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Article

Local Metabolic-Hypoxic Conditioning as a Spatial Modulator of Immune-Mediated Tissue Injury: A Systems Framework with Application to Multiple Sclerosis

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Abstract

Immune-mediated tissue injury is typically conceptualized as a consequence of aberrant immune activation; however, spatial patterns of lesion formation and selective tissue vulnerability across diseases suggest that immune activity alone may not determine where damage becomes established. We propose a generalizable systems framework in which regional metabolic preconditioning, defined by local perfusion dynamics, oxygen availability, and bioenergetic resilience, modulates the threshold for immune-mediated injury. In this model, tissue susceptibility emerges from the interaction between (1) immune activation intensity and (2) region-specific metabolic state. Reduced perfusion and relative hypoxia stabilize hypoxia-inducible signaling pathways, alter endothelial integrity, reprogram cellular metabolism, and amplify inflammatory responsiveness. These processes do not initiate autoimmunity but reshape the energetic and vascular landscape in which immune mechanisms operate, thereby governing spatial lesion topology and progression. We formalize this interaction as a threshold-modulation framework in which tissue injury probability is a function of both immune effector load and metabolic resilience. Applied to multiple sclerosis as a model system, this perspective integrates cerebral hypoperfusion, mitochondrial dysfunction, blood-brain barrier instability, and compartmentalized inflammation into a unified explanatory structure. The framework generates falsifiable predictions regarding perfusion-lesion coupling, metabolic biomarkers of susceptibility, and cross-disease parallels in immune-driven pathology. By positioning metabolic state as a dynamic modifier of immune injury thresholds, this model shifts emphasis from single-axis causation toward systems-level interaction, offering a conceptual template for understanding spatial selectivity and progression in immune-mediated diseases.

Keywords: hypoxic priming; immune-metabolic interaction; multiple sclerosis; spatial heterogeneity; threshold modulation; tissue susceptibility; systems biology

1. Introduction

Immune-mediated tissue injury is commonly conceptualized as a direct consequence of dysregulated immune activation. Yet across organ systems, inflammatory damage displays striking spatial selectivity: certain regions repeatedly exhibit vulnerability, while adjacent tissues remain relatively spared. Such patterned lesion topology suggests that immune effector activity alone may be insufficient to determine where injury becomes established. Instead, regional physiological states may modulate tissue susceptibility by altering energetic resilience, vascular dynamics, and stress-response signaling.

Multiple sclerosis (MS) provides a well-characterized model in which this principle may be examined. Although demyelination is mediated by adaptive immune mechanisms, lesion distribution follows a highly stereotyped spatial pattern, particularly involving periventricular and deep white-matter territories supplied by vascular architectures with limited perfusion reserve [2].

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Imaging studies demonstrate cerebral hypoperfusion and metabolic abnormalities within normal-appearing white matter early in the disease course, in some cases preceding overt lesion formation [3]. Moreover, progressive disability frequently advances despite suppression of acute inflammatory activity [4].

These observations suggest that immune activation alone does not fully determine lesion susceptibility or long-term tissue injury. We propose that regional vascular-metabolic state functions as a conditioning variable that modulates the threshold for immune-mediated damage. In this framework, tissue vulnerability emerges from the interaction between immune effector load and local bioenergetic resilience, positioning MS as a paradigmatic example of a broader systems-level principle governing spatial selectivity in immune-driven pathology.

2. A Systems Model of Vascular-Metabolic Susceptibility

We propose that regional tissue injury in immune-mediated disease is governed not solely by immune effector intensity but by an interaction between immune activation and local metabolic state. In this framework, regional hypoperfusion generates relative hypoxia within metabolically vulnerable tissue compartments, thereby altering the energetic landscape in which immune mechanisms operate. Hypoxia does not directly initiate autoimmunity; rather, it modulates the threshold at which immune-mediated damage becomes established.

Hypoxic signaling stabilizes hypoxia-inducible transcriptional pathways that influence endothelial permeability, cellular metabolic allocation, oxidative stress handling, and inflammatory responsiveness [5–7]. These processes link vascular dynamics to immune amplification through coordinated changes in barrier integrity, oligodendrocyte energy balance, and innate immune activation. In multiple sclerosis, endothelin-1-mediated vasoconstriction and impaired neurovascular coupling provide plausible contributors to region-specific reductions in effective oxygen delivery [8].

We conceptualize tissue susceptibility (S) as an emergent property of two interacting variables: immune effector load (I) and metabolic resilience (M), where resilience reflects perfusion adequacy, mitochondrial capacity, and oxygen availability. Injury probability increases when I exceeds a dynamic threshold determined by M. Under conditions of reduced perfusion or hypoxic stress, M declines, effectively lowering the injury threshold and permitting immune-mediated damage to occur at levels of activation that would otherwise be tolerated.

These interactions may form a feed-forward system: inflammation increases metabolic demand and microvascular dysfunction, which further reduces effective oxygen delivery, reinforcing hypoxic signaling and sustaining tissue injury [9]. Such reciprocal coupling creates spatially stable zones of vulnerability.

Importantly, this model preserves the central role of adaptive immunity in demyelination. It instead reframes lesion localization and persistence as consequences of regional threshold modulation within a coupled immune-metabolic system.

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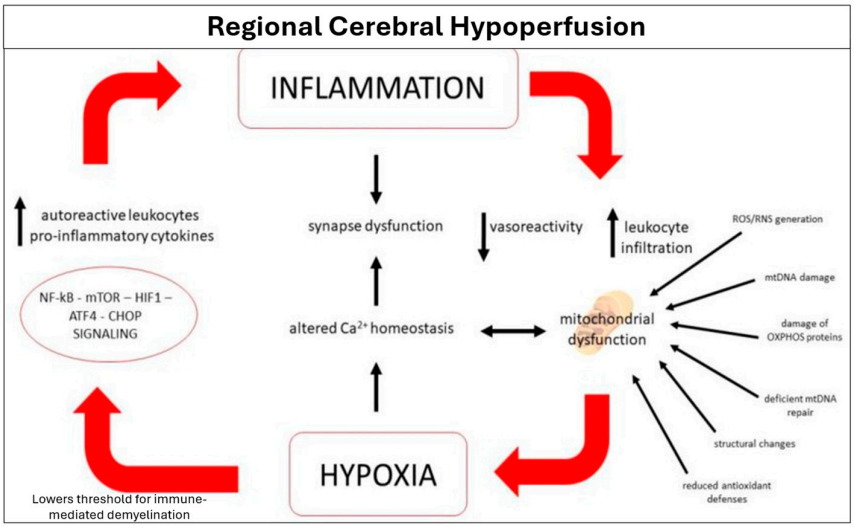


Figure 1. Conceptual model of hypoxic priming as a threshold modulator of immune-mediated tissue injury.

Regional reductions in perfusion decrease metabolic resilience, lowering the immune activation threshold required for tissue damage. Bidirectional coupling between inflammation and hypoxia stabilizes spatially selective zones of vulnerability.

3. Model Consistency with Observed Pathological Patterns

To evaluate the plausibility of a hypoxic-priming framework, observed features of multiple sclerosis pathology can be examined as system-level consequences of threshold modulation rather than as isolated disease characteristics.

3.1. Spatial Lesion Topography

The stereotyped periventricular and deep white-matter distribution of lesions corresponds to vascular territories supplied by long medullary arteries with limited collateral redundancy [2]. Within the proposed framework, such regions possess intrinsically reduced perfusion reserve and therefore diminished metabolic resilience (M). Even modest reductions in oxygen delivery may lower the immune-injury threshold locally, rendering these territories disproportionately susceptible when immune effector load (I) rises. Spatial lesion selectivity thus emerges as a predictable consequence of heterogeneous baseline resilience across vascular networks.

3.2. Normal-Appearing White Matter (NAWM) Abnormalities

Perfusion and metabolic imaging studies demonstrate hypoperfusion, altered oxygen utilization, and mitochondrial dysfunction within normal-appearing white matter prior to overt lesion formation [3]. In the threshold model, these findings are interpreted not as secondary effects of inflammation but as indicators of reduced metabolic resilience preceding focal immune-mediated injury. Tissue stress therefore becomes a conditioning variable that modulates subsequent lesion probability, consistent with a primed but not yet structurally damaged state.

3.3. Inflammation-Hypoxia Coupling

Inflammatory activity increases metabolic demand, oxidative stress, and microvascular dysregulation [9]. Within a coupled system, such changes further decrease effective oxygen availability, thereby reducing metabolic resilience and amplifying susceptibility. This reciprocal interaction creates a feed-forward loop in which immune activation and hypoxic signaling stabilize

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each other, potentially explaining chronic lesion expansion and progression despite partial suppression of systemic immune activity.

4. System Transition and Progressive Disease Dynamics

Progressive multiple sclerosis is characterized by compartmentalized inflammation, mitochondrial dysfunction, and slowly expanding lesions [4]. These features are difficult to reconcile with models that conceptualize disease activity as episodic immune infiltration alone. Instead, progression may represent a transition in system dynamics rather than a simple increase in immune intensity.

Within the hypoxic priming framework, chronic reductions in metabolic resilience (M) shift the system toward a persistently lowered injury threshold. Over time, cumulative mitochondrial stress, impaired oxidative phosphorylation, and reduced perfusion reserve diminish the tissue's capacity to buffer inflammatory and oxidative insults. The system thus enters a state in which even modest immune activation sustains tissue injury.

Smoldering or slowly expanding lesions can be interpreted as locally stabilized zones of reduced resilience, maintained by reciprocal coupling between inflammation and hypoxia. In this regime, injury persistence no longer requires recurrent waves of peripheral immune infiltration; instead, bioenergetic insufficiency and compartmentalized immune activity become self-reinforcing.

Progression therefore reflects a shift from a primarily immune-triggered injury phase to a metabolically constrained state in which resilience collapse governs ongoing damage. Vascular-metabolic dysfunction may thus serve as a systems-level bridge linking relapsing inflammatory episodes to later neurodegenerative progression.

5. Relationship to Established Risk Factors

A threshold-modulation framework does not displace established environmental or infectious risk factors; rather, it positions them within a systems interaction model. In this formulation, disease emergence reflects the interaction between immune activation intensity (I) and regional metabolic resilience (M), with injury occurring when immune load exceeds a resilience-dependent threshold.

Epstein-Barr virus (EBV), strongly associated with multiple sclerosis susceptibility, likely contributes to the immunologic substrate for autoreactivity by increasing or sustaining immune activation (I) [10]. However, EBV exposure alone does not determine lesion topology or regional vulnerability. Within the present framework, autoreactive immune activity becomes pathogenic preferentially in tissue compartments where metabolic resilience is reduced. Thus, EBV-associated immune priming and hypoxic-metabolic conditioning operate on complementary axes of the system.

Similarly, the latitude gradient in MS prevalence and associations with vitamin D status, sun exposure, and genetic variants may influence both immune regulation and endothelial-metabolic function [11]. Rather than acting directly through oxygen availability, these factors may subtly modify mitochondrial efficiency, vascular tone, and stress-response signaling, thereby shaping baseline resilience (M). In this sense, environmental and genetic influences alter the physiological landscape in which immune mechanisms operate.

By mapping established risk factors onto interacting immune and metabolic dimensions, the model reconciles epidemiological associations with spatial lesion selectivity and progression dynamics, reinforcing the concept that disease expression arises from coupled system variables rather than a single pathogenic axis.

6. Model-Derived Predictions

The hypoxic priming framework generates falsifiable predictions derived from the interaction between immune effector load (I) and metabolic resilience (M). If tissue injury probability reflects a resilience-dependent threshold, several observable consequences should follow:

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6.1. Temporal Preconditioning

Regional reductions in perfusion or markers of impaired oxygen utilization should precede focal lesion formation in longitudinal imaging studies. In this model, decreased metabolic resilience (M) is expected to emerge prior to overt structural injury, defining a pre-threshold vulnerable state [3].

6.2. Resilience-Severity Coupling

The magnitude of hypoperfusion or metabolic dysfunction should correlate with subsequent lesion expansion and progression dynamics. Regions with persistently reduced resilience should demonstrate higher probability of sustained or enlarging injury, even when immune activation intensity is comparable across regions [9].

6.3. Threshold Modulation by Vascular-Metabolic Intervention

Interventions that improve microvascular function, endothelial regulation, or mitochondrial efficiency should raise the effective injury threshold. Consequently, tissue damage should diminish or stabilize even in the absence of major changes in systemic immune activation [8].

6.4. Biomarkers of Resilience Collapse

Molecular or imaging markers reflecting hypoxic signaling, oxidative stress, or mitochondrial dysfunction should associate with progressive disease trajectories. In advanced stages, persistent injury should correlate more strongly with indices of reduced metabolic resilience than with markers of acute immune infiltration.

6.5. Spatial Heterogeneity as a Predictable Property

Lesion topology should align with baseline vascular architecture and perfusion reserve maps, reflecting intrinsic heterogeneity in metabolic resilience across tissue compartments.

These predictions are measurable using existing perfusion imaging, metabolic profiling, and longitudinal clinical platforms. Failure to observe resilience-injury coupling, or demonstration that immune activation alone fully predicts lesion localization independent of metabolic state, would argue against the proposed threshold-modulation framework.

7. System-Level Intervention Implications

Within a threshold-modulation framework, therapeutic effects can be conceptualized as parameter shifts within a coupled immune-metabolic system rather than as isolated suppression of a single pathway. If metabolic resilience (M) determines the injury threshold at which immune effector load (I) produces tissue damage, then interventions that increase resilience should elevate this threshold and reduce injury probability without necessarily altering immune activation intensity.

Such resilience-enhancing strategies may include modulation of cerebrovascular tone, optimization of endothelial function, and augmentation of mitochondrial efficiency or oxidative metabolism. Rather than replacing immunomodulatory therapy, these approaches would act on a complementary axis of the system, altering the conditions under which immune activity becomes pathogenic.

From a systems perspective, combined modulation of immune activation (reducing I) and metabolic resilience (increasing M) may shift the system away from a vulnerable attractor state toward a more stable regime in which tissue integrity is preserved. This dual-parameter approach reframes therapeutic design as manipulation of interacting variables governing injury thresholds rather than targeting a single causal pathway.

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8. Limitations and Alternative Interpretations

The hypoxic priming framework does not posit hypoxia as a universal initiating cause of immune-mediated pathology. Rather, it proposes that metabolic resilience functions as a conditioning variable within a coupled system. Multiple sclerosis is heterogeneous, and the relative contribution of vascular–metabolic modulation may vary across disease stages, anatomical compartments, or phenotypic subtypes. In some contexts, immune activation intensity (I) may dominate system behavior independently of measurable reductions in metabolic resilience (M).

A central limitation concerns causal directionality. Hypoxia and inflammation are dynamically coupled processes, and disentangling primary from secondary effects in vivo remains challenging. The framework allows for bidirectional interaction: immune activation may reduce metabolic resilience, and reduced resilience may amplify immune-mediated injury. The model therefore predicts interaction rather than strict temporal primacy. Observations such as transient hyperperfusion preceding lesion formation [12] may reflect compensatory responses within a stressed metabolic system rather than direct refutation of hypoxic conditioning.

Empirical constraints also include the limited availability of direct regional oxygen-tension measurements in human disease. Current inference relies primarily on perfusion imaging and metabolic biomarkers, which approximate but do not directly quantify tissue oxygen dynamics. The model would be weakened if robust longitudinal studies demonstrate that lesion topology and progression are fully explained by immune activation intensity independent of measurable metabolic state.

Finally, alternative frameworks, including purely immune-driven, purely vascular, or stochastic lesion models, remain plausible explanations for aspects of disease expression. The present proposal does not exclude these mechanisms but argues that threshold modulation by metabolic state offers a unifying systems-level account capable of integrating spatial selectivity, progression, and risk-factor interaction within a single conceptual structure.

9. Conclusions

Immune-mediated tissue injury is often interpreted through a single-axis framework centered on dysregulated immune activation. The present analysis instead advances a systems-level perspective in which injury probability emerges from the interaction between immune effector load and regional metabolic resilience. Within this threshold-modulation framework, local hypoxic priming reshapes the energetic and vascular landscape, altering the conditions under which immune mechanisms become pathogenic.

Applied to multiple sclerosis as a model system, this approach integrates spatial lesion selectivity, normal-appearing white-matter abnormalities, progression dynamics, and epidemiologic risk factors within a unified conceptual structure. Rather than displacing immune causality, the framework situates immunity within a coupled immune–metabolic network in which tissue vulnerability is dynamically regulated.

More broadly, the model illustrates how spatial heterogeneity in metabolic state can govern the topology and persistence of immune-mediated injury. By formalizing metabolic resilience as a modifiable determinant of injury thresholds, this perspective encourages investigation of tissue vulnerability as a systems property across immune-driven diseases. The integration of vascular dynamics, bioenergetic capacity, and immune activation into a single interactional model provides a testable template for understanding how localized susceptibility emerges within complex biological systems.

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