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Energy Trade-offs in Host Defense: Immunology Meets Physiology

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Host defense relies not only on microbicidal mechanisms (resistance), but also on management of collateral damage (tolerance). Here, we discuss how this immunology concept converges with a physiology-born theory on the dichotomy of thermometabolic responses in infection (fever versus hypothermia), yielding a model of immunity that transcends discipline barriers.

Introduction

Originally applied to host defense in plants, the Disease Resistance versus Tolerance Theory has been incorporated into animal immunology over the past decade [1]. It postulates that hosts can defend themselves from pathogens not only by employing energy-consuming microbicidal mechanisms (resistance), but also by dampening the negative impacts of pathogens on host fitness (tolerance). This theory has now gained a new perspective with a study by Ganeshan *et al.* [2], who showed that development of hypothermia and hypometabolism promotes disease tolerance in mice challenged with bacterial lipopolysaccharide (LPS) or viable bacteria. These results are exciting, as they pave the way for bridging the Disease Resistance versus Tolerance Theory with a physiology-born theory on the dichotomous nature of thermal responses in severe infection (sepsis): the Fever versus Hypothermia Theory [3]. The latter theory postulates that a regulated, brain-driven form of hypothermia naturally replaces fever when the need to clear the pathogen is outweighed by the need to preserve vital bodily functions, as is often the case when the immune challenge is too strong. Here, we discuss how these theories can reciprocally enhance each other. Our goal is not to modify the theories, but rather to fit them together within a single framework of host defenses.

On the Causes of Pathogen-Induced Hypothermia and Hypometabolism

A question that emerged in connection with both theories was whether the hypometabolism associated with LPS-induced hypothermia could be a mere reflection of metabolic failure. Using a whole-animal physiology approach, Corrigan *et al.* [4] have ruled out this possibility by showing that, during LPS-induced hypometabolism and hypothermia, rats were fully capable of increasing oxygen consumption when their metabolic demands were heightened by a β_3-adrenergic agonist. Now, Ganeshan *et al.* [2] have addressed the same question using a cell biology approach and showed that mitochondrial electron transport in liver, heart, and brown fat is not disrupted by a hypothermia-inducing dose of LPS. These findings indicate that LPS-induced hypometabolism is not a symptom of thermoregulatory failure, but rather the manifestation of altered body temperature control, a notion that is consistent with the involvement of the brain and behavior in this phenomenon (see below).

In this scenario, it is important to consider that thermoregulatory control is more complex and refined than generally envisioned. Such refinement has been incorporated into the Fever versus Hypothermia Theory, but has yet to be considered by proponents of the Disease Resistance versus Tolerance Theory. For example, in their recent article linking hypothermia to disease tolerance, Ganeshan *et al.* [2] have interpreted their findings based on the set-point model of thermoregulation, which postulates that a single thermostat/controller in the central nervous system drives all heat-production and heat-loss effectors in unison. This model, however, is inadequate to explain the fever–hypothermia switch that occurs with increasing doses of LPS in rats and mice, since this switch relies on the dissociation of heat-production and heat-loss effectors [5]. Although such dissociation renders body core temperature dependent on the ambient temperature (the poikilothermic mode of thermoregulation), the body core temperature is still regulated (e.g., by using thermal preference behavior) [6]. Indeed, while rats challenged with lower doses of LPS seek a warmer environment in which fever develops as the result of cutaneous heat conservation, rats challenged with higher doses of LPS seek a cooler environment in which hypothermia develops as the result of suppressed metabolic heat production [7]. This finding also indicates that the strength of the immune challenge is a primary operator of the fever–hypothermia switch (Figure 1). This switch can be under additional control by trade-off factors traditionally studied by eco-immunologists in connection with the Disease Resistance versus Tolerance Theory, such as food availability and reproduction [8].

Another relevant aspect of the Fever versus Hypothermia Theory is that the inflammatory mediators and neural pathways involved in the development of fever versus hypothermia are as dichotomous as the thermal responses themselves. For example, whereas interleukin-6 and prostaglandin E_2 derived from cyclooxygenase-2 are mediators of fever, tumor necrosis factor-α

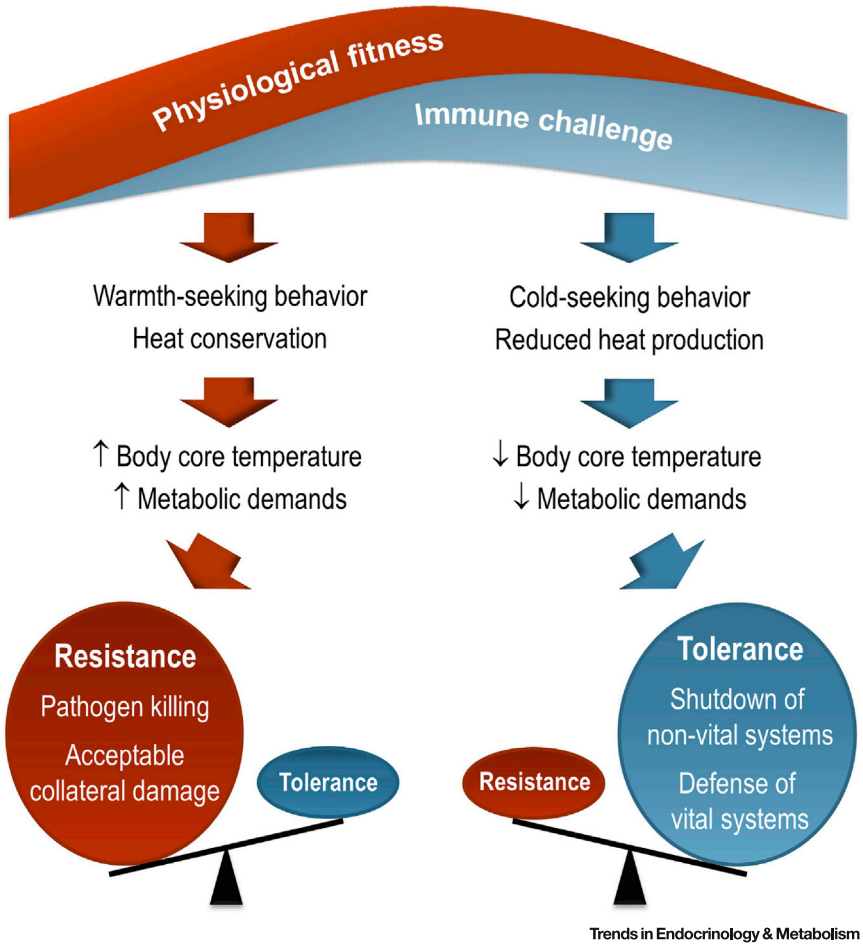

Figure 1. The Balance between Immune and Physiological Cues Alters Thermoregulatory Control to Promote Fever or Hypothermia, Which, In Turn, Aids Host Resistance or Tolerance, Respectively.

On the one hand, a mild immune challenge in a physiologically fit host promotes fever and resistance at the expense of the host's energy reserves. On the other hand, a fall in physiological fitness associated with a strong immune challenge is met with regulated hypothermia and energy conservation, which together aid host tolerance.

and a yet unidentified product of cyclooxygenase-1 are mediators of hypothermia [3]. Additionally, whereas neurons located at the border of the dorsomedial and ventromedial hypothalamic nuclei play a key role in the cold-seeking behavior induced by a high LPS dose, they are not essential for the warmth-seeking behavior induced by a low LPS dose [7]. The available evidence also indicates that the bias towards hypothermia during a strong immune challenge does not result from attenuation of febrigenic signaling, but rather from enhancement of hypothermia-promoting signals [3]. This mechanistic independence prompts us to speculate that fever and hypothermia might have distinct evolutionary origins, having evolved to deal with different demands, possibly resistance versus tolerance. Future research is needed to put this idea to the test.

On the Consequences of Hypothermia and Hypometabolism to Host Defense

Although both theories discussed herein are based upon the premise that energy conservation may be more adaptive than an active immune response in certain contexts, the perspective of each field on such contexts is quite different. In the Disease Resistance versus Tolerance Theory, the costs of resistance are typically inferred from immunometabolomic studies showing that leukocytes respond to pathogens with metabolic reprogramming, which increases their demands for nutrients and oxygen [9]. In the Fever versus Hypothermia Theory, such costs are usually inferred from whole-body estimates of metabolic rate and from assessment of cardiorespiratory dysfunction in febrile versus afebrile animals [10,11]. In our view, though, these are not different contexts at all, but rather different facets of the same context, considering that fever-range temperatures enhance leucocyte activation, presumably impacting their metabolic reprogramming, in addition to imposing metabolic and oxidative burden on many other cell types. These effects can be synergistic to immunity, but only when the host has sufficient fitness (effective resistance). When there is no fitness to spare (e.g., excessively strong immune challenge, undernutrition, or other comorbidities), life-threatening damage can ensue [10,11].

The Fever versus Hypothermia Theory was originally proposed in the late 1990s [12,13], but it was only in 2012 that compelling proof in its support was obtained by Liu *et al.* [14]. In the latter study, rats subjected to a strong immune challenge with high doses of LPS or *Escherichia coli* were either allowed to develop hypothermia in a mildly cool environment (which they prefer), or were 'forced' to develop

fever in a warm environment. In this model, development of hypothermia instead of fever was protective to the lungs, liver, kidneys, and pancreas, ultimately reducing mortality rates. At that time, however, those findings were not interpreted in connection with the Disease Resistance versus Tolerance Theory. Using a similar approach in mice, Ganeshan *et al.* [2] have now linked hypothermia to disease tolerance based on the fact that hypothermia improves host fitness without abating the bacterial burden or the cytokine storm. Notably, this has been observed not only by Ganeshan *et al.* [2], but also by Liu *et al.* [14]. These two studies also complement each other by showing that the value of hypothermia does not come for free. Liu *et al.* [14] reported that although hypothermia reduced overall mortality in *E. coli*-infected rats, it accelerated mortality in some of the rats that succumbed. Ganeshan *et al.* [2] observed that failure to recover from hypothermia within 48 h (the case in $Ucp^{-/-}$ mice) overturned the benefits of hypothermia in *E. coli* infection, yielding higher mortality.

The mechanisms by which hypothermia/hypometabolism promote host tolerance are still largely unknown, but evidence rooted in the Fever versus Hypothermia Theory suggests that matching of oxygen delivery to metabolic demands may be a key factor. Indeed, a fall in oxygen delivery is among the main challenges faced by humans and experimental animals with severe forms of infection. The relevant evidence in this respect is that, in unanaesthetized rats, metabolic rate and oxygen delivery fall synchronously when the environment is sufficiently cold to allow development of LPS-induced hypothermia [4]. Matching of oxygen delivery and demand can be so effective in this condition that no hypoxia could be detected in tissues using a sensitive index of cellular oxygenation (the NAD^+/NADH ratio). However, when exposure to a warm environment renders LPS-injected rats unable to develop hypometabolism and hypothermia, mismatches between oxygen delivery and demand occur and tissue hypoxia becomes detectable [4].

Perspectives

This article highlights points of convergence of the Disease Resistance versus Tolerance Theory with the Fever versus Hypothermia Theory. Recognition of such convergence is likely to result in a better understanding of the mechanisms by which immune and physiological cues affect the thermoregulatory system to match host resistance or tolerance strategies with an adequate thermometabolic state, in a way that fever and hypermetabolism are matched with host resistance, whereas hypothermia and hypometabolism are matched with host tolerance (Figure 1). This recognition will inevitably open new avenues of investigation at the interface of immunology and physiology, perhaps even ecology. It may also have important clinical implications, since patients with severe infection (sepsis) are known to develop not only fever, but also hypothermia. Healthcare providers generally see this spontaneous form of hypothermia as a dysfunction associated with organ failure, which will get progressively worse if active rewarming is not applied. Recently, however, this perception has been challenged by a retrospective study showing that hypothermia in septic patients not subjected to active rewarming is transient, self-limiting, and, most importantly, usually absent when organ failure is at its peak in the hours preceding death [15]. Prospective interventional studies are now warranted to determine whether hypothermia is, in fact, a regulated response in septic patients, as well as to verify its potential connection with a switch in host defense strategy from resistance to tolerance.

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Disclaimer Statement

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