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From DINOMIT to Systemic Leaky Barrier Syndrome

Vitamin D as a Master Regulator of Biological Barrier Integrity

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Honoring a Foundational Insight While Advancing a Systems Perspective

For more than two decades, the work of Cedric Garland and colleagues-including Frank Garland, Edward Gorham, and collaborators-has profoundly shaped our understanding of vitamin D as a central determinant of cancer risk and immune health (Garland et al., 2009).

Among these contributions, the DINOMIT model stands as a landmark conceptual framework describing a sequence of biological processes associated with vitamin D deficiency: Disjunction, Initiation, Natural selection, Overgrowth, Metastasis, Involution, and Transition.

DINOMIT was not merely descriptive-it was prescient. It recognized early that disruption of intercellular adhesion and tissue integrity represents a foundational step in disease progression.

As vitamin D research has advanced, accumulating molecular, immunological, and clinical evidence suggests that DINOMIT captured not only downstream disease manifestations, but also a deeper upstream vulnerability: the loss of biological barrier integrity across multiple organ systems.

This article proposes that DINOMIT can be further understood and extended within a broader systems framework: Systemic Leaky Barrier Syndrome (SLBS), a systems-level model describing the role of barrier dysfunction in chronic disease development (Cheng, 2026a).

DINOMIT: A Model Ahead of Its Time

DINOMIT recognized that vitamin D deficiency contributes to:

- Loss of intercellular adhesion
- Selection of aggressive cellular phenotypes
- Enhanced angiogenesis
- Tissue invasion and metastasis

These insights were supported by epidemiologic observations linking low serum 25-hydroxyvitamin D levels with increased risk of multiple cancers (Garland et al., 1980; Garland et al., 1985; Garland et al., 1989), and by mechanistic studies on cellular differentiation and junctional biology (Pálmer et al., 2001; Farquhar and Palade, 1963).

At the time the model was proposed, the molecular understanding of epithelial barriers, tight junctions, and vitamin D receptor signaling was still emerging. Today, these mechanisms are far better characterized-and they strongly support the biological plausibility of DINOMIT.

Vitamin D and Biological Barrier Integrity

Vitamin D is now recognized as a key regulator of barrier function across multiple systems, including intestinal epithelium, vascular endothelium, blood-brain barrier, pulmonary epithelium, renal filtration barrier, and skin.

Through vitamin D receptor-mediated signaling, vitamin D regulates tight junction proteins such as claudins, occludin, and ZO-1, while also modulating antimicrobial peptides, immune tolerance, and inflammatory pathways (Chun et al., 2014; Hewison, 2012; Cheng, 2026b).

Vitamin D deficiency has been associated with increased intestinal permeability ("leaky gut"), endothelial dysfunction, and disruption of the blood-brain barrier (Assa et al., 2014; Garcion et al., 2002; Talmor-Barkan et al., 2021). Conversely, vitamin D repletion has been shown to improve junctional integrity and reduce inflammatory leakage.

Importantly, barrier dysfunction does not occur in isolation. Multiple barriers may become progressively permeable, allowing microbial products, inflammatory mediators, and oxidative stress signals to enter systemic circulation, contributing to chronic low-grade inflammation.

Systemic Leaky Barrier Syndrome (SLBS): A Systems-Level Extension

Systemic Leaky Barrier Syndrome (SLBS) is not a replacement for DINOMIT, but an extension of it, grounded in systems-level models of barrier dysfunction in chronic disease (Cheng, 2026a).

Within this framework:

- Vitamin D deficiency acts as an upstream driver
- Barrier dysfunction becomes the central organizing pathology
- DINOMIT processes emerge downstream as biological consequences

In this sense, DINOMIT describes what happens, while SLBS helps explain why it happens systemically.

Broader Disease Implications

The barrier-centered model provides a unifying framework across multiple conditions.

In cancer, vitamin D sufficiency may help stabilize epithelial and endothelial barriers, reducing inflammatory and angiogenic signaling that support tumor development.

In autoimmune and inflammatory diseases, barrier dysfunction is increasingly recognized as a common underlying feature. Vitamin D plays an important role in maintaining immune tolerance at barrier interfaces (Aranow, 2011).

In Type 1 diabetes, epidemiologic and mechanistic models suggest that vitamin D deficiency may contribute to disease risk through barrier dysfunction and immune dysregulation (Mohr et al., 2008).

In aging, increased barrier permeability contributes to chronic inflammation. Vitamin D insufficiency may accelerate this process.

Clinical and Research Implications

A barrier-centered understanding of vitamin D suggests:

- A shift from single-organ to systems-level thinking
- Recognition of variability in clinical response to vitamin D
- Greater emphasis on maintaining sufficient serum 25-hydroxyvitamin D levels
- Consideration of nutrient interactions and overall metabolic context

Population-level evidence suggests that maintaining serum 25-hydroxyvitamin D concentrations at or above 50 ng/mL may be associated with reduced risks of cancer and chronic disease (Lappe et al., 2017; McDonnell et al., 2018).

Honoring a Scientific Legacy

The contributions of Cedric Garland and colleagues laid the conceptual foundation for understanding vitamin D as a root determinant of disease, rather than a secondary association.

The SLBS framework is offered in that same spirit: to refine and extend these insights using contemporary systems biology.

Scientific progress is cumulative. DINOMIT established the foundation; barrier biology helps complete the architecture.

Closing Perspective

Vitamin D is not simply a nutrient or hormone. It functions as a regulator of biological boundaries-the interfaces between internal physiology and the external environment.

Viewing DINOMIT together with Systemic Leaky Barrier Syndrome provides a more complete and clinically actionable framework for understanding the role of vitamin D in human health.

Author Note

A peer-review-ready version of this framework has been submitted for academic publication.

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