Proportional Danger Theory: Energy Availability, Stress Physiology, and Immune Function Within the EPK Framework

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Status: conceptual/hypothesis-generating working paper. Not peer reviewed. This revision adds primary-study appraisal and prospective tests; it reports no new participant data.

Abstract

Polly Matzinger's Danger Theory shifted immunological thinking away from a simple self versus non-self model toward contextual signals of tissue damage and danger. Proportional Danger Theory extends this idea by proposing that the magnitude and resilience of immune responses are constrained by the energetic and physiological capacity of the organism. The theory integrates EPK, immunometabolism, stress physiology and aging.1,2,3,4 This revision separates dietary intake from cellular utilisation and proposes prospective comparison of EPK with its component measurements; the added mechanistic evidence does not validate EPK.

From Self/Non-Self to Danger

Self versus non-self models cannot alone explain sterile inflammation, tumour tolerance, pregnancy, commensal tolerance and autoimmunity. Danger Theory emphasises tissue context and damage signals. Proportional Danger Theory adds a second question: even when danger is recognised, what energetic capacity does the organism have to mount, regulate and resolve the response?[1,2]

Immunometabolism

Immune activation is metabolically expensive. Activated T cells, macrophages and other immune populations can markedly increase glucose uptake and glycolytic flux to support proliferation, cytokine production and biosynthesis. This does not mean that sugar intake directly boosts immunity. It means that immune behaviour is inseparable from cellular metabolism and substrate availability.[3,4]

Stress-Supported Physiology

During energetic insufficiency, cortisol, catecholamines, glucagon and other counter-regulatory systems help preserve circulating fuel. Acute activation is adaptive. Chronic dependence on these systems may alter sleep, glucose regulation, inflammation and immune function. The proposed mechanism is therefore not that stress hormones literally occupy immune capacity, but that persistent allostatic and energetic demands can reduce adaptive reserve and change immune regulation.[5,6]

Aging and Immunosenescence

Older adults show immune remodeling, poorer vaccine responses, increased infection vulnerability and chronic low-grade inflammation. Established immunosenescence cannot be reduced to energy deficiency. Proportional Danger Theory instead asks whether declining movement, muscle mass, glucose handling, sleep, recovery and chronic stress materially modify age-related immune decline. In this model, apparent loss of immune competence may reflect both cellular aging and a progressively less resilient energetic environment.[1,2,5,6,7,8]

The Proportional Danger Hypothesis

The central proposition is that danger signals and physiological capacity interact to shape immune responsiveness. This remains a context-dependent hypothesis, not a demonstrated proportional law. Adequate, regulated responses and effective resolution are distinct from simply greater immune activation.

Mitochondrial regulation beyond ATP supply

Heras-Murillo et al. found that respiratory complex III disruption impaired dendritic-cell responsiveness through metabolic and epigenetic changes without a corresponding fall in ATP [R1]. The effects depended on dendritic-cell subtype. This provides a mechanistic link between mitochondrial state and immune function, but challenges an account based only on available caloric energy.

For Proportional Danger Theory, physiological resources must therefore include regulatory and redox capacity as well as fuel supply. The word proportional describes a proposed context-dependent relationship, not an established linear equation. The desirable outcome is an appropriate response and resolution; stronger activation is not always beneficial. EPK has not been shown to measure these cellular capacities.

Human evidence from the PubMed search

A randomized crossover investigation in 12 female endurance athletes examined immune-cell redox responses during low energy availability. It adds a human link between the exposure and cellular physiology, but biomarkers do not establish infection risk or vaccine effectiveness. This report and Caldwell et al. appear to concern the same intervention cohort and should not be counted as independent replications. [H1]

These studies test energy restriction or sports energy availability, not EPK as an intake-to-total-mass ratio. Their populations and intervention durations bound interpretation; none validates an EPK threshold. The human literature requires the framework to allow beneficial, adverse and null responses in different contexts.

Testing the immune hypothesis

Does EPK predict functional outcomes beyond total energy intake, body composition, carbohydrate availability and activity, and could fuel switching or mitochondrial function explain any association?

For prospective testing, EPK is defined here as mean dietary energy intake in kcal per day divided by body mass in kg, expressed as kcal/kg/day. This intake ratio is not the sports energy-availability measure, which subtracts exercise energy expenditure from intake and divides by fat-free mass. Exercise expenditure, fat-free mass, carbohydrate intake and weight trajectory must therefore be recorded separately. No diagnostic EPK threshold is established by this revision.

A prospective study could measure baseline intake and body composition, then assess a prespecified vaccine response or standardised ex vivo immune challenge. Record age, prior antigen exposure, infection, sleep, medication and relevant disease. Separate response magnitude from resolution and adverse inflammation. Where feasible, measure immune-cell subtype, respiration and redox state rather than inferring them from a whole-body calorie ratio.

EPK is calculated from intake and mass and therefore contains no information absent from those inputs. Its value must be judged as a useful summary, not an independent biological variable. Compare a preregistered EPK model with a flexible model of energy intake and mass, including relevant nonlinear terms and interactions, under the same validation procedure. Adding the ratio to a simple linear baseline would not by itself establish unique physiological information. Report out-of-sample prediction error, calibration and uncertainty; favour the simpler model if performance is comparable.

The proposed pathway requires evidence connecting EPK to the cellular phenotype and that phenotype to subsequent immune function. Cell experiments establishing mitochondrial dependence do not establish the first link. Prespecified mediation analysis requires temporal order and confounding assumptions; a cross-sectional correlation would not demonstrate it. Failure to find an association, or an effect restricted to one subtype, should narrow or reject the relevant proposition.

Conclusion

Proportional Danger Theory does not replace antigen recognition, innate sensing or immunological memory. It proposes an additional systems-level constraint: immune function occurs within an energetic organism. EPK provides a framework for testing whether energy availability, stress burden, metabolic flexibility and recovery predict immune resilience across the lifespan.[9,10,11,12,13,14,15]

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Primary studies added in version 1.1

[R1] Heras-Murillo I, et al. Mitochondrial metabolism regulates the immunogenic responsiveness of dendritic cells. Cell Metab. 2026;38:1097–1112.e8. https://doi.org/10.1016/j.cmet.2026.03.012. See also the published correction: https://doi.org/10.1016/j.cmet.2026.04.010

Human studies added in version 1.1

[H1] Jeppesen JS, et al. Low energy availability increases immune cell formation of reactive oxygen species and impairs exercise performance in female endurance athletes. Redox Biol. 2024;75:103 250. doi:10.1016/j.redox.2024.103250. https://pubmed.ncbi.nlm.nih.gov/38 936 255/

Publication Note

This manuscript is part of the EPK (Energy Per Kilogram) paper series developed by Billy Craig, MSc. The paper should be cited as a working/preprint paper until peer-reviewed publication. EPK-specific propositions are presented as hypotheses where they extend beyond the cited evidence.

Revision record

Version 1.1 adds the mechanistic discussion and prospective study design above. The original numbered bibliography remains distinct from the new R-prefixed mechanistic and H-prefixed human-study citations. Studies discovered through haidut.me are cited to their original research publications; the blog commentary is not treated as primary evidence.

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