

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

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Abstract

Proportional Danger Theory proposes that immune responses depend on both the stimulus and the organism's physiological resources. This is a context-dependent hypothesis, not an established proportional law. The revision integrates immunometabolism, glucocorticoid context, human low-energy-availability biomarkers and recent tissue-specific inflammatory findings. It distinguishes appropriate defence and resolution from simply greater immune activation, and separates dietary energy exposure from cellular regulatory capacity. No EPK threshold or dietary treatment for immune disease is established.

Scope and evidence selection

This is a targeted narrative synthesis and hypothesis paper, updated through 2 October 2026. Sources were selected from the existing EPK evidence library, primary publications and the recent companion reviews. Selection was question-led and not systematic; no pooled effect, formal risk-of-bias score or new participant dataset is reported. Bibliographic records and available abstracts/full texts were used. Abstract-only access limits appraisal of allocation, missing data, confounding and adverse events. Supporting, contrary and null findings are retained.

1. The proposition and its boundaries

Danger Theory emphasises the role of tissue context and damage signals in immune activation. The proposed EPK extension asks whether physiological resources help explain differences in the magnitude, appropriateness and resolution of a response. It neither replaces antigen recognition and memory nor establishes a numerical law of proportionality. [1]

EPK is defined as mean dietary energy intake in kcal/day divided by body mass in kg. It is an intake-to-total-mass ratio, not a direct measure of energy balance, ATP production or nutritional sufficiency. Sports energy availability instead subtracts exercise expenditure from intake and divides by fat-free mass. Those quantities must be recorded separately; sports thresholds cannot be transferred numerically to EPK. [2]

Resource availability should not be represented solely by calories. Cell type, substrate access, signalling, redox control and tissue state may change responses in different directions. The desirable outcome is effective defence with appropriate resolution, not maximal activation.

2. Immunometabolism beyond energy quantity

Immunometabolism describes changes in metabolic pathways accompanying immune-cell activation and quiescence. These changes support both energetic and biosynthetic requirements. They do not mean that sugar ingestion directly strengthens immunity. [3]

Heras-Murillo et al. linked respiratory-complex disruption to dendritic-cell responsiveness through metabolic and epigenetic effects, with cell-subtype differences and without a corresponding fall in ATP. This challenges a simple calorie-to-ATP-to-immunity chain. The published correction should be consulted with the original report. [4] [5]

An EPK study must independently establish whether its intake exposure predicts a relevant cellular state. Demonstrating that mitochondria matter for immunity does not establish that EPK measures mitochondrial function.

3. Stress hormones and tissue context

Glucocorticoids have permissive, preparative, stimulatory and suppressive actions depending on timing and context. A high cortisol result alone is not evidence of energy insufficiency or immune failure. [6]

An obese-mouse exercise study associated increased local lung glucocorticoid activation with reduced inflammation. It was assessed at indexed-summary level. It illustrates why systemic and tissue-specific hormone activity should not be conflated, without establishing a human dietary intervention. [7]

Dietary macronutrient changes can affect cortisol metabolism without increasing circulating concentrations. Stress exposure, hormone turnover and immune outcome should therefore be specified separately. [8]

4. Human energy-availability evidence

Jeppesen et al. reported immune-cell reactive-oxygen-species changes and poorer exercise performance in a small female endurance-athlete crossover study. Biomarkers do not establish infection incidence or vaccine protection. The related Caldwell paper appears to report the same intervention cohort and must not be counted as independent replication. [9] [10]

The IOC consensus provides a sports context for health consequences of problematic low energy availability. It does not validate a total-body-mass intake cutoff for immune function in the general population. [2]

Evidence on starvation, sleep or perceived stress can motivate covariates but does not directly test Proportional Danger Theory. A general immune claim requires functional immune measurements and clinically relevant follow-up.

5. Recent inflammatory and lipid studies

Adipocyte loss in a rare lipodystrophy condition co-occurred with altered metabolism and inflammatory programmes. A low-fat mouse diet experiment also showed that carbohydrate source could change gut inflammatory outcomes. These findings point to tissue and dietary context rather than a one-dimensional calorie scale. [11] [12]

Cultured-cell inhibition of protein synthesis by arachidonic acid cannot determine a dietary PUFA ceiling or demonstrate immune benefit from an app toggle. Essential-fat adequacy must be preserved, and any comparison should specify the fatty-acid substitution and achieved intake. [13] [14]

Endurance-related red-cell oxidation describes an exercise exposure, not necessarily immune impairment. Likewise, cellular hypermetabolism under chronic stress is not evidence that a higher whole-body calorie target restores immune resilience. [15] [16]

6. An immune study that could reject the hypothesis

Select a standardised ex vivo immune challenge or a clinically appropriate vaccine-response study, with specialist oversight. Preregister whether the primary outcome is response magnitude, resolution or protection. Measure baseline immune status, age, prior antigen exposure, recent infection, medication, sleep and relevant disease.

Because the ratio is determined entirely by intake and mass, it cannot contain information absent from those inputs. Its usefulness is a question of practical summarisation and predictive performance. Compare a prespecified EPK model with flexible models of intake, mass, fat-free mass and activity, including nonlinear terms where justified. Use the same held-out validation procedure, report calibration and uncertainty, and prefer the simpler model if performance is similar. A favourable comparison with a deliberately weak linear model would not establish a new biological quantity.

Collect energy exposure before the immune outcome. Record cell-subtype composition and assay conditions; a change in mixed-cell measurements may reflect changing cell populations. Where feasible, measure respiration and redox state directly rather than infer them from dietary intake.

A useful test must permit no association, a nonlinear relationship, or harm from excessive activation. A positive intake-response correlation does not demonstrate causation. A trial would need to show that changing the specified intervention alters the functional outcome, not merely a selected biomarker.

This immune project is a later specialist component of the research programme. It should not be appended as an underpowered set of exploratory tests to the first general EPK feasibility study, then presented as validation if one result reaches significance.

Conclusion

Proportional Danger Theory is a proposed framework for testing resource-dependent immune regulation. Recent evidence makes it more important to separate energy supply, cellular state and appropriate response. Direct, prespecified immune outcomes are required before clinical claims are warranted.

Version and disclosure

Version 1.2 narrows the proportionality claim, integrates human and tissue-specific evidence, corrects cortisol and biomarker interpretations, and specifies independent tests of the proposed immune relationship. This version supersedes v1.1.1 for the current text; the earlier PDF and DOI remain an archive of that release. Reference numbering has been rebuilt for this version and must not be transferred from earlier editions.

The author develops EPK and has an intellectual and potential commercial interest in its evaluation. AI-assisted editorial drafting and source checking were used. This independent working paper has not undergone external peer review. No new human intervention or participant analysis is reported. Copyright 2026 Billy Craig. Author-owned text is licensed CC BY-ND 4.0; third-party material retains its own rights.

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Version history

v1.2 - 2 October 2026: scientific and editorial revision, refreshed reference mapping and integrated recent evidence. Unverified MSc quantitative claims are excluded from the evidential basis.

v1.1.1 - 11 September 2026: earlier licensing release. Archived DOI: [10.5281/zenodo.22710102](https://doi.org/10.5281/zenodo.22710102). Earlier versions remain available through Zenodo.

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