detect microbial metabolites and relay information to both ENS neurons and vagal afferents. Recent studies demonstrate that microbial metabolites can even influence motivation to exercise by activating gut-to-brain sensory circuits. This highlights the surprising breadth of influence the gut–brain–immune axis exerts, extending from immune tone to behavior [55-58].

Together, these findings depict a complex multi-layered network: immune signals, microbial metabolites, and neural reflexes collectively shape the brain's inflammatory environment and resilience against degeneration.

6. Diet as a Programmable Input

Diet represents one of the most powerful and modifiable levers influencing the gut–immune–brain axis. Population studies consistently demonstrate that adherence to Mediterranean and MIND diets correlates with reduced risk of cognitive decline and Alzheimer's disease. These patterns emphasize plant-based foods, fiber, polyphenols, and omega-3 fatty acids, while minimizing processed sugars and saturated fats [59-68].

Mechanistic studies provide explanatory pathways. Dietary fiber fuels microbial fermentation into SCFAs, which in turn regulate T cell differentiation and maintain BBB integrity. Polyphenols from berries, tea, and cocoa modulate NF-κB signaling and enrich microbial taxa associated with anti-inflammatory profiles. Omega-3 fatty acids enhance synaptic function, resolve inflammation through specialized lipid mediators, and counteract microglial overactivation. Caloric restriction and intermittent fasting further reprogram immune responses, reducing systemic inflammation and improving resilience against autoimmunity [69-74].

By contrast, obesogenic diets promote systemic inflammation, metabolic dysfunction, and increased BBB permeability, all of which contribute to cognitive decline. Diet thus emerges as a programmable input—capable of either protecting against or accelerating neurodegeneration depending on composition and context [75-79].

7. Therapeutic Frontiers

The convergence of neuroimmunology and microbiome science has inspired new therapeutic strategies. Microbiome-directed interventions—probiotics, prebiotics, synbiotics, and postbiotics—are being tested for their ability to reshape microbial ecology and modulate neuroinflammation. Early-phase trials show modest cognitive benefits, though mechanistic clarity is still developing [80-86].

Pharmacologic approaches are advancing rapidly. GLP-1 receptor agonists, initially developed for diabetes, have shown neuroprotective effects in Alzheimer's and Parkinson's trials, likely via anti-inflammatory and metabolic pathways. Biologics targeting specific immune pathways, such as anti-TNF therapies, are under investigation, though safety and specificity remain concerns. Novel factors such as platelet factor 4 offer glimpses into the possibility of rejuvenating aged immune networks [87-92].

Beyond pharmacology, device-based strategies are emerging. Vagus nerve stimulation and transcranial alternating current stimulation have both demonstrated capacity to modulate immune tone and enhance cognition in preliminary studies. The concept of "bioelectronic medicine" is gaining traction, aiming to precisely tune neural-immune circuits to restore balance [93-96].

8. Conclusion

The accumulated evidence dismantles the notion of the brain as an immunologically isolated organ. Instead, the CNS exists within a dynamic network of immune surveillance, microbial signaling, and metabolic regulation. Neurodegeneration emerges not as a linear cascade of protein misfolding, but as a systems-level failure of immune regulation, influenced by aging, genetics, and environment.

The gut microbiome and diet stand out as key modulators within this network. They not only provide mechanistic insight but also represent actionable therapeutic levers. Interventions that harmonize brain–immune communication—whether through dietary patterns, microbiome modulation, or immune rejuvenation—hold the promise of delaying or even preventing neurodegenerative disease.

The next decade will likely redefine prevention and treatment strategies, shifting the focus toward precision nutrition, immune profiling, and integrative therapeutics. By embracing the brain as part of a larger immune-metabolic ecosystem, we open new avenues to preserve cognitive health across the lifespan.

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«Ми-иммунитет-ішек» өсі: Иммунология, микробиома және тамақтану тұрғысынан нейродегенеративті ауруларға жаңа қырынан қарау

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Түйіндеме

Нейродегенеративті аурулар бұрынырақта ақуыздың ұюындағы бұзылыстары және нейрондардың жойылуы ретінде қарастырылғанмен, бүгінде жүйелік иммундық-зат алмасулық синдром ретінде жиі танылуда. Мидың иммундық артықшылыққа ие орган ретіндегі дәстүрлі түсінігі глифаттық клиренстің, менингеальды лимфа жүйесінің, сондай-ақ, орталық және перифериялық иммунитетті біріктіретін тікелей нейроиммундық интерфейстердің ашылуынан кейін теріске шығарылды. Мида микроглия патологияның қорғаушысы рөлінде де, қозғаушы күші ретінде әрекет етеді. Ал APOE4 және TREM2 сияқты генетикалық қауіп факторлары иммундық жүйе қызметінің туа біткен бұзылысын Альцгеймер ауруы және онымен байланысты деменциямен байланыстырады. ОЖЖ-нен басқа, ішекпен байланысты лимфоидты тін және микробиом микробтық метаболиттер, өт қышқылының трансформациясы және вагус жүйке тізбектері арқылы иммундық тонусты реттеуде маңызды рөл атқарады. Қартаю иммундық және «қабынудан болған қартаюды» жеделдету арқылы аталмыш осалдықты одан әрі күшейтіп, синаптикалық төзімділікті төмендетеді. Диета және тамақтану «Ми-иммундық жүйе-ішек» өсі ішінде басқарылатын рычагтар ретінде әрекет етеді. Тағамдық талшықтар, полифенолдар және Омега-3 май қышқылдары иммундық төзімділік пен нейропротекцияны күшейтеді, ал семіздікке алып келетін тамақтану үрдісі нейроқабынуды күшейтеді. Микробиомға бағытталған араласулар мен GLP-1 рецепторларының агонистерінен бастап, биоэлектронды нейромодуляцияға және иммундық жасарту стратегияларына дейінгі жаңа ем жолдары осы парадигманы тәжірибелік қолдану әлеуетін көрсетеді. Бұл шолу «Ми-иммундық-ішек» өсін нейродегенеративті аурулардың орталық қозғаушы күші ретінде көрсететін дәлелдерді қорытындылайды, сонымен қатар, иммундық реттеуді, микробтық экологияны және диеталық факторларды алдын алу мен емдеу үшін қалай пайдалануға болатынын талдайды.

Түйін сөздер: нейродегенеративті аурулар, ми, ішек, иммунитет, микробиом, тамақтану.

Ось «Мозг-иммунитет-кишечник»: Переосмысление нейродегенеративных заболеваний с точки зрения иммунологии, микробиома и питания

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Резюме

Нейродегенеративные заболевания, ранее рассматривавшиеся преимущественно как нарушения сворачивания белков и гибель нейронов, все чаще признаются системными иммунометаболическими синдромами. Традиционное представление о головном мозге как об органе с иммунопривилегированным статусом было опровергнуто открытиями глифатического клиренса, менингеальной лимфатической системы и прямых нейроиммунных интерфейсов, которые интегрируют центральный и периферический иммунитет. В головном мозге микроглия выступает как в роли защитников, так и в роли движущих сил патологии. А генетические факторы риска, такие как APOE4 и TREM2, связывают дисфункцию врожденного иммунитета с болезнью Альцгеймера и связанными с ней деменциями. За пределами ЦНС лимфоидная ткань, ассоциированная с кишечником и микробиомом, играют ключевую роль в регуляции иммунного тонуса посредством микробных метаболитов, трансформаций желчных кислот и вагусных нейронных цепей. Старение еще больше усиливает эту уязвимость, ускоряя иммуностарение и «воспалительное старение», что снижает синаптическую устойчивость. Диета и питание выступают в качестве программируемых рычагов в рамках оси «Мозг-иммунитет-кишечник»: пищевые волокна, полифенолы и Омега-3 жирные кислоты способствуют иммунной толерантности и нейропротекции, тогда как диеты, способствующие ожирению, усугубляют нейровоспаление. Новые методы лечения — от вмешательств, направленных на микробиом, агонистов рецепторов GLP-1 до биоэлектронной нейромодуляции и стратегий омоложения иммунитета — подчеркивают потенциал применения этой парадигмы на практике. В этом обзоре обобщаются данные, позиционирующие ось «Мозг-иммунитет-кишечник» как центрального фактора нейродегенеративных заболеваний, и подчеркивается, как иммунная регуляция, микробная экология и диетические факторы могут быть использованы для профилактики и лечения.

Ключевые слова: нейродегенеративные заболевания, мозг, кишечник, иммунитет, микробиом, питание.

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