

Review

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Review

Vitamin D as a Master Regulator of Biological Barrier Integrity: A Systems Framework Linking Vitamin D Deficiency to Systemic Leaky Barrier Syndrome

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Abstract

Vitamin D is traditionally recognized for its role in calcium homeostasis and skeletal health; however, growing molecular and clinical evidence indicates that vitamin D signaling is a central regulator of biological barrier integrity across multiple organ systems. Epithelial and endothelial barriers—including the intestinal mucosa, vascular endothelium, blood–brain barrier, pulmonary epithelium, renal filtration barrier, and cutaneous barrier—depend on intact tight junctions, adherens junctions, and immune–redox homeostasis to maintain systemic health. We propose that vitamin D deficiency may contribute to a unifying pathophysiological state characterized by multi-barrier dysfunction, recently conceptualized as **Systemic Leaky Barrier Syndrome (SLBS)**. Through regulation of junctional proteins (e.g., claudins, occludin, ZO-1), modulation of innate and adaptive immunity, suppression of chronic inflammation, and maintenance of redox balance, vitamin D plays a pivotal role in preserving barrier resilience. Failure of these protective mechanisms promotes translocation of microbial products, inflammatory mediators, and metabolic toxins, driving chronic diseases including cardiovascular disease, neurodegeneration, autoimmune disorders, cancer progression, and metabolic dysfunction. This review synthesizes mechanistic, translational, and clinical evidence supporting vitamin D as a barrier-protective hormone and positions SLBS as a systems-level framework for understanding the broad disease consequences of vitamin D insufficiency.

Keywords: vitamin D; VDR signaling; biological barriers; epithelial integrity; endothelial dysfunction; tight junctions; inflammation; redox biology; Systemic Leaky Barrier Syndrome; chronic disease

1. Introduction: From Vitamin D Deficiency to Barrier Failure

Vitamin D deficiency is globally prevalent and increasingly recognized as a contributor to a wide spectrum of chronic diseases. While many reviews focus on vitamin D's immunomodulatory or endocrine effects, fewer integrate its **barrier-protective functions** across organ systems.

In this review, the term 'vitamin D deficiency' is used broadly to encompass both deficiency and insufficiency, unless otherwise specified.

Biological barriers serve as the body's primary defense interfaces, separating internal compartments from environmental, microbial, and metabolic stressors. Loss of barrier integrity represents an early and often underappreciated step in disease pathogenesis. Vitamin D exerts its effects through the VDR, a nuclear receptor that regulates gene expression involved in cell proliferation, differentiation, and intercellular adhesion — forming a molecular link to barrier-related functions [1].

Recently, a systems-medicine construct—**Systemic Leaky Barrier Syndrome (SLBS)**—was proposed to describe the coordinated breakdown of multiple biological barriers as a shared

mechanism underlying diverse chronic diseases [2]. Vitamin D deficiency emerges as a central upstream driver within this framework.

This review integrates molecular, experimental, and clinical evidence to examine vitamin D signaling across major biological barriers and situates these findings within the emerging systems-medicine framework of Systemic Leaky Barrier Syndrome (SLBS).

This review is conceptual and integrative in nature, intended to synthesize existing mechanistic and clinical evidence rather than to propose diagnostic criteria or therapeutic guidelines.

2. Vitamin D Signaling and Barrier Biology

2.1. Vitamin D Receptor (VDR) Expression in Barrier Tissues

The vitamin D receptor (VDR) is widely expressed in:

- Intestinal epithelial cells
- Vascular endothelial cells
- Pulmonary epithelium
- Renal tubular and glomerular cells
- Keratinocytes
- Microglia and brain endothelial cells

In addition to structural barrier cells, VDR is also expressed on immune cells and can be upregulated by pro-inflammatory cytokines such as IL-15 and IFN- γ , highlighting a direct link between vitamin D signaling and immune modulation relevant to barrier defense [3].

The vitamin D receptor (VDR) is a ligand-activated nuclear receptor that functions as a transcription factor, regulating diverse target genes involved in cell adhesion, immune function, and tissue barrier homeostasis [1].

This distribution strongly suggests a conserved evolutionary role in **interface defense and barrier regulation**.

2.2. Regulation of Tight and Adherens Junctions

Vitamin D signaling upregulates and stabilizes key junctional proteins:

- Tight junctions: **claudin-1, claudin-5, occludin, ZO-1**
- Adherens junctions: **E-cadherin, β -catenin**

Experimental models demonstrate that VDR knockout or vitamin D deficiency leads to junctional disorganization, increased permeability, and heightened inflammatory signaling via modulation of key tight junction proteins such as claudins and occludin (e.g., 1,25-D-VDR effects on epithelial tight junction integrity)[4]. Notably, vitamin D signaling has been shown to directly regulate intestinal epithelial tight junction integrity via VDR-dependent control of junctional protein expression and epithelial permeability, providing a molecular link between vitamin D deficiency and gut barrier dysfunction [5].

3. Vitamin D and Major Biological Barriers

3.1. Intestinal Barrier and the Gut-Systemic Axis

Vitamin D maintains gut barrier integrity by:

- Enhancing tight junction expression
- Suppressing zonulin-mediated permeability
- Regulating antimicrobial peptides (e.g., cathelicidin)
- Modulating gut immune tolerance

In addition, experimental evidence shows that epithelial VDR upregulates tight junction protein claudin-5, protecting intestinal epithelial barrier integrity in inflammation-associated tumorigenesis and reducing permeability, whereas loss of VDR leads to barrier dysfunction in vivo [6].

Although claudin-5 is classically considered an endothelial tight junction protein, emerging evidence supports its functional relevance in intestinal epithelial barrier regulation under inflammatory and neoplastic conditions.

In experimental infection models, vitamin D supplementation preserved intestinal epithelial barrier function, reduced pathogen-induced permeability, and mitigated epithelial injury, whereas vitamin D deficiency exacerbated colonic barrier dysfunction and inflammatory responses, reinforcing its role in gut mucosal defense [7].

These effects are mediated in part by direct VDR signaling within intestinal epithelial cells, where vitamin D deficiency or VDR disruption results in increased epithelial permeability and susceptibility to inflammatory injury [5].

These mechanisms include direct regulatory effects of 1,25-dihydroxyvitamin D on tight junction protein expression and epithelial permeability, reinforcing the role of vitamin D in maintaining mucosal barrier function [4].

Disruption promotes endotoxemia and systemic inflammation — core features of SLBS.

3.2. Vascular Endothelium and Cardiovascular Disease

Endothelial dysfunction is increasingly viewed as a **barrier disease**. Vitamin D:

- Preserves endothelial junctions
- Reduces oxidative stress and NF- κ B activation
- Improves nitric oxide bioavailability

Vitamin D deficiency correlates strongly with atherosclerosis, hypertension, and microvascular leakage, aligning with the SLBS framework.

Consistent with these mechanistic insights, a systematic review and meta-analysis of randomized controlled trials found that vitamin D supplementation significantly improved vascular endothelial function, as measured by flow-mediated dilation, underscoring the relevance of vitamin D status to human endothelial health and barrier resilience [8].

Mechanistically, vitamin D/VDR signaling has been shown to upregulate key endothelial tight junction and adherens junction proteins — including claudin-5, ZO-1, and VE-cadherin — and to preserve vascular barrier integrity under inflammatory and injury conditions [9].

3.3. Blood–Brain Barrier and Neuroinflammation

Vitamin D protects BBB integrity by:

- Suppressing pro-inflammatory cytokines
- Stabilizing endothelial tight junctions
- Modulating microglial activation

Moreover, the vitamin D receptor is expressed in neurons of the human substantia nigra and developing rat midbrain, highlighting the broad distribution of VDR within the central nervous system and supporting the receptor's potential relevance to neurovascular and barrier functions [10].

Epidemiologically, lower circulating 25(OH)D levels are associated with increased prevalence of all-cause dementia, Alzheimer's disease, stroke, and MRI indicators of cerebrovascular pathology in older adults, suggesting that vitamin D insufficiency may contribute to neurovascular dysfunction and BBB compromise in human populations [11].

Barrier breakdown permits peripheral inflammatory mediators to access the CNS, contributing to neurodegenerative and neuropsychiatric disorders.

Consistent with this model, prospective human data demonstrate that higher serum 25-hydroxyvitamin D levels are associated with a substantially reduced risk of developing multiple sclerosis, supporting a role for vitamin D status in maintaining neuroimmune and neurovascular integrity relevant to blood–brain barrier function [12].

3.4. Pulmonary, Renal, and Cutaneous Barriers

Across lung, kidney, and skin, vitamin D:

- Maintains epithelial differentiation
- Reduces inflammatory permeability
- Enhances antimicrobial defense

Vitamin D deficiency is associated with ARDS severity, proteinuric kidney disease, and chronic inflammatory dermatoses.

In the respiratory epithelium, vitamin D–VDR signaling localizes active 1,25(OH)₂D synthesis and influences innate immune defenses, including antimicrobial peptide production and modulation of immune responses, which together help preserve barrier integrity and decrease susceptibility to infection and inflammatory injury [13].

In the kidney, vitamin D receptor signaling in podocytes plays a critical barrier-protective role; experimental loss of VDR signaling exacerbates proteinuria, podocyte injury, and glomerulosclerosis, whereas VDR activation preserves slit diaphragm integrity and protects against diabetic nephropathy [14].

In the epidermis, vitamin D receptor signaling—together with nuclear receptor coactivators SRC-2 and SRC-3—directly regulates sphingolipid (ceramide) synthesis essential for permeability barrier formation; disruption of this pathway impairs epidermal barrier integrity and increases transepidermal water loss [15].

4. Vitamin D, Redox Homeostasis, and Barrier Resilience

Barrier integrity is highly sensitive to oxidative stress. Vitamin D:

- Reduces ROS generation
- Enhances antioxidant systems
- Supports mitochondrial function

In parallel, a systematic review of immune cell studies demonstrated that adequate vitamin D levels consistently suppress pro-inflammatory cytokine production and promote a more regulated immune phenotype across multiple immune cell types, highlighting vitamin D's central role in restraining inflammation-driven barrier disruption [16].

At the molecular level, VDR activation modulates redox-sensitive signaling pathways including NF- κ B, Nrf2, and mitochondrial oxidative phosphorylation, thereby linking vitamin D status directly to cellular oxidative resilience and barrier stability.

Within the SLBS framework, redox imbalance acts synergistically with inflammation to accelerate barrier failure.

Supporting this, a meta-analysis of randomized trials found that vitamin D supplementation decreases circulating pro-inflammatory cytokines (e.g., TNF- α , IL-6, CRP), underscoring vitamin D's role in ameliorating inflammation-associated endothelial barrier dysfunction [17].

5. Systemic Leaky Barrier Syndrome (SLBS): A Unifying Framework

SLBS conceptualizes chronic disease as a **multi-barrier failure state**, rather than isolated organ pathology. Vitamin D deficiency intersects with SLBS by:

- Weakening structural barriers
- Amplifying immune dysregulation
- Promoting chronic inflammatory signaling
- Impairing tissue repair mechanisms

This model explains why vitamin D insufficiency is linked to seemingly unrelated diseases, from ASCVD and cancer progression to autoimmune and neurodegenerative disorders.

In oncology, extensive experimental, translational, and epidemiologic evidence indicates that vitamin D signaling suppresses tumor initiation, proliferation, inflammation, angiogenesis, and metastatic potential, and that vitamin D deficiency is associated with increased cancer risk and

disease progression, supporting its role as a systemic modifier of cancer biology rather than a tissue-restricted factor [18].

Consistent with this systems perspective, vitamin D deficiency has been proposed as an upstream accelerator of biological aging and age-related diseases through cumulative dysregulation of calcium signaling, mitochondrial function, immune balance, and cellular resilience, providing a broader aging framework that aligns with SLBS as a multi-barrier failure state [19].

6. Clinical and Therapeutic Implications

- Vitamin D sufficiency should be viewed as **barrier maintenance therapy**, not merely bone support
- Target serum 25(OH)D levels in chronic inflammatory or barrier-related diseases remain an area of active investigation and should be individualized under the supervision of trained and experienced healthcare professionals.
- Vitamin D repletion should be integrated with strategies addressing inflammation, redox imbalance, and metabolic stress.

7. Conclusions

Vitamin D functions as a master regulator of biological barrier integrity across multiple organ systems. Its deficiency promotes a systemic permeability state consistent with Systemic Leaky Barrier Syndrome, providing a mechanistic bridge between vitamin D insufficiency and diverse chronic diseases. Recognizing vitamin D as a barrier-protective hormone reframes its role in preventive and therapeutic medicine.

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