Review

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Mechanisms and Therapeutic Potential of Nutritional Immunity

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Highlights

- Nutritional immunity is a multifaceted network of host mechanisms that sequester, redistribute, or toxify essential nutrients, including transition metals, vitamins, and lipids, thereby imposing metabolic limitations on invading pathogens.
- In response, pathogens have developed countermeasures such as siderophores, heme uptake systems, and high-affinity transporters, underscoring the evolutionary arms race that defines host–pathogen nutrient interactions.
- Cytokine-driven pathways such as the interleukin-6-hepcidin axis reprogram systemic and local nutrient pools, integrating nutritional immunity into broader inflammatory and immunometabolic circuits.
- Although dysregulation of nutritional immunity can lead to pathologies, the artificial modulation of nutritional immunity with precision offers novel therapeutic intervention points.
- Emerging approaches, including AI-guided drug design, nanomedicine-based nutrient modulators, multiomics, and microbiota-targeted strategies, represent promising avenues for harnessing nutritional immunity in precision anti-infective and immunometabolic therapies.

Abstract

Nutritional immunity is a major facet of host defense, wherein the host immune system strategically limits pathogen access to critical nutrients, including iron, zinc, vitamins, lipids, and amino acids, to repress microbial proliferation and virulence. This review provides a comprehensive synthesis of the

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molecular mechanisms that power nutrient immunity, including metal homeostasis, transporter modulation, hormonal regulation, and direct antimicrobial actions. We examine nutrient-specific strategies employed by the host, from iron withholding mechanisms to vitamin deprivation and copper-mediated toxicity. We also explore how diverse pathogens, including extracellular, intracellular, and eukaryotic, adapt to these hostile nutritional landscapes through siderophore diversification, regulatory integration, and metabolic rewiring. Comparative genomic analyses reveal convergent evolution in nutrient acquisition systems, illuminating the dynamic arms race between host restriction and microbial evasion. Further, we discuss the translational potential of nutritional immunity, cutting across nutrient-based therapies, host-directed interventions, and emerging diagnostic biomarkers. Finally, we suggest future directions that synergize nutritional immunity with microbiome ecology, global malnutrition, and personalized medicine. By elucidating the interconnection between metabolism and immunity, this review highlights the therapeutic promise of starving the pathogen to save the host.

Keywords: nutritional immunity; host–pathogen interactions; metal sequestration; immunometabolism; pathogen adaptation; host-directed therapeutics; antimicrobial resistance

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1. Introduction

Infectious diseases constitute a major public health concern across the globe [1]. The situation is further aggravated by the increasing emergence of antimicrobial resistance and inadequate development of new antibiotics [2,3]. At the heart of every infection lies a fierce competition for nutrients between the host and an invading pathogen [4]. Pathogens, including bacteria, fungi, and protozoa, need access to essential elements such as zinc, iron, manganese, amino acids, and vitamins to uphold structural integrity, power replication, and initiate their virulence programs [5,6]. In response, the host deploys a repertoire of defense mechanisms collectively known as nutritional immunity, which are strategies that limit microbial access to these resources while maintaining host metabolic homeostasis [7]. Interestingly, this nutrient tug-of-war is not just a passive consequence of infection but rather a dynamic and evolutionarily conserved interface between metabolism and immunity. For example, iron sequestration via transferrin, lactoferrin, and hepcidin is tightly controlled to restrict microbial proliferation while minimizing oxidative stress [8]. Similarly, calprotectin-mediated zinc and manganese chelation hampers bacterial enzymatic function and growth [9]. These host strategies are opposed by microbial adaptations, including siderophore production, metal transporter upregulation, and metabolic rewiring, underlining the complexity of host-pathogen nutrient interactions [10]. Furthermore, nutritional immunity is increasingly recognized as a key pillar of innate and adaptive defense. It borders cytokine signaling, hormonal regulation, and cellular immunity, determining the outcome of infections across different anatomical niches [5,11]. For instance, macrophages regulate phagosomal nutrient availability through NRAMP1-mediated metal efflux and autophagy-linked amino acid deprivation [12,13]. In parallel, systemic responses such as hypoferremia and altered vitamin metabolism reveal the host's attempt to starve pathogens while maintaining immune function [14]. Notably, the concept of nutritional immunity is not only true within the context of bacterial infections. Eukaryotic pathogens such as *Plasmodium falciparum*, *Leishmania* spp., and *Candida albicans* also exhibit complex nutrient acquisition systems that allow immune evasion and persistence [6,15]. Importantly, the interplay between nutrient availability and pathogen virulence is further modulated by host nutritional status, microbiome composition, and environmental factors, making nutritional immunity a nexus of immunology, metabolism, and ecology [16,17]. This review aims to provide a comprehensive synthesis of the mechanisms, pathogen-specific strategies, and therapeutic implications of nutritional immunity. We begin by detailing the molecular and cellular processes through which the host limits pathogen access to critical nutrients. We then explore nutrient-specific strategies, such as iron

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sequestration, copper toxicity, and amino acid deprivation, and examine how diverse pathogens adapt to these pressures. We offer comparative genomic insights that reveal evolutionary patterns in nutrient acquisition and translational perspectives that highlight emerging therapies and diagnostics rooted in nutritional immunity. We conclude by outlining future directions that would interlink nutritional immunity with microbiome science, personalized medicine, and global health.

2. Mechanisms of Nutritional Immunity

The concept of nutritional immunity encompasses a suite of host strategies designed to restrict microbial access to essential nutrients within the host milieu, thereby impairing pathogen proliferation and virulence. These mechanisms, illustrated in **Figure 1** and described extensively in **Table 1**, are multifaceted and involve metal sequestration, metal toxicity, nutrient competition, metabolic reprogramming, hormonal regulation, siderophore interference, and direct antimicrobial actions. Together, they constitute a dynamic and context-dependent defense system that integrates innate and adaptive immune responses. This section presents the various strategies employed by the host to exert nutritional immunity.

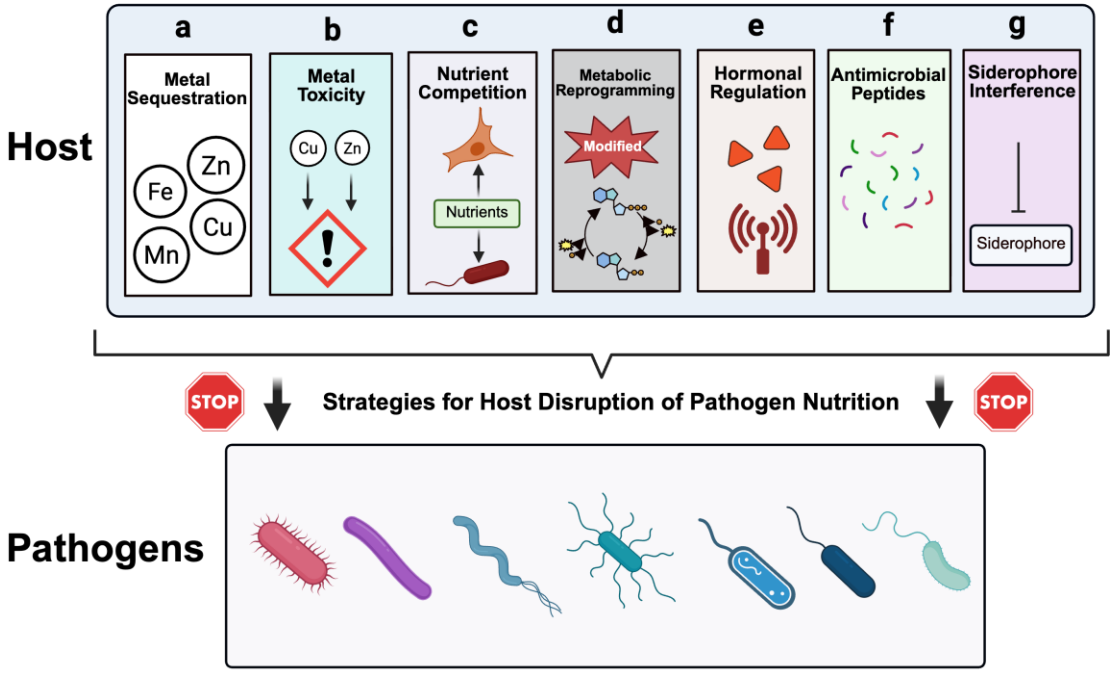

Figure 1. Schematic illustration of nutritional immunity mechanisms. Illustrated here are the various strategies used by the host to disrupt pathogen nutrition. **a**, metal sequestration; the host sequesters essential metals like iron (Fe), zinc (Zn), manganese (Mn), and copper (Cu) that pathogens need to grow and multiply. **b**, metal toxicity; host intentionally delivers toxic levels of certain transition metals into pathogen-containing compartments, which overwhelms microbial detoxification systems, and may have pathogens incorporate incorrect metals into their enzymes, such as copper instead of iron, leading to dysfunctional proteins and impaired microbial survival. **c**, nutrient competition; host cells and immune cells compete with pathogens for key nutrients like glucose, lipids, and amino acids. **d**, metabolic reprogramming; the host alters its own metabolism during infection to reduce the availability of nutrients like glucose and amino acids to pathogens. **e**, hormonal regulation; inflammatory cytokines and hormones like hepcidin regulate iron homeostasis by decreasing iron absorption and trapping iron in storage sites. **f**, production of antimicrobial peptides; molecules like calprotectin bind and sequester multiple metals, including zinc and manganese, but also have direct

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antimicrobial effects. **g**, siderophore interference; hosts produce proteins like lipocalin-2 that bind bacterial siderophores, which are iron-scavenging molecules, preventing pathogens from retrieving iron.

Table 1. Summary of nutritional immunity mechanisms.

S/n	Mechanism	Description	Main host factors	Targeted nutrients	Impact on pathogen	Examples	References
1	Metal sequestration	Host proteins bind essential transition metals firmly, restricting their availability to invading microbes.	Ferritin, lactoferrin, transferrin, ceruloplasmin, hemopexin, haptoglobin.	Fe, Mn, Cu, Zn.	Limits cofactor accessibility for bacterial enzymes such as superoxide dismutase and ribonucleotide reductase, thereby impairing replication.	Neutrophil lactoferrin reduce iron accessibility to *Staphylococcus aureus*, calprotectin sequesters zinc and manganese from *Candida albicans*	[5,18–20]
2	Metal Toxicity	Host intentionally delivers toxic levels of certain transition metals into pathogen-containing compartments.	Copper transporters (ATP7A, ATP7B), Zinc transporters (ZIP8, ZnT family), NRAMP1 (SLC11A1).	Excess Cu or Zn causing toxicity and/or replacing Fe/Mn.	Overwhelms microbial detoxification systems, causes mis-metalation, and interferes with critical metabolic processes.	Copper toxicity against *Mycobacterium tuberculosis*, Zinc-mediated intoxication of *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*	[5,17,21,22]
3	Nutrient competition	Host cells outcompete pathogens for limited nutrients in inflamed tissues.	Activated macrophages, neutrophils, T cells.	Fe, Glucose, fatty acids, amino acids like tryptophan and arginine.	Stress induced by starvation, forcing bacteria into alternative metabolic pathways or non-replicating forms.	Gut commensals competing with *Salmonella enterica* for iron and carbon sources decrease pathogen colonization	[4,23,24]
4	Metabolic reprogramming	Host cells shift metabolic flux to starve pathogens, such as Warburg-like glycolysis, and reduced amino acid availability	HIF-1α, mTOR, autophagy pathways.	Glucose, glutamine, arginine, serine.	Limits access to central carbon and nitrogen sources	Macrophage glycolytic reprogramming restricting *Mycobacterium tuberculosis growth and altering* CCV environment for *Coxiella burnetii*.	[4,25,26]
5	Hormonal regulation	Hormones and inflammatory cytokines regulate systemic nutrient availability.	Hepcidin, TNF-α, IL-6.	Iron via regulation of ferroportin.	Reduces plasma iron, trapping it in macrophages and hepatocytes.	IL-6–induced hepcidin release suppressing iron availability during *Salmonella* infection.	[10,14]

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6	Production of antimicrobial peptides (AMPs)	AMPs bind essential metals and exert direct antimicrobial effects.	Psoriasin (S100A7), calprotectin (S100A8/A9), defensins.	Zn, Mn.	Blocks metalloenzyme activity, triggers oxidative stress.	Calprotectin limiting *Staphylococcus aureus* growth in neutrophil extracellular traps (NETs).	[20,27,28]
7	Siderophore interference	Host proteins arrest or neutralize bacterial siderophores to block iron retrieval.	Lipocalin-2 (NGAL), siderocalin.	Iron via siderophore sequestration.	Suppresses iron uptake despite active siderophore production.	Lipocalin-2 binding *Escherichia coli* enterobactin, blocking bacterial iron acquisition.	[29–32]

2.1. Metal Homeostasis and Disruption

Metal homeostasis is a major cornerstone in nutritional immunity, particularly in the regulation of iron, zinc, manganese, and copper. A diagrammatic snapshot of various mechanisms employed by the host to sequester critical metal nutrients from pathogens, as well as pathogens' counterstrategies, is presented in **Figure 2**. Iron, an essential cofactor for DNA synthesis and microbial respiration, is tightly controlled by host proteins such as transferrin, ferritin, lactoferrin, hemopexin, and haptoglobin [7]. During infection, the liver amplifies hepcidin, a peptide hormone that degrades ferroportin, the sole iron exporter, thereby lowering serum iron levels and restricting microbial access [11]. Similarly, zinc and manganese are sequestered by calprotectin, a neutrophil-derived protein that chelates these metals at sites of inflammation [33]. This sequestration disrupts microbial enzymatic functions, especially those involved in DNA replication and oxidative stress resistance. Pathogens respond by upregulating high-affinity transporters such as ZnuABC and MntH, highlighting the evolutionary arms race between host sequestration and microbial acquisition [17]. On the other hand, the host weaponizes transition metals like copper and zinc as toxic antimicrobial agents. For example, macrophages accumulate copper and zinc in phagosomes via ATP7A transporters and zinc transporters (ZIP8, ZnT family), respectively [34,35]. These toxic metal levels overwhelm microbial detoxification systems and interfere with critical metabolic processes. For instance, the correct metalation of bacterial enzyme cofactors is disrupted when excess copper and zinc replace iron and manganese. Also, excess metals in phagosomes catalyze the generation of reactive oxygen species and impair microbial iron-sulfur clusters [36]. Pathogens negate this by expressing copper efflux pumps and chaperones, such as CopA and CueO, which attenuate toxicity and preserve intracellular homeostasis [21]. The implementation of metal homeostasis during infection portrays a finely tuned balance between host defense and systemic physiology. Dysregulation can lead to immunopathology, as observed in anemia of inflammation or metal overload syndromes [37,38]. Thus, an understanding of the molecular mechanisms of metal sequestration and toxicity is critical for the development of targeted therapies that promote nutritional immunity without impairing host health.

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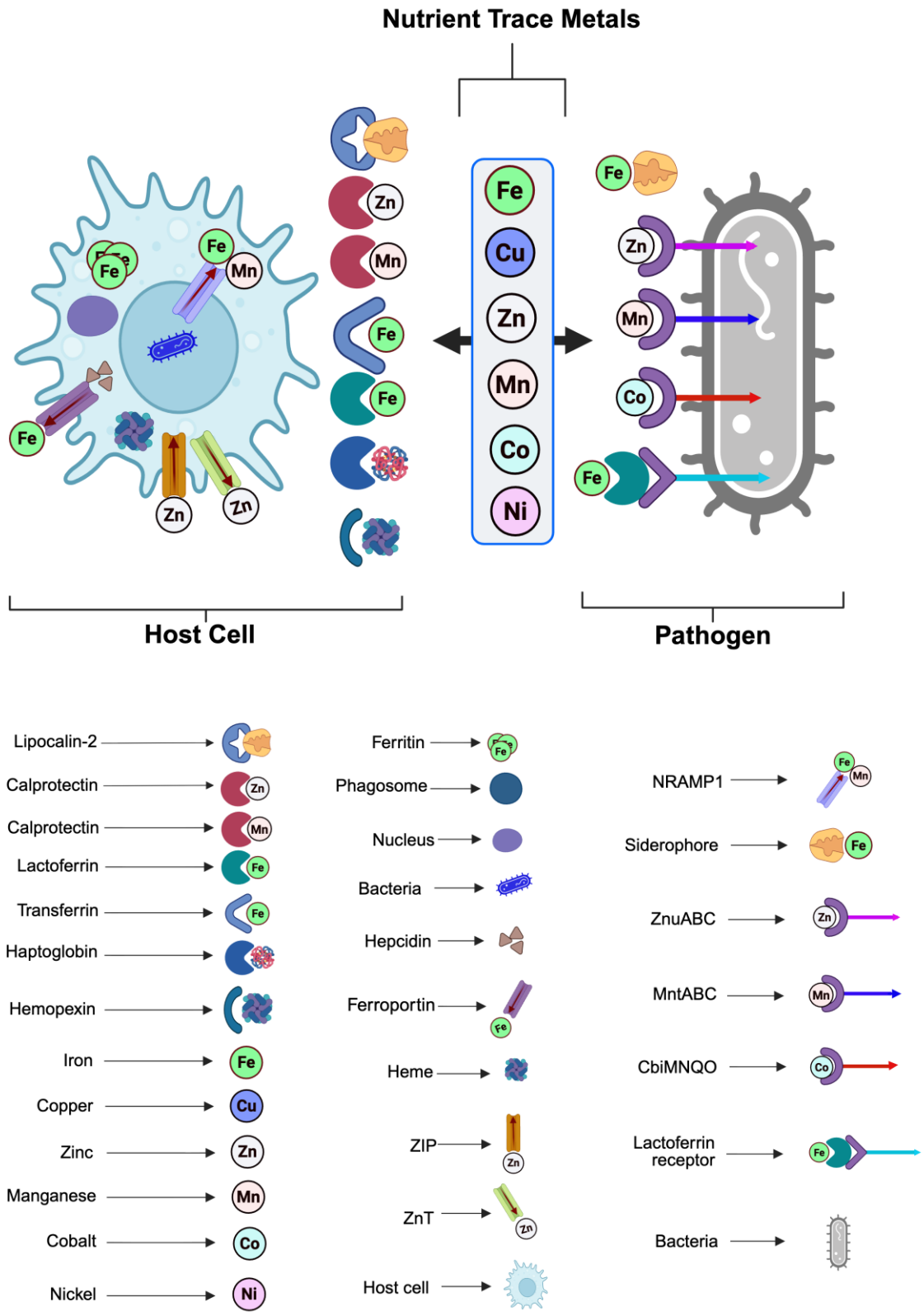

Figure 2. Host-pathogen tug of war for nutrient trace metals. Upon pathogen entry, the host deploys mechanisms to hide nutrient trace metals from the pathogen. These mechanisms include host proteins like transferrin, which binds Fe in blood, limiting extracellular Fe; lactoferrin, a high-affinity Fe-binding glycoprotein in mucosal secretions and neutrophil granules; ferritin, an intracellular Fe storage, that restricts cytoplasmic Fe availability; hemopexin, which binds free heme, limiting bacterial access to the Fe in heme; haptoglobin, which binds free

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hemoglobin (Hb), preventing bacterial Hb uptake; lipocalin-2, which binds bacterial siderophores, thereby, blocking Fe scavenging; hepcidin, a hormone that degrades ferroportin, reducing Fe export from cells into circulation; calprotectin, a neutrophil protein that sequesters Zn and Mn; ZIP/ZnT transporters, which control intracellular Zn flux to deprive intracellular or extracellular pathogens; and NRAMP1, which pumps Fe and Mn out of phagosomes to deprive intracellular bacteria. In response, the pathogen, also deploy counter mechanisms that allow them to still access these critical nutrients, including bacterial siderophores like enterobactin, pyoverdine, yersiniabactin, staphyloferrin, mycobactin, which are secreted molecules that chelate Fe with very high affinity. Bacterial pathogens also deploy high-affinity transporters like the ZnuABC system, a high-affinity Zn transporter; MntABC transporter, a high-affinity Mn uptake system; the CbiMNQO transporters that import Co for cobalamin biosynthesis; and lactoferrin receptors, which bind lactoferrin and facilitate pathogen acquisition of Fe. Fe: Iron, Cu: Copper, Zn: Zinc, Mn: Manganese, Co: Cobalt, Ni: Nickel, ZIP: Zrt, Irt-like proteins, ZnT: Zinc transporter, NRAMP1: Natural Resistance-Associated Macrophage Protein 1.

2.2. Metabolic and Hormonal Regulation

Metabolic and hormonal regulation plays a key role in nutritional immunity by regulating nutrient availability and immune cell function [4,39]. For example, immune cells undergo metabolic reprogramming during infection by shifting from oxidative phosphorylation to glycolysis to support rapid proliferation and cytokine production [40]. This shift elevates host immune cells' consumption of glucose and glutamine, depriving pathogens of major carbon sources and creating a competitive metabolic environment. Hormonal signals further control nutrient flux. For instance, hepcidin, induced by interleukin-6 (IL-6) during inflammation, diminishes the export of iron and facilitates intracellular sequestration [41]. Similarly, indoleamine 2,3-dioxygenase (IDO), which is switched on by interferon-γ, catabolizes tryptophan into kynurenine, lowering its availability to intracellular pathogens such as *Toxoplasma gondii* and *Chlamydia trachomatis* [42]. These hormonal pathways interconnect immune signaling with nutrient control, boosting host defense. Metabolic regulation also influences the differentiation and function of immune cells. For example, the depletion of arginine by arginase activity represses T cell proliferation and facilitates the development of regulatory T cells, thereby controlling the immune response to chronic infections [43]. Contrarily, amino acid sufficiency promotes cytokine production and effector functions, which underlines the dual role of nutrients as both substrates and stimuli [44]. The interplay between metabolism, hormones, and immunity highlights the complexity of nutritional immunity. The therapeutic modulation of these pathways, through metabolic inhibitors, hormone analogs, or dietary interventions, could present promising avenues for boosting host defense. However, such strategies must be carefully calibrated to avert inadvertent immunosuppression or metabolic dysregulation.

2.3. Resource Competition

Resource competition is a fundamental mechanism of nutritional immunity, wherein host cells alongside commensal microbes compete with pathogens for critical nutrients. This competition occurs at multiple levels, including direct substrate limitation, niche exclusion, and metabolic interference. For instance, activated macrophages consume large amounts of glucose and amino acids, reducing their availability to intracellular pathogens [26]. This metabolic competition is further elevated by the Warburg effect, which amplifies glycolytic flux in immune cells [45]. Additionally, commensal microbiota play a pivotal role in resource competition. For example, beneficial microbes in the gut withhold iron and synthesize siderophores, which inhibit pathogen growth, effectively increasing the host's nutritional immunity [16]. These microbes also compete for amino acids and vitamins, which lowers the nutrient pool available to invading pathogens. Notably, dysbiosis or microbial imbalance can impair this competitive landscape and elevate susceptibility to infection [46]. Pathogens retaliate to resource competition by developing flexible metabolic pathways and high-affinity transport systems. For instance, *Listeria monocytogenes* can turn to host-derived glycerol and acetate during intracellular growth, bypassing glucose restriction [47]. Likewise, *Salmonella enterica* expresses multiple carbon and amino acid transporters to adapt to nutrient-limited vacuoles [48].

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These adaptations portray the selective pressure imposed by host and microbial competitors. Understanding resource competition dynamics is necessary for designing interventions that fortify host and microbiome defenses. Dietary modulation, probiotic therapies, and prebiotic supplementation can improve competitive exclusion and decrease pathogen colonization [49,50]. Moreover, targeting pathogen-specific nutrient acquisition pathways may tip the balance in favor of host immunity, presenting a novel approach to infection control.

2.4. Host Regulation of Nutrient Transporters and Storage

Nutrient transporters and storage proteins are highly regulated by the host to control systemic and local nutrient availability during infection. For instance, iron transport is controlled by ferroportin, the only known iron exporter, and its regulation by hepcidin ensures that iron is kept within hepatocytes and macrophages during inflammation [11]. Also, transferrin and lactoferrin bind extracellular iron, while ferritin stores intracellular iron, collectively diminishing the levels of free iron and restricting microbial access [7]. Similarly, the Zrt-/Irt-like Proteins (ZIP) and Zinc Transporters (ZnT) families of transporters regulate zinc and manganese transport, thereby controlling their cellular influx and efflux [51]. During infection, immune cells upregulate metallothioneins to neutralize excess zinc and avert toxicity, while downregulating transporters to limit pathogen access [52]. These changes are directed by metal-responsive transcription factors like MTF-1 and NRF2, which integrate oxidative stress and nutrient signals [53]. Furthermore, amino acid transporters are also modulated during infection. For example, SLC1A5 and SLC7A5, which mediate leucine and glutamine uptake, are amplified in activated T cells to support proliferation and cytokine production [54]. By contrast, downregulation of tryptophan transporters and activation of IDO restricts pathogen access and modulates immune responses [55]. These changes illustrate the bipartite role of transporters in acquiring nutrients and regulating immunity. Storage proteins such as albumin, ferritin, and transferrin serve as reservoirs and buffers, maintaining homeostasis while limiting pathogen access [56–58]. Their expression and localization are dynamically controlled during infection, influenced by cytokines, hormones, and cellular stress. Therapeutic modulation of transporter and storage protein activity, through small molecules, biologics, or gene editing, offers a promising strategy for strengthening nutritional immunity and infection control.

2.5. Direct Antimicrobial Actions

Nutritional immunity also involves direct antimicrobial actions mediated by nutrient-binding proteins and metabolic byproducts. For example, calprotectin not only chelates zinc and manganese but also punctures microbial membranes and blocks enzymatic activity, exerting bacteriostatic effects [59]. Also, lipocalin-2 binds bacterial siderophores, hampering iron uptake and triggering oxidative stress in pathogens [29]. These proteins act as both nutrient scavengers and antimicrobial effectors. Oxidative radicals, such as reactive oxygen species (ROS) and nitrogen oxygen species (RNS), generated during immune activation, further facilitate nutritional immunity. For instance, these molecules oxidize and degrade microbial cofactors, such as iron-sulfur clusters and thiol groups, compromising metabolic function and replication [60]. Also, copper and zinc, concentrated in phagosomes, catalyze ROS production, which impairs microbial redox balance, enhancing killing efficiency [21]. Metabolic byproducts also play a role in enhancing nutritional immunity. As an example, kynurenine, produced from tryptophan catabolism via IDO, has immunomodulatory and antimicrobial properties. It suppresses T cell proliferation and triggers apoptosis in infected cells, facilitating pathogen clearance [42]. Similarly, lactate and succinate, produced during glycolysis and the TCA cycle, modulate immune responses and suppress pathogen growth in specific contexts [61]. These direct antimicrobial actions complement other nutritional immunity strategies, creating an unwelcome environment for pathogens. Essentially, we see the integration of metabolic, immunological, and biochemical defenses in nutritional immunity. Future research should explore the therapeutic potential of these antimicrobial molecules, including their use as adjuvants, antimicrobial agents, or immunomodulators in treating infectious diseases.

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3. Nutrient-Specific Strategies in Nutritional Immunity

Nutritional immunity is orchestrated through the targeted restriction of specific nutrients that are critical for microbial survival and virulence. Each nutrient plays a unique role in microbial physiology, and the host has developed specialized mechanisms to restrict their availability during infection. This section examines the molecular and immunological strategies engaged by the host to restrict iron, zinc, manganese, copper, magnesium, sulfur, nitrogen, vitamins, carbon sources, and amino acids, and how pathogens adapt to these pressures.

3.1. Iron Limitation: A Key Mechanism of Nutritional Immunity

Iron is indispensable for almost all living organisms owing to its role in enzymatic reactions, oxygen transport, DNA synthesis, and cellular respiration [62]. During infection, the host withholds iron using a pool of proteins, including ferritin, lactoferrin, transferrin, hemopexin, and haptoglobin, which bind iron and iron-containing complexes in extracellular and intracellular compartments [7]. The liver-derived peptide hormone, hepcidin, plays a pivotal role by degrading ferroportin, the only known iron exporter, thereby lowering serum iron levels and trapping iron within macrophages [11]. This strategy of iron sequestration is particularly effective against extracellular pathogens that depend on free iron for replication [63]. However, many bacteria have developed countermeasures, including the production of siderophores, which are small, high-affinity iron-chelating molecules [64]. Pathogens like *Escherichia coli* and *Salmonella enterica* produce covert siderophores like salmochelin [65,66]. This salmochelin evades host proteins like lipocalin-2, which normally neutralize traditional siderophores (Smith, 2007). These adaptations illustrate the evolutionary arms race between host iron sequestration and microbial iron acquisition. Meanwhile, iron limitation also influences host immunity beyond direct antimicrobial effects. For instance, iron deprivation can modulate macrophage polarization, increase oxidative burst, and regulate cytokine production [68]. Moreover, iron status affects the outcome of infections such as tuberculosis and malaria, where both iron deficiency and overload can aggravate disease [69]. Iron regulation, therefore, is a double-edged sword that must be well balanced to optimize host defense. Notably, iron chelation has been therapeutically explored as an adjunct to antimicrobial therapy [70–72]. For example, agents like deferiprone and deferoxamine can diminish iron availability to pathogens, although they must be used with care to avert the impairment of host hematopoiesis and immune function [73]. A complete understanding of the nuances of iron metabolism during infection is necessary for developing safe and effective interventions that leverage nutritional immunity.

3.2. Zinc and Manganese: Essential Metals in Host-Pathogen Interactions

Zinc and manganese are critical cofactors for several microbial enzymes, including those involved in metabolic regulation, oxidative stress resistance, and DNA replication [9]. The host limits pathogen access to these metals through calprotectin, a neutrophil-derived protein that chelates zinc and manganese at inflammation sites [33]. This sequestration disrupts microbial enzymatic function and facilitates pathogen clearance [9]. In response, pathogens counteract this strategy by upregulating high-affinity metal transporters. For example, the ZnuABC system in Gram-negative bacteria and the MntABC system in Gram-positive bacteria promote zinc and manganese uptake under limiting conditions [17]. These transporters are often controlled by metal-responsive transcription factors such as Zur and MntR, which direct gene expression based on intracellular metal concentrations [74]. Furthermore, zinc limitation also affects host immunity. For instance, zinc is critical for cytokine production, T cell development, and barrier integrity [75]. During infection, zinc redistribution promotes the activation of immune cells while restricting microbial access [52]. However, excessive zinc sequestration can compromise host function [76], which underlines the need for careful regulation of zinc homeostasis. Manganese plays a special role in microbial resistance to oxidative stress by serving as a cofactor for superoxide dismutase and other antioxidant enzymes [77]. By reducing manganese availability, the host leaves the pathogens prone to reactive oxygen

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species, facilitating microbial killing [68]. This twofold role of manganese in microbial metabolism and immune defense underpins its relevance in nutritional immunity.

3.3. Copper Toxicity and Homeostasis

Contrary to zinc and iron, the host employs copper as a toxic antimicrobial agent [78]. For instance, under hypoxic conditions, which commonly occur during infections, macrophages have been shown to ramp up copper concentrations in phagosomes via ATP7A transporters, where copper catalyzes the production of reactive oxygen species and disrupts microbial iron-sulfur clusters [36]. This targeted copper delivery depicts a direct antimicrobial strategy rooted within nutritional immunity. Copper toxicity impairs multiple microbial processes, including DNA repair, respiration, and redox balance [79]. Pathogens respond by expressing chaperones, copper efflux pumps like CopA, and detoxifying enzymes that alleviate copper-induced damage [21]. *Mycobacterium tuberculosis*, for example, activates the RicR regulon to handle copper stress during intracellular infection [80]. Host copper homeostasis is highly regulated to avert collateral damage. Excess copper can be toxic to host cells, which necessitates the use of metallothioneins and copper-binding proteins to buffer intracellular levels [81]. Striking a balance between antimicrobial efficacy and host toxicity is an important consideration in copper-based immunity. Therapeutically, copper-enhancing agents and copper-mimetic compounds are being explored as adjuncts to antimicrobial therapy [82,83]. These strategies aim to exploit pathogen vulnerabilities to copper stress while maintaining host homeostasis. Further research into copper trafficking and regulation during infection may produce novel approaches to utilizing this potent antimicrobial metal.

3.4. Magnesium Limitation and Membrane Integrity

Magnesium is necessary for stabilizing cellular membranes, nucleic acids, and ribosomes in both host and microbes [84]. During infection, the host restricts magnesium availability within phagosomes, disrupting bacterial membrane integrity and signaling pathways [85]. This strategy is precisely potent against intracellular pathogens that depend on magnesium for survival in acidic vacuolar environments. *Salmonella enterica* senses magnesium limitation through the PhoP/PhoQ two-component system, which activates genes that reinforce resistance to acid stress and antimicrobial peptides [86]. This system also controls virulence factors, connecting magnesium sensing to pathogenicity. *S. enterica* mutants deficient in PhoP/PhoQ signaling exhibit reduced survival in macrophages, highlighting the significance of magnesium adaptation [87]. Magnesium starvation from pathogens makes them vulnerable to host defense mechanisms [4]. It impairs ATP synthesis, disrupts membrane potential, and heightens susceptibility to antibiotics and immune effectors. The host takes advantage of these vulnerabilities by modulating magnesium transport and buffering systems during infection [4]. Despite its significance, magnesium restriction is not as well-characterized as iron or zinc limitation. Future research should probe the molecular mechanisms of magnesium sequestration, its impact on immune cell function, and its potential as a therapeutic target. A deeper understanding of magnesium dynamics may present new strategies for controlling intracellular infections.

3.5. Sulfur and Nitrogen Metabolism

Sulfur and nitrogen are vital elements for microbial survival, which serve as building blocks for nucleotides, amino acids, and cofactors [88,89]. The host can limit pathogen access to these nutrients through enzymatic degradation and metabolic rerouting. For nitrogen, a major host strategy is the depletion of arginine[90] and tryptophan [55]. Arginine is consumed by host arginase, which diminishes its availability for the synthesis of nitric oxide and microbial growth, while tryptophan is broken down by indoleamine 2,3-dioxygenase (IDO), generating immunomodulatory metabolites like kynurenine [55]. Interestingly, pathogens have also developed mechanisms to bypass these restrictions. For example, *Chlamydia trachomatis* encodes tryptophan synthase, with which it synthesizes tryptophan de novo when host levels drop [91]. Similarly, *Mycobacterium tuberculosis*

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upregulates nitrogen absorption pathways under nutrient stress, promoting the bacteria's survival within macrophages [48]. These adaptations point to the metabolic flexibility of intracellular pathogens in response to nitrogen limitations orchestrated by the host. Sulfur metabolism is not much characterized in nutritional immunity, but it is gaining attention. Meanwhile, amino acids that contain sulfur, such as methionine and cysteine, are necessary for microbial antioxidant defenses and protein synthesis [92]. The host may decrease sulfur availability by downregulating the expression of transporters and enzymes involved in sulfur intake (Kies & Hammer, 2022). Additionally, oxidative stress caused by immune cells can oxidize sulfur compounds, making them inaccessible to the invading pathogens [94]. An in-depth understanding of how the host restricts sulfur and nitrogen will unveil new avenues for antimicrobial development. For example, targeting microbial sulfur assimilation or exploiting nitrogen starvation responses could facilitate pathogen clearance. Moreover, modulating host enzymes like arginase and IDO offers potential for immunotherapy, particularly in chronic pathogenic infections and cancer, where nutrient metabolism is intertwined with immune regulation.

3.6. Vitamin Sequestration

Vitamins are critically required as cofactors in metabolic pathways and enzymatic reactions (Hanna et al., 2022; Tardy et al., 2020). Following bacterial infection, the host can restrict access to vitamins such as folate, biotin, and vitamin B12, which creates an impediment for microbial metabolism [97]. This strategy is particularly potent against microbes that depend on host-derived vitamins due to incomplete biosynthetic pathways. Lipocalin-2, classically known for binding bacterial siderophores, has also been implicated in withholding vitamins. It can bind vitamin-like molecules and interfere with microbial uptake, extending its role beyond iron restriction [98]. Additionally, host cells may downregulate vitamin transporters or alter vitamin metabolism during infection, further limiting pathogen access. For example, human cytomegalovirus (CVM) infection has been shown to downregulate the vitamin D receptor (VDR) in host cells, impacting the vitamin D system and influencing immunity [99]. Some pathogens overcome this roadblock by synthesizing vitamins *de novo*. For example, *Salmonella typhimurium* possesses a full vitamin B12 biosynthesis pathway, which permits it to flourish in the nutrient-limited gastric mucosa [100]. Also, *Mycobacterium tuberculosis* expresses high-affinity transporters for biotin and folate, which are critical for fatty acid synthesis and nucleotide metabolism, respectively [101]. Fungal pathogens like *Candida albicans* and *Cryptococcus neoformans* also possess redundant vitamin acquisition systems, enabling survival in nutrient-limited niches [102,103]. Therapeutically, vitamin restriction presents a novel angle for antimicrobial intervention as inhibitors of microbial vitamin biosynthesis or transport could selectively hamper pathogen metabolism without affecting host cells. Overall, vitamin sequestration is a budding edge in nutritional immunity, and understanding how pathogens obtain and utilize these micronutrients could uncover new weak points for therapeutic targeting.

3.7. Carbon Source Restriction

Carbon sources such as glucose, amino acids, and fatty acids are fundamental to microbial biosynthetic processes and energy production (Bhagwat et al., 2025; Passalacqua et al., 2016). The host restricts carbon availability for the invading pathogens by modifying transporter expression, nutrient compartmentalization, and metabolic flux [106,107]. Upon activation, immune cells utilize large amounts of glucose and glutamine, denying pathogens of these substrates and creating a competitive metabolic environment [40]. Pathogens adapt by resorting to alternative carbon sources or scavenging metabolites generated by the host. *Listeria monocytogenes*, for example, circumvents glucose limitation during intracellular growth by utilizing host glycerol and acetate [47]. Also, *Salmonella enterica* expresses several carbon transporters and metabolic enzymes that help it to thrive in nutrient-poor vacuoles [48]. These adaptations demonstrate the metabolic versatility required for intracellular survival. Carbon source restriction also shapes immune responses. For example, metabolites such as lactate and succinate, generated during glycolysis and the TCA cycle, modulate

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cytokine production and immune cell differentiation [61]. Therefore, nutrient competition between host and pathogen not only affects microbial survival but also influences the immune landscape. Consequently, targeting microbial carbon metabolism offers therapeutic potential. For example, inhibitors of key glycolytic enzymes, glycerol uptake, or acetate metabolism could hinder pathogen replication. Moreover, modulating host metabolism to increase nutrient competition or immune activation may offer synergistic benefits in infection control.

3.8. Amino Acid Deprivation and Metabolic Reprogramming

Amino acids are necessary for protein synthesis, metabolic regulation, and immune signaling [44,108]. The host limits amino acid availability to pathogens through enzymatic degradation and transporter modulation. For instance, tryptophan is broken down by IDO, while arginine is used up by arginase, reducing their availability to pathogens and modulating immune responses [42,43]. These mechanisms are particularly efficacious against intracellular pathogens that depend on host amino acids [25]. Pathogens respond by amplifying biosynthetic pathways or scavenging peptides from the host. For example, *Chlamydia trachomatis* generates tryptophan de novo, while *Salmonella enterica* expresses amino acid transporters that enhance uptake under limiting conditions [48,91]. These adaptations are often controlled by nutrient-sensing systems that coordinate metabolic and virulence gene expression. Further, amino acid deprivation also reprograms host immunity by activating autophagy, stress responses, and metabolic checkpoints that facilitate pathogen clearance. For instance, glutamine and leucine availability influence mTOR signaling, which regulates T cell activation and differentiation [54]. Thus, amino acid metabolism is a junction of nutritional immunity and immune regulation. Manipulating amino acid availability presents therapeutic opportunities for infection control and immunomodulation. Arginase modulators, IDO inhibitors, and amino acid analogs are being researched in infectious disease and cancer. Understanding the context-specific effects of amino acid deprivation will be key to safely and effectively exploiting these strategies.

4. Nutritional Immunity in the Context of Specific Pathogens

Nutritional immunity is not a monolithic defense strategy. Rather, it is dynamic, pathogen-specific, and shaped by the ecological niche, virulence mechanisms, and metabolic dependencies of invading microbes. This section examines how different classes of pathogens, including extracellular, intracellular, and eukaryotic, interact with host nutrient sequestration systems, and how comparative genomics illustrate evolutionary adaptations in nutrient acquisition.

4.1. Extracellular Pathogens: Confronting Nutrient Sequestration Head-On

Extracellular pathogens, which dwell outside host cells, are directly exposed to the host's nutrient-sequestering proteins at mucosal surfaces and the bloodstream (**Figure 2**) [109]. For example, *Neisseria meningitidis* must compete with iron-binding proteins like lactoferrin and transferrin in the cerebrospinal fluid and blood [110]. To overcome this, *N. meningitidis* expresses transferrin-binding proteins like TbpA and TbpB, which directly extract iron from host transferrin [111,112]. This direct contest for iron is a major attribute of extracellular pathogens, which often develop surface receptors that mimic host ligands. A different strategy is employed by *Streptococcus pneumoniae*, which expresses pneumococcal surface protein A (PspA) that suppresses complement deposition and indirectly protects against nutritional immunity by inhibiting immune activation [113,114]. *S. pneumoniae* also uses ABC transporters to obtain zinc and manganese, opposing sequestrations mediated by calprotectin [115]. These metal acquisition systems are highly regulated and often connected with virulence gene expression, highlighting the twofold role of nutrient sensing in pathogenesis. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are particularly proficient at surviving in nutrient-constrained settings. For example, *S. aureus* expresses iron-regulated surface determinant (Isd) proteins, which extract heme from hemoglobin and deliver it across the bacterial envelope [116]. Similarly, *P. aeruginosa* synthesizes multiple siderophores, including pyochelin and pyoverdine, which scavenge iron from host proteins and are regulated by quorum sensing [117,118].

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These systems are critical for survival in iron-deprived niches such as abscesses. Another extracellular pathogen, *Escherichia coli*, especially uropathogenic strains (UPEC), deploys covert siderophores like salmochelin to elude lipocalin-2, a host protein that binds and neutralizes bacterial siderophores [65,119]. Multiple iron acquisition systems are also expressed by UPEC, allowing it to adjust to different iron sources in the urinary tract [120]. Altogether, extracellular pathogens express a diverse array of nutrient acquisition strategies that demonstrate their exposure to host defenses and their need for rapid adaptation.

4.2. Intracellular Pathogens: Navigating the Nutrient Desert Within

Intracellular pathogens contend with a different challenge of surviving within host cells, where nutrients are highly regulated and often withheld in organelles [121]. Interestingly, this group of pathogens has also evolved various strategies for overcoming these nutrient limitations. *Mycobacterium tuberculosis,* for example, resides within macrophage phagosomes [122], where iron and zinc are restricted [123]. To overcome this limitation, the pathogen expresses siderophores called mycobactins and amplifies the expression of iron acquisition genes in low-iron situations [124]. Additionally, *M. tuberculosis* modulates host lipid metabolism to acquire fatty acids as carbon sources, revealing its metabolic flexibility [125]. *Salmonella enterica* survives within *Salmonella*-containing vacuoles (SCVs) in macrophages and epithelial cells [126]. It recognizes magnesium limitation through the PhoP/PhoQ system and activates genes that increase survival in magnesium-limited environments [127]. It also expresses ZnuABC and SitABCD transporters to acquire zinc and manganese, respectively, countering calprotectin-mediated sequestration [128,129]. These adaptations are necessary for the pathogen's intracellular replication and systemic dissemination. *Toxoplasma gondii*, an obligate intracellular parasite, lives in a parasitophorous vacuole that is largely detached from host endocytic pathways [130]. It scavenges host amino acids and cholesterol through specialized transporters and manipulates host autophagy to access nutrients [131,132]. Nutrient limitation triggers stage conversion from tachyzoite to bradyzoite, a dormant form that enhances persistence[133]. This developmental plasticity is a trademark of intracellular eukaryotic pathogens. *Coxiella burnetii*, *Chlamydia trachomatis*, and *Rickettsia prowazekii* each occupy distinct intracellular niches[25]. For example, *C. burnetii* thrives in acidic lysosome-like vacuoles and expresses transporters for amino acids and metals [134]. *C. trachomatis* resides in an inclusion body and encodes tryptophan synthase to compensate for host IDO-mediated tryptophan depletion [91]. *R. prowazekii*, which replicates in the cytosol, scavenges host amino acids and ATP, reflecting its reductive genome and reliance on host metabolism [25]. Overall, these pathogens embody the diverse strategies used to navigate intracellular nutrient deserts.

4.3. Eukaryotic Pathogens: Complexity, Redundancy, and Immune Evasion

Eukaryotic pathogens, including fungi, parasites, and protozoa, have complex life cycles and redundant metabolic pathways that help them evade nutritional immunity [4,6]. For example, *Plasmodium falciparum*, the protozoan causative agent of malaria, invades red blood cells and breaks down hemoglobin to access amino acids and heme [135,136]. It detoxifies heme into hemozoin and expresses transporters for iron and other metals [136]. Host iron status determines malaria severity, and iron supplementation can worsen infection, underscoring the delicate balance of iron homeostasis [137]. *Leishmania* species reside in macrophage phagolysosomes and express ZIP family transporters for iron and zinc [138]. They also synthesize surface glycoconjugates like lipophosphoglycan (LPG) that manipulate host immune responses, enhancing nutrient acquisition [139]. The ability of *Leishmania* to survive in acidic, nutrient-limited compartments highlights its evolutionary adaptation to unfriendly intracellular environments. Fungal pathogens such as *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* possess robust nutrient acquisition systems. For instance, *C. albicans* expresses siderophore transporters and ferric reductases to acquire iron, and its metabolic flexibility permits it to flourish in diverse host niches [140]. *C. neoformans* synthesizes melanin and capsule components that defend the pathogen against oxidative stress and

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facilitate iron uptake [141]. *A. fumigatus* expresses high-affinity iron transporters and secretes siderophores, which are critical for virulence in immunocompromised hosts [142]. These eukaryotic pathogens also dodge nutritional immunity through immune modulation, antigenic variation, and metabolic redundancy [143,144]. The fact that their genomes encode multiple isoforms of nutrient transporters and enzymes allows them to adapt to varying host environments. Furthermore, their ability to modulate host cell signaling and immune responses adds a layer of complexity to their nutrient acquisition strategies, making them formidable adversaries in the context of nutritional immunity.

4.4. Comparative Genomics: Mapping the Evolutionary Landscape of Nutrient Acquisition

Comparative genomics has elucidated the evolutionary trajectories of nutrient acquisition systems across diverse pathogens. By evaluating genome content, gene expression, and regulatory networks, researchers have spotted conserved and lineage-specific adaptations that depict ecological niches and host interactions. For instance, siderophore biosynthesis genes are common among Gram-negative bacteria but differ in structure and regulation, indicating convergent evolution under iron-constrained settings [145]. Intracellular pathogens often exhibit genome reduction, shedding redundant metabolic pathways while preserving or expanding nutrient transporters [25]. *Chlamydia* and *Rickettsia* species, for example, have streamlined genomes but encode specialized systems for extracting host metabolites, which illustrates their obligate intracellular lifestyle [146,147]. Contrastingly, facultative intracellular pathogens like *Salmonella* maintain versatile metabolic networks, allowing survival in both intracellular and extracellular environments[148]. Eukaryotic pathogens show extensive gene duplication and diversification in nutrient acquisition genes [149,150]. For example, *Plasmodium* species have several copies of enzymes and transporters involved in amino acid and metal metabolism, demonstrating their complex life cycle and host transitions [151]. Also, fungal pathogens possess expanded gene families for oxidative stress resistance and iron uptake, which corresponds with their capacity to colonize diverse tissues [152]. Comparative genomics also reveals horizontal gene transfer events that facilitate nutrient acquisition [153]. Pathogens may acquire metal transporters, or vitamin synthesis genes, or siderophore biosynthesis clusters from other microbes, expanding their metabolic repertoire. These genomic insights underline the evolutionary arms race between host nutritional immunity and microbial adaptation, presenting targets for therapeutic intervention and vaccine development.

5. Pathogen Adaptation and Evasion

Pathogens have evolved sophisticated mechanisms to counteract nutrient restrictions imposed by the host. These adaptations not only ensure survival in hostile environments but also boost virulence and persistence. This section examines the molecular strategies pathogens employ to overcome nutritional immunity and the evolutionary dynamics that shape nutrient acquisition systems.

5.1. Pathogen Strategies to Overcome Nutritional Immunity

5.1.1. Siderophore Diversification and Stealth

Siderophores are high-affinity iron-chelating molecules produced by bacteria to scavenge iron from host proteins [154]. Pathogens have diversified their siderophore structures to evade host defenses such as lipocalin-2, which binds and neutralizes siderophores [64]. Escherichia coli, for instance, synthesizes salmochelin, a glycosylated derivative of enterobactin that is not recognized by lipocalin-2 [155]. This structural modification permits pathogens to sustain iron acquisition under immune pressure. Diversification also includes the production of multiple siderophores with unique chemical properties. For example, Pseudomonas aeruginosa produces both pyochelin and pyoverdine, which differ in regulatory control and affinity, allowing the pathogen to adapt to varying iron availability [117]. Similarly, Yersinia pestis synthesizes yersiniabactin, which not only chelates iron but also binds copper, playing a twofold role in metal acquisition and detoxification[156]. Stealth

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siderophores are often encoded within pathogenicity islands and controlled by iron-responsive transcription factors such as Fur (Katumba et al., 2022; Leon-Sicairos et al., 2015). These systems are highly connected with virulence, as iron acquisition is critical for replication and immune evasion. The ability to overcome host sequestration while sustaining iron uptake underlines the evolutionary pressure driving siderophore innovation.

5.1.2. Metal Transporter Upregulation

In response to metal limitation imposed by the host, pathogens upregulate high-affinity transporters for zinc, manganese, and magnesium. For instance, the ZnuABC and MntH systems are widely conserved among Gram-negative bacteria and are critical for survival under calprotectin-mediated sequestration [33]. These transporters are often regulated by metal-responsive repressors such as Zur [159,160] and MntR [161,162], which fine-tune expression based on intracellular metal levels. *Staphylococcus aureus* exemplifies this strategy by expressing multiple metal transporters and metalloregulatory proteins [163]. It uses the MntABC system for manganese uptake and adapts its metalloproteome to replace scarce metals with available alternatives [164]. This flexibility permits pathogens to sustain enzymatic function and combat oxidative stress even under metal deprivation. Transporter upregulation is usually integrated with virulence gene expression. For example, *Salmonella enterica* activates SitABCD [165] and ZnuABC [166] during intracellular infection, enhancing survival in macrophage phagosomes. These systems facilitate nutrient acquisition and also contribute to immune evasion and persistence, underscoring their dual role in pathogenesis.

5.1.3. Metabolic Rewiring and Carbon Source Flexibility

Pathogens often reprogram their metabolism to utilize alternative carbon sources when preferred substrates are limited [167]. This metabolic adaptability is important for survival in nutrient-restricted environments such as inflamed tissues or intracellular compartments. For instance, *Listeria monocytogenes* transitions from glucose to host-derived acetate and glycerol during intracellular growth [168,169]. This switch is governed by PrfA, a master virulence regulator that integrates metabolic and pathogenic signals [168]. Similarly, *Mycobacterium tuberculosis* displays extreme metabolic plasticity by utilizing host lipids as carbon sources during intracellular infection. For example, it upregulates genes involved in β-oxidation and the glyoxylate shunt, allowing it to persist in macrophages where glucose is scarce [125]. This adaptation not only supports energy production but also manipulates immune responses by reshaping host lipid metabolism. Carbon source flexibility often supports virulence and immune evasion, in that pathogens that can exploit host metabolites are better prepared to survive nutrient limitation and immune activation. Therefore, metabolic rewiring represents a strategic adaptation that improves microbial fitness and pathogenicity in diverse host environments.

5.1.4. Amino Acid Scavenging and Biosynthesis

Amino acid restriction is a common host strategy to repress pathogen growth [170,171]. In response, pathogens either upregulate biosynthetic pathways or scavenge amino acids from the host. For example, *Chlamydia trachomatis* encodes tryptophan synthase to counteract host IDO-mediated tryptophan depletion, enabling sustained replication in epithelial cells [91]. This enzyme is controlled by nutrient availability and immune signals, highlighting its role in adaptation. Similarly, *Mycobacterium tuberculosis* [172] and *Salmonella enterica* [173] also express biosynthetic enzymes and amino acid transporters that are upregulated during intracellular infection. These systems permit the pathogens to thrive in vacuoles where amino acid levels are tightly controlled [48]. Amino acid scavenging is often coupled with stress responses and the expression of virulence genes, which altogether improve survival under immune pressure. Further, some pathogens manipulate host autophagy to access amino acids. *Toxoplasma gondii* [174] and *Coxiella burnetii* [175], for instance, both induce host autophagy to release nutrients into the parasitophorous vacuole. This strategy not only

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supplies amino acids to the pathogens but also modulates host immunity, illustrating the multidimensional role of amino acid acquisition in pathogenesis.

5.1.5. Host Manipulation and Immune Evasion

Aside from acquiring nutrients, pathogens actively modulate host processes to evade nutritional immunity. For example, *Leishmania* spp alter phagosome maturation and acidification, creating a niche for optimal nutrient acquisition and minimized immune detection [176]. These modifications are facilitated by surface glycoconjugates and secreted effectors that interfere with host signaling. Similarly, *Plasmodium falciparum* reprograms red blood cells to enhance nutrient uptake and waste disposal [177]. It sends out proteins that form new permeability pathways, creating access to amino acids and glucose [178]. These alterations also decrease immune recognition, improving parasite survival and replication. Immune evasion strategies often involve modulation of host cytokine responses and antigen presentation [179]. *Mycobacterium tuberculosis* produces ESAT-6 and other effectors that block phagosome-lysosome fusion and suppress pro-inflammatory signaling [180]. These tactics not only keep the pathogen from immune clearance but also preserve access to intracellular nutrients, reinforcing the connection between immune evasion and nutritional adaptation.

5.2. Evolution of Nutrient Acquisition Mechanisms in Pathogens

5.2.1. Gene Expansion and Operon Architecture

Pathogens often expand gene families involved in acquiring nutrients to increase redundancy and adaptability [181]. Genes involved in siderophore biosynthesis and transport are frequently duplicated and organized into operons, enabling coordinated expression [182–184]. For example, *Pseudomonas aeruginosa* has several operons for pyoverdine synthesis, each controlled by the availability of iron and environmental cues [185]. Operon architecture promotes rapid response to nutrient limitation, since genes encoding transporters, regulators, and biosynthetic enzymes are co-transcribed, ensuring efficient resource allocation. This organization is particularly visible in metal acquisition systems such as ZnuABC and SitABCD, which are tightly regulated by metal-responsive repressors [186]. The expansion of genes also supports functional diversification. The duplicated genes may develop new substrate specificities or regulatory mechanisms, elevating pathogen fitness in diverse environments [187]. This evolutionary strategy illustrates the selective pressure imposed by nutritional immunity and the need for pathogens' metabolic versatility.

5.2.2. Horizontal Gene Transfer and Convergent Evolution

Horizontal gene transfer (HGT) plays a critical role in the dissemination of nutrient acquisition and catabolism systems [153]. Pathogenicity islands commonly contain siderophore biosynthesis genes, metal transporters, and vitamin synthesis pathways obtained from other microbes [188]. *Yersinia pestis*, for example, acquired the yersiniabactin cluster via HGT, improving its iron acquisition capabilities [189]. Convergent evolution also determines nutrient acquisition strategies. Thus, unrelated pathogens may develop similar mechanisms to conquer host defenses, such as stealth siderophores or high-affinity transporters. This convergence reflects general selective pressures and underscores the functional importance of these adaptations [145]. HGT and convergence contribute to the speedy evolution of virulence characteristics. By acquiring and optimizing nutrient acquisition genes, pathogens can adapt to new hosts and niches, expanding their ecological range and pathogenic potential. These evolutionary dynamics reflect the fluidity of microbial genomes and the pivotal role of nutritional immunity in determining pathogen evolution.

5.2.3. Reductive Evolution in Obligate Intracellular Pathogens

Obligate intracellular pathogens commonly undergo reductive evolution, losing redundant metabolic pathways while preserving essential nutrient acquisition systems. For instance, *Rickettsia* and *Chlamydia* species have streamlined genomes but encode specialized transporters for amino

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acids, nucleotides, and ATP [147,190]. This dependency highlights their adaptation to nutrient-rich intracellular environments. Reductive evolution is fueled by genome decay and host dependency. Genes that are no longer needed for extracellular survival are lost, while those involved in host interaction and nutrient uptake are preserved or expanded. While reductive evolution increases efficiency by transferring biosynthetic functions to the host, it simultaneously creates **nutritional fragility for the pathogen**. For example, the reliance of *Chlamydia* on host tryptophan makes it highly susceptible to IDO-mediated starvation [91]. Likewise, *Coxiella*'s requirement for host-derived lipids and amino acids restricts its replication to the specialized parasitophorous vacuole [191]. These vulnerabilities highlight how nutritional immunity may not only limit pathogen growth but also influence long-term genome evolution.

6. Therapeutic Implications

Nutritional immunity not only serves as a major pillar for host defense but also presents a fertile landscape for therapeutic innovation. Through the comprehension and manipulation of nutrient availability, researchers and clinicians can develop targeted interventions that either starve pathogens or strengthen host defenses. Therapeutic strategies inspired by nutritional immunity, including their mechanisms of action, examples, clinical trials, challenges, and translational outlook, are presented in **Table 2**. Overall, this section evaluates the translational potential of nutritional immunity across antimicrobial strategies, host-directed therapies, and diagnostic applications.

Table 2. Therapeutic approaches inspired by nutritional immunity.

S/N	Therapeutic strategy	Mechanism of action	Examples/clinical trials	Challenges	Translational outlook
1	Iron chelation therapy	Starves pathogens of iron by binding free iron, mimicking host nutritional immunity	Deferasirox and its derivatives used against *Candida albicans*, *Candida glabrata*, and *Cryptococcus neoformans* [192,193]; Deferiprone as an adjunctive therapy against *Mycobacterium abscessus* [194,195]; Lactoferrin supplementation in trials studies for neonatal sepsis [196,197].	Risk of host iron depletion, impaired immune function, and anemia.	Early / late clinical (iron chelators already approved for other indications; infection-specific use experimental) .
2	Metal supplementation to cause toxicity	Deliver toxic levels of metals such as zinc, copper, or manganese into pathogen-containing compartments	Zinc oxide nanoparticles antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* [198–200]; Copper ionophores such as disulfiram, elesclomol studied for antimicrobial activity against *Mycobacterium tuberculosis*, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* [201–203]	Balancing pathogen killing with minimal host toxicity	Preclinical / early clinical.
3	Siderophore decoys and mimics	Neutralize bacterial siderophores or prevent their uptake by pathogens	Gallium potency against chronic *Pseudomonas aeruginosa* airway infections in clinical trials [204]; Lipocalin-2 facilitating host defense	Toxicity at high doses and pathogen adaptation	Early clinical (gallium); other decoy approaches preclinical.

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			against *Klebsiella pneumoniae* [205] *and Escherichia coli* [206]		
4	Siderophore–antibiotic conjugates as "Trojan horse" drugs	Antibiotics fused to siderophores leverage bacterial uptake systems to facilitate intracellular drug delivery	Cefiderocol, an FDA-approved drug against multidrug resistant Gram-negative bacteria and nosocomial pneumonia and complicated urinary tract infections [207]; siderophore-monobactam (BAL30072) potency against multidrug-resistant *Acinetobacter* and multidrug resistant gram negative bacteria [208,209]; synthetic sideromycin conjugates under development [207].	Resistance through altered siderophore receptors and high cost	FDA approved (cefiderocol); siderophore-monobactam and synthetic sideromycin conjugates in preclinical.
5	Immunometabolic modulation	Remodel host metabolism to limit key nutrients such as glucose, amino acids, and vitamins from pathogens	IDO activators for tryptophan depletion in viral and bacterial infections [210,211]; Methionine restriction shown to limit intestinal barrier dysfunction and inflammation caused by *Salmonella typhimurium* [212]; Vitamin D supplementation enhances therapeutic outcomes in tuberculosis [210,211].	Systemic metabolic adverse effects and pathogen metabolic flexibility	Early clinical (IDO, vitamin D).
6	Probiotic-pathogen competition	Beneficial microbes compete with pathogens for nutrients and synthesize siderophores to limit pathogen growth	*Lactobacillus rhamnosus* GG in clinical trials for treating pediatric infections [213,214]; *Bifidobacterium longum* modulates iron metabolism, reduces pathogen colonization [215]; *Escherichia coli* Nissle 1917 competes for iron and prevents pathogen expansion [216,217].	Variability in microbiome responses and context-dependent efficacy	Late clinical / approved (some strains widely marketed, regulated as supplements).
7	Fecal microbiota transplant (FMT)	Restores gut microbial diversity and competitive exclusion against pathogens, restricting access to critical nutrients	FMT for recurrent *Clostridium difficile* infection in Phase III RCTs showing >85% efficacy [218–221]; studies indicating FMT efficacy and safety against multidrug-resistant Enterobacteriaceae colonization (222,222–227); emerging FMT trials in sepsis and systemic infections [228,229].	Regulatory challenges, donor variability, and risk of pathogen transfer.	Late clinical / approved (FDA-approved for recurrent *Clostridium difficile*).
8	Phytobiotics (plant-derived compounds)	Plant-derived polyphenols, flavonoids, and alkaloids chelate	Curcumin anti-*Mycobacterium* activity via iron chelation [230,231]; Quercetin enhances	Bioavailability, limited clinical validation, and	Preclinical/early clinical.

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		metals, impair microbial metabolism, and modulate host immunity	zinc uptake and modulates immune responses [232]; Antimicrobial activity of Epigallocatechin gallate (EGCG) from green tea against *Pseudomonas aeruginosa* and *Escherichia coli* [233].	variability in plant extracts.	
9	Nanotechnology-based nutrient modulation	Engineered nanocarriers deliver metals, chelators, or metabolic modulators directly to infection sites	Iron oxide nanoparticles investigated for iron sequestration and pathogen restriction [234,235]; Antibacterial activity and mechanistic insights of gallium-based nanoparticles [236,237]; Silver nanoparticles as next-generation antimicrobial agents [238–241].	Safety, targeted delivery, and long-term stability concerns	Preclinical

6.1. Targeting Nutrient Availability for Infection Control

Manipulating the availability of nutrients is a promising approach for controlling infections, particularly in an era of rising antimicrobial resistance. Iron chelation, for example, has been considered as a strategy to restrict microbial growth by depriving pathogens of this critical cofactor. Agents such as deferoxamine and deferiprone bind free iron, lowering its bioavailability and thereby hindering the proliferation of iron-dependent pathogens like *Staphylococcus aureus* and *Escherichia coli* [242]. However, therapeutic iron chelation must be delicately balanced to avoid exacerbating anemia or impairing host immunity [7]. Beyond iron, zinc and manganese sequestration have emerged as viable antimicrobial strategies. For instance, calprotectin, a host protein that chelates these metals, has inspired the development of synthetic mimetics that mimic calprotectin's metal-binding properties[243]. These agents can be deployed locally at infection sites to increase metal starvation without systemic toxicity [33]. Moreover, targeting microbial metal transporters with small-molecule inhibitors offers a pathogen-specific approach that circumvents traditional antibiotic mechanisms [244,245]. Carbon source restriction is another avenue for controlling infection. By manipulating host metabolism or blocking microbial access to key substrates, such as glucose or fatty acids, researchers can create unfavorable environments for pathogens. For instance, inhibitors of bacterial glycerol uptake have demonstrated efficacy against *Listeria monocytogenes*, which depends on host-derived glycerol during intracellular growth [47]. These strategies underscore the potential of metabolic interference as a non-antibiotic antimicrobial approach. Nevertheless, targeting nutrient availability must factor in host-pathogen specificity and tissue context. This is because nutrient manipulation may have inadvertent implications on host cells, particularly immune cells that depend on similar substrates for their activation and function. Thus, precision targeting, guided by pathogen biology and host physiology, is critical for the safe and effective deployment of nutrient-based therapies.

6.2. Novel Therapeutic Strategies Based on Nutritional Immunity

Recent advances in molecular biology and immunology have enabled the design of novel therapeutics that exploit or mimic nutritional immunity. One example of such a strategy involves the development of siderophore-antibiotic conjugates, also known as "Trojan horse" antibiotics. These compounds utilize bacterial iron uptake systems to deliver antibiotics directly into the pathogen. For instance, cefiderocol, a siderophore-cephalosporin conjugate, has shown potent activity against multidrug-resistant Gram-negative bacteria by seizing iron transport pathways [246]. Another innovative approach involves the use of engineered probiotics that battle with pathogens for

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nutrients. These beneficial microbes can be designed to sequester iron, zinc, or amino acids in the gut, thereby impeding pathogen colonization. For example, *Lactobacillus* strains engineered to express siderophore receptors have demonstrated the potential to reduce *Salmonella* burden in animal models [16]. Such strategies present a microbiome-friendly alternative to conventional antimicrobials. Also, standard antibiotics combined with nutrient iron chelators have shown amplified antimicrobial activity. For instance, the impregnation of catheters with both antimicrobial agents and iron chelators gave increased antimicrobial and anti-biofilm activity than just antimicrobial agents alone [72]. Also, thiostrepton, a Gram-positive thiopeptide antibiotic imported via pyoverdine receptors, synergized with the iron chelator deferasirox to yield higher growth suppression for *P. aeruginosa* and *Acinetobacter baumannii* in clinical isolates than thiostrepton alone [247]. Further, nanotechnology finds application in nutritional immunity-based therapeutics. For example, nanoparticles functionalized with metal-binding ligands can be employed to sequester iron or zinc at infection sites, creating localized nutrient deserts [248]. These platforms can be further adjusted to deliver immunomodulatory agents or antibiotics, enhancing their therapeutic efficacy [249,250]. The modularity of nanomedicine permits tailored interventions based on infection site and pathogen type. Essentially, these novel strategies must be evaluated for their impact on host nutrient homeostasis and immune function. While mimicking nutritional immunity can improve pathogen clearance, excessive nutrient deprivation may impair tissue repair or compromise immune activation. Thus, therapeutic design must integrate insights from host-pathogen interactions, nutrient biology, and immunometabolism to ensure the best outcomes.

6.3. Nutrient-Based Therapies for Specific Infections

Nutrient-based therapies have demonstrated promise, particularly in treating infections where nutrient acquisition is closely linked to pathogenesis. Malaria, caused by *Plasmodium falciparum*, is a prime example where the parasite digests hemoglobin to access amino acids and iron [135,177], making iron availability a pivotal determinant of disease severity [251]. Consequently, iron chelation therapy using agents like deferoxamine has been explored to control parasite growth, although its clinical utility remains controversial owing to potential host toxicity [252–254]. In tuberculosis, iron and lipid metabolism are pivotal to *Mycobacterium tuberculosis* survival [255]. Host-directed therapies that modulate iron availability or lipid metabolism have also been proposed to improve bacterial clearance. Similarly, statins, which alter host lipid metabolism, may hinder *M. tuberculosis* access to carbon sources and improve immune responses [256]. Fungal infections also offer opportunities for nutrient-based interventions. *Candida albicans* and *Cryptococcus neoformans* depend on iron acquisition for virulence [141,192]. Iron chelation has been shown to lower fungal burden in animal models, and iron-binding compounds are being researched as adjuncts to antifungal therapy [257]. These approaches are especially relevant in immunocompromised patients, where conventional antifungals may be inadequate [258]. However, nutrient-based therapies must be essentially customized for the pathogen's metabolic profile and the host's nutritional status. Iron chelation, for example, may be unadvised in anemic patients or those with chronic infections. Personalized medicine approaches that integrate nutritional biomarkers, pathogen genomics, and host physiology are necessary for the safe and effective use of these therapies.

6.4. Host-Directed Therapies to Enhance Nutritional Immunity

Host-directed therapies (HDTs) aim to strengthen the host's natural defenses, including nutritional immunity, to fight infection. One strategy involves increasing the expression or activity of nutrient-sequestering proteins such as calprotectin, hepcidin, and lipocalin-2. For example, synthetic hepcidin analogs have been developed to lower serum iron levels and repress bacterial growth in sepsis models [11]. These agents mimic the host's iron-chelating response and may serve as supplements to antibiotic therapy. Immunomodulatory agents can also be used to switch on pathways that limit nutrient availability. Interferon-γ, for instance, triggers indoleamine 2,3-dioxygenase (IDO), which depletes tryptophan and restrains intracellular pathogens like *Toxoplasma*

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gondii and *Chlamydia trachomatis* [42]. Enhancing IDO activity or mimicking its effects may present therapeutic benefits in chronic infections where immune evasion is common. Further, gene therapy and RNA-based approaches are emerging tools for controlling host nutrient responses. CRISPR-based editing of genes involved in iron metabolism or metal transport could also be used to improve resistance to specific pathogens. Similarly, siRNA targeting of host nutrient transporters may lower pathogen access to critical substrates without impairing host function [259]. These technologies provide precision control over host-pathogen interactions. Despite their potential, HDTs must be carefully examined for off-target effects and long-term safety. Modulating nutrient availability can affect immune cell function, tissue repair, and systemic metabolism [260]. Therefore, HDTs should be integrated into a broader therapeutic framework that considers nutritional status, pathogen biology, and host immunity.

6.5. Diagnostic Biomarkers of Nutritional Immunity

The active interplay between host nutrient sequestration and pathogen adaptation produces quantifiable changes in biomarker profiles that can be explored for diagnostics. The levels of ferritin, transferrin, and hepcidin saturation in the serum are commonly used to determine iron status and inflammation. For example, elevated ferritin and hepcidin levels are suggestive of iron sequestration during infection and can help differentiate between iron-deficiency anemia and anemia of inflammation [11]. Calprotectin, a manganese- and zinc-binding protein, is a well-established biomarker of neutrophil activation and mucosal inflammation [261,262]. Fecal calprotectin is commonly used to monitor inflammatory bowel disease, and its elevation in systemic infections may indicate the activation of nutritional immunity [263]. Similarly, the serum levels of lipocalin-2 may correlate with bacterial infection and may serve as a marker of iron-chelating responses [264]. Metabolomic profiling presents a high-resolution view of nutrient flux during infection. Changes in amino acid levels, such as tryptophan depletion and kynurenine accumulation, portray IDO activity and immune modulation. These metabolites can be measured using mass spectrometry and integrated into diagnostic algorithms for infections like HIV and tuberculosis [42]. Such approaches allow real-time monitoring of host-pathogen interactions. Emerging technologies such as biosensors and wearable devices may further improve the utility of nutritional immunity biomarkers. By continuously tracking nutrient-related parameters, clinicians can personalize therapy and assess the efficacy of treatment. Ultimately, merging biomarker data with genomic and immunologic profiles will facilitate precision diagnostics and targeted therapeutic interventions.

7. Future Directions

As the field of nutritional immunity evolves, it is increasingly clear that nutrient sequestration is not merely a passive defense but a dynamic and integrative component of host-pathogen interactions. Future efforts and research must address the mechanistic complexity, translational potential, and global significance of nutritional immunity, particularly in the context of emerging infectious diseases, malnutrition, and microbiome science. Essentially, this section offers a window into the future of a complete understanding of the components and applications of the concept of nutritional immunity.

7.1. Emerging Research Areas in Nutritional Immunity

Recent advances in systems biology and high-throughput technologies offer new avenues for exploring nutritional immunity at unprecedented resolution. For example, single-cell transcriptomics and spatial proteomics now permit researchers to map nutrient sequestration responses at the cellular and tissue level during infection [265]. These platforms are unveiling heterogeneity in immune cell responses, including differential expression of metal transporters, amino acid catabolic enzymes, and nutrient-sensing receptors across immune subsets. Another emerging area involves the exploration of non-classical nutrients and their role in immunity. For instance, while iron, manganese, and zinc have been extensively studied, elements such as copper, selenium, and molybdenum are receiving

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attention for their roles in redox regulation and enzymatic activity during infection [266]. A good understanding of how these trace elements are regulated and exploited by pathogens could reveal novel therapeutic targets and biomarkers. The interconnection between nutritional immunity and immunometabolism is also a rising field. For example, we now know that immune cells undergo metabolic reprogramming during activation, consuming large quantities of glucose, glutamine, and fatty acids [267]. This competition for nutrients between host and pathogen creates a metabolic tug-of-war that shapes the outcome of infection [40]. Investigating how nutrient availability affects immune cell fate decisions, cytokine production, and pathogen clearance will be relevant for creating new metabolic interventions. Finally, not much is known yet about the role of nutritional immunity in viral infections. While most research has focused on bacterial and fungal pathogens, viruses also modulate host nutrient pathways in a way that supports replication. For instance, HIV [69] and SARS-CoV-2 [268] alter iron metabolism and amino acid availability, which impacts immune function and disease progression. Expanding nutritional immunity studies to include viral pathogens will provide a more comprehensive understanding of host defense.

7.2. Translating Nutritional Immunity Into Clinical Applications

Translating the principles of nutritional immunity into clinical practice needs a multidisciplinary approach that synergizes microbiology, immunology, pharmacology, and nutrition science. One promising direction is the development of host-directed therapies that amplify nutrient sequestration. For example, synthetic hepcidin analogs are being explored to treat iron overload disorders and limit iron availability during bacterial infections [269–271]. These agents could be repurposed to boost nutritional immunity in sepsis or chronic infections. Another translational route involves the use of nutritional biomarkers to inform clinical decision-making. For instance, serum levels of ferritin, hepcidin, and calprotectin can tell the inflammatory status and predict infection severity. Incorporating these biomarkers into diagnostic panels may enhance early detection and stratification of infectious diseases [272]. Further, metabolomic profiling of amino acid and metal fluxes could offer real-time insights into host-pathogen dynamics and therapeutic efficacy. Personalized medicine strategies are also gaining traction. This is because genetic polymorphisms in immune regulators and nutrient transporters shape individual susceptibility to infection and response to therapy. For instance, mutations in the SLC11A1 gene, which encodes the NRAMP1 transporter, affect macrophage metal handling and resistance to intracellular pathogens [273]. Genotyping patients for such variants could guide tailored interventions that improve nutritional immunity. Clinical translation must also factor in safety and off-target effects. The manipulation of nutrient availability can influence host metabolism, immune function, and tissue repair. Thus, therapeutic strategies must be precisely targeted and context-specific. Robust clinical trials, pharmacokinetic modeling, and long-term safety assessments will be necessary to ensure that nutritional immunity-based therapies are both safe and effective.

7.3. Nutritional Immunity in the Context of Global Health and Malnutrition

Nutritional immunity has immense implications for global health, especially in regions burdened by infectious diseases and malnutrition. For example, iron deficiency is the most common nutritional disorder globally and can impair immune function while paradoxically protecting against certain infections like malaria [137]. A major challenge in public health nutrition remains how to balance iron supplementation with the risk of infection. Malnutrition alters the host's ability to mount effective nutritional immunity. Protein-energy malnutrition and micronutrient deficiencies hamper the synthesis of key immune proteins such as hepcidin, calprotectin, and lipocalin-2, weakening the host's ability to sequester nutrients from pathogens [274]. This creates a vicious cycle where infection aggravates malnutrition, and malnutrition impairs immune defense, particularly in children and immunocompromised populations. Global health efforts must integrate nutritional immunity into their frameworks for disease prevention and treatment. Programs that offer micronutrient supplementation should review infection status and tailor interventions accordingly. Zinc

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supplementation, for instance, has been shown to lower the duration and severity of diarrheal diseases in children, partly by improving innate immune responses [275]. Increasing our understanding of the immunological context of nutrient interventions will help in enhancing their efficacy and safety. Notably, urbanization, climate change, and food insecurity are modifying the landscape of infectious disease and nutrition [276,277]. Consequently, emerging pathogens may take advantage of novel nutrient niches, while shifts in dietary patterns could affect host immunity. Future global health strategies must embrace a systems-level perspective that considers the interplay between nutrition, immunity, and pathogen ecology to build strong health systems.

7.4. Nutritional Immunity and the Microbiome

The human microbiome plays a critical role in shaping nutritional immunity. Commensal microbes compete with pathogens for nutrients, generate antimicrobial metabolites, and influence host nutrient metabolism [23,278]. For example, gut bacteria can sequester iron and produce siderophores that inhibit pathogen growth, effectively acting as an extension of the host's nutritional defense [279,280]. This microbial competition is a major determinant of colonization resistance. The composition of the microbiome also influences host nutrient sensing and immune responses. For example, short-chain fatty acids (SCFAs) synthesized by microbial fermentation of dietary fiber modulate immune cell function and elevate barrier integrity [281–283]. These metabolites affect the expression of nutrient transporters and immune regulators, influencing the host's ability to respond to infection [284]. Dysbiosis, or microbial imbalance, can disrupt these processes and compromise nutritional immunity [285,286]. Probiotic and prebiotic interventions offer a promising strategy to improve nutritional immunity [49]. By promoting beneficial microbes that compete with pathogens and support host nutrient metabolism, these therapies can reinforce immune defenses. For instance, *Lactobacillus* and *Bifidobacterium* strains have been shown to amplify host antimicrobial peptides and modulate iron metabolism, lowering susceptibility to enteric infections [287–289]. Such strategies are especially relevant during antibiotic treatment and in vulnerable populations. Future research must illuminate the molecular mechanisms by which the microbiome interacts with nutritional immunity. Integrating microbiome profiling with immunometabolic analysis will essentially provide a holistic view of the interactions between host, pathogen, and microbe. Ultimately, harnessing the microbiome to support nutritional immunity is a frontier in precision medicine and infectious disease prevention.

8. Conclusion

Nutritional immunity is a chief cornerstone of host defense, which is intricately intertwined with the molecular and cellular fabric of immune responses. Its role in influencing pathogen behavior, determining disease outcomes, and guiding therapeutic innovation has become increasingly evident across disciplines. Notably, the concept of nutritional immunity has evolved from a narrow focus on iron sequestration to a multifaceted framework encompassing a wide array of nutrients, including metals, vitamins, amino acids, and carbon sources. Host organisms deploy a sophisticated arsenal of nutrient-binding proteins, transport regulators, and metabolic reprogramming strategies to deprive pathogens of critical resources. These mechanisms are not independent but are deeply interwoven with immune signaling pathways, cellular stress responses, and tissue-specific defense programs. In response, pathogens have equally developed complex countermeasures, including the synthesis of stealth siderophores, amplification of high-affinity transporters, metabolic rewiring, and modulation of host nutrient pathways. The diversity of these adaptations illustrates the ecological niches and evolutionary pressures faced by different microbial taxa. Therapeutically, nutritional immunity presents a rich landscape for innovation. For instance, strategies that mimic or bolster nutrient sequestration, such as siderophore-antibiotic conjugates, metal chelators, and host-directed therapies, have shown promise in preclinical and clinical settings. Additionally, diagnostic biomarkers derived from nutrient fluxes and immune responses are also emerging as critical tools for infection monitoring and personalized medicine. Future research must essentially prioritize the integration of nutritional immunity into clinical frameworks. This includes the creation of diagnostic platforms that

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monitor nutrient-related biomarkers, the design of therapeutics that modulate host nutrient responses, and the refinement of nutritional interventions based on infection status. To optimize these strategies, personalized medicine approaches that take into account genetic variation in nutrient handling, immune function, and microbiome composition will be relevant. Importantly, global health initiatives must also factor in the principles of nutritional immunity, such as understanding the interplay between nutrient status and immune competence in regions affected by malnutrition and infectious disease. Accordingly, programs that provide micronutrient supplementation should be tailored to local pathogen burdens and host nutritional profiles. Moreover, emerging infectious diseases, facilitated by urbanization, ecological disruption, and climate change, may take advantage of novel nutrient niches, necessitating adaptive public health responses. Finally, the microbiome represents a frontier for nutritional immunity research. Commensal microbes affect host nutrient metabolism, compete with pathogens, and influence immune responses. Harnessing the microbiome to support nutritional immunity, through probiotics, prebiotics, and microbiome-targeted therapies, offers a promising approach to prevent and control infections. As studies continue to unravel the molecular complexities of nutritional immunity, its translation into clinical and public health practice could redefine the landscape of infectious disease control.

Significance. Beyond metals and small metabolites, host lipids, including fatty acids, cholesterol, phospholipids, and lipid droplets (LDs), are both critical nutrient sources and structural building blocks for many pathogens, and they actively shape intracellular niches [290]. Host control over lipid trafficking and storage therefore functions as a form of nutritional immunity that can limit pathogen growth or, paradoxically, be subverted to enhance pathogen persistence [291,292].

Mechanisms and host responses. Infected cells reprogram lipid metabolism. For example, macrophages and other innate cells ramp up the uptake and esterification of cholesterol, synthesize neutral lipids, form LDs, and alter fatty-acid flux. LDs act as metabolic hubs and may be "weaponized" by the host, for example, by concentrating antimicrobial lipids or lipid-derived mediators, or, if hijacked, provide a nutrient depot for invaders [292–294].

Pathogen strategies. Intracellular bacteria and parasites exploit host lipids in multiple ways. These include import and catabolism of host cholesterol as seen in *Mycobacterium tuberculosis* [125], redirection of host fatty-acid metabolism [293], and interception of LDs and secretory trafficking to obtain membranes and energy as observed in *Chlamydia*, *Salmonella*, and *Toxoplasma* [290]. Dedicated bacterial systems such as *M. tuberculosis* cholesterol uptake and degradation pathways, coordinated by proteins like LucA enable utilization of host sterols for persistence [125,290,295].

Consequences and translational outlook. Targeting lipid access or utilization with statins, inhibitors of microbial cholesterol catabolism, modulation of LD biology, or host-directed metabolic reprogramming, offers promising adjunctive strategies to traditional antimicrobials especially in the wake of rising antibiotic resistance. However, given that lipids are central to host physiology, therapeutic windows are narrow and require precision [291,293].

Box 1. Nutritional immunity with lipids: nutrients and niche modulators.

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Nutritional immunity has been predominantly studied in bacterial and fungal pathogenesis. Yet, accumulating evidence illuminates its relevance during **viral infections**. Unlike bacteria, viruses do not directly acquire metals for replication but rely heavily on host cellular metabolic processes that are metal-dependent, including enzymatic activity, DNA/RNA synthesis, and immune signaling [296]. Therefore, the **host–virus interaction with nutritional immunity is largely indirect**, mediated through regulation of metal homeostasis, nutrients redistribution, and modulation of host immune responses.

Iron metabolism is strongly implicated in viral infections. Many viruses, including **Human Immunodeficiency Virus (HIV), hepatitis C virus (HCV), and cytomegalovirus (CMV),** exploit host iron-dependent pathways for replication [297]. High iron levels can enhance viral replication, while iron limitation via **hepcidin upregulation** or therapeutic chelation can suppress viral spread [298]. Conversely, iron overload in conditions such as hemochromatosis predisposes patients to more severe viral infections [299].

Zinc plays a twofold role in antiviral defense and viral pathogenesis. For instance, intracellular zinc bolsters antiviral immunity by promoting interferon signaling and stabilizing antiviral proteins, while **zinc-finger antiviral protein (ZAP)** directly restricts viral RNA [300]. Supplementation of zinc has been shown to lower the replication of **coronaviruses, influenza virus, and HIV** in vitro [300,301]. However, pathogens may oppose host zinc redistribution strategies. For instance, HIV can alter zinc transporter expression to favor its persistence in macrophages [300].

Copper and manganese also intersect with viral infections. For example, copper possesses intrinsic antiviral activity, disrupting viral proteins and nucleic acids, a property exploited in both innate immunity and copper-based surface coatings for infection control [302]. Meanwhile, manganese, is critical for the **cGAS–STING pathway**, a pivotal antiviral sensing mechanism, and its depletion impairs interferon-mediated viral clearance [303].

Taken together, nutritional immunity in viral infections represents a **subtler and more host-centric phenomenon** than in bacterial infections, where the pathogen directly competes for metals. Viruses rewire host nutrient availability to their benefit, while the host leverages nutrient redistribution to limit viral replication and enhance immune defense. This emerging field opens new therapeutic avenues, including **modulation of iron homeostasis, zinc supplementation, and copper-based antivirals which** are already under investigation in both preclinical and clinical settings [304–308].

Box 2. Nutritional immunity in the context of viral infections.

A common clinical axis. Nutritional immunity is fundamental to several clinical syndromes and therapeutic dilemmas, including anemia of inflammation, infection

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risk in iron-overloaded hosts, and both the promise and perils of altering metal metabolism in patients.

Anemia of inflammation. Proinflammatory cytokines (notably IL-6) trigger hepatic hepcidin, which downregulates ferroportin and hides iron within macrophages and hepatocytes [309]. This adaptive response restricts extracellular iron available to pathogens but also causes hypoferremia and anemia that can worsen patient outcomes if prolonged [7,308]. Managing anemia in infection therefore requires balancing limiting pathogen access to iron with host oxygen-carrying needs.

Iron overload and infection susceptibility. Patients with hereditary hemochromatosis or transfusional iron overload have an elevated risk for siderophilic infections because excess labile iron overwhelms host sequestering mechanisms [310,311]. Similarly, iron chelation can be protective in some infections but may exacerbate others if it becomes bioavailable to microbes via their strategies of recapturing withheld iron [7,56,312].

Therapeutic manipulation: promise and caveats. Clinical interventions that modulate metal availability, including localized metal delivery, systemic chelators, or hepcidin-modulating agents, are evolving. However, risks include inducing iatrogenic anemia, impairing immune cell function, or unintentionally supplying accessible iron to pathogens [313,314]. There is need, therefore, for translational strategies such as localized delivery and pathogen-directed siderophore conjugates to be precisely targeted and tested in context-specific clinical trials.

Box 3. Clinical relevance of nutritional immunity.

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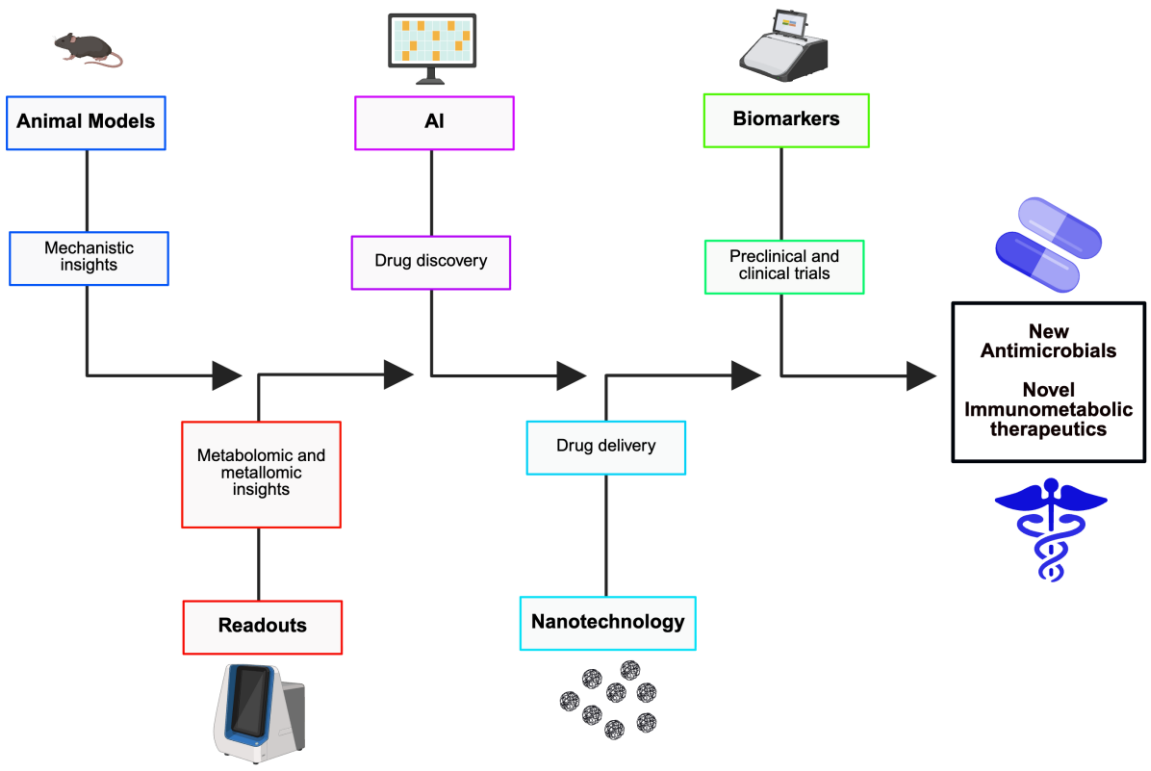

Convergence of fields. Nutritional immunity presents mechanistic targets for new therapeutics. However, the realization of that potential will be facilitated through the integration of computational design, nanomedicine, and immunometabolic insight. Recent advances in artificial intelligence (AI)-driven molecule discovery, precision nanodelivery, and systems immunometabolism offers a pipeline for agent development that is faster and more targeted than conventional antibiotic screens.

AI and discovery. Machine-learning and deep-learning platforms have already identified novel antimicrobial scaffolds and optimized siderophore-antibiotic conjugates in silico and in vitro, expediting hit discovery and de-risking medicinal chemistry [315,316]. AI can prioritize compounds that selectively impair pathogen metal acquisition or exploit species-specific uptake systems.

Nanomedicine and targeted modulation. Nanocarriers allow for precise spatial control in that they can deliver chelators, metal-mimetic agents (e.g., gallium), or zinc/copper payloads to infected tissues or intracellular vacuoles while limiting systemic toxicity [317–320]. Functionalization with targeting ligands such as antibodies and peptides can improve pathogen-cell specificity.

Immunometabolic therapeutics. Host-directed modulation of immune cell metabolism such as altering macrophage metabolism to support nutrient withholding or enhanced antimicrobial effector functions, complements direct antimicrobial strategies and can lower resistance pressure [55,321].

Roadmap. A translational program should: (1) pair mechanistic animal models with multiomics readouts, especially metabolomics and metallomics (2) use AI to triage candidate chemistries that engage pathogen

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uptake systems, (3) validate targeted nanodelivery in safety models, and (4) design early-phase trials with robust biomarkers, including hepcidin, labile plasma iron, and tissue metallome, to ascertain on-target effects before large efficacy trials [315,317]. This integrated approach promises host-informed, pathogen-targeted therapeutics that exploit nutritional immunity while lowering collateral host injury.

Box 4. Future perspectives: nutritional immunity meets drug discovery.

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