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New Idea

Did pathogens facilitate the rise of endothermy?

Michael L. Logan

Michael L. Logan (mike.logan1983@gmail.com), University of Nevada, Reno, Department of Biology, Reno, NV, USA 89557 and *Smithsonian Tropical Research Institute, Ciudad de Panamá, Panamá*

Abstract

The evolutionary success of endothermy in mammals and birds represents an enduring enigma. Relative to an ectotherm of equivalent body size, endotherms expend many times the energy to maintain high, stable body temperatures. What source or sources of selection could have favored such an energetically costly strategy? Several hypotheses have been proposed for agents of selection that may have facilitated the rise of endothermy, with mixed support for each. Here, I discuss the possibility that an additional agent of selection, pathogens, may have played an important role in the evolution and maintenance of obligate endothermy in mammals and birds. I draw on recent work demonstrating that the immune system is highly thermally sensitive and individuals that maintain warm body temperatures have enhanced ability to reduce pathogen burdens. To further increase immune function when encountering a pathogen, ectotherms often employ the environmentally constrained and costly strategy of behavioral fever, whereas endotherms maintain body temperatures close to the optimum for immune performance at most times, essentially 'priming' their immune systems for a rapid response to infection. An evolutionary arms race in an ancient ectotherm, in which better behavioral thermoregulators were favored by increasingly virulent pathogens (and vice versa) could have contributed to the evolution of obligate endothermy in mammals and birds.

Keywords: Behavioral fever, disease, homeothermy, host-pathogen co-evolution, metabolic rate, thermoregulation

The endothermy enigma

Obligate endothermy evolved independently in the stem groups of modern mammals and birds (Grigg et al. 2004). These taxa have given rise to tens of thousands of species that dominate many ecosystems. The success of these groups is somewhat surprising given the energetic cost of endothermy, that is, the cost of maintaining a relatively constant, heightened basal metabolic rate. Indeed, endotherms consume as much as 30 times the energy per unit time as an ectotherm of equivalent body size (Bennett and Ruben 1979). This extreme cost suggests that an extreme benefit (or benefits) would have been required for obligate endothermy to evolve.

Three primary hypotheses have been proposed to explain the evolution of endothermy in mammals and birds (Table 1). While each of these models has found mixed support, debate continues over which of these agents of selection were particularly important, and at what times, during the radiations of mammals and birds. Here, I propose an additional agent of selection that may have played a role in facilitating the evolution of obligate endothermy that has been largely overlooked.

Fever and the thermal sensitivity of immune function

The febrile response ("fever") is a highly conserved trait in animal evolution (Evans et al. 2015), originating at least 600 million years ago (Kluger 1979). Once the innate immune systems of both endotherms and ectotherms recognize the presence of a pathogen, they mount a febrile response following very similar neurological pathways (invading cells trigger the prostaglandin-hypothalamus axis) (Rakus et al. 2017a, Rakus et al. 2017b). Whereas endotherms achieve fever-range body temperatures largely by increasing heat

Table 1. Primary models for the evolution of endothermy.

Model	Description
Thermoregulation (Crompton et al. 1978)	Endothermy evolved for the benefits conferred by high, stable body temperatures per se.
Aerobic capacity (Bennett and Ruben 1979)	Endothermy evolved because it increased the capacity for animals to sustain activity over long periods of time. High basal metabolic rates evolved as a correlated response to selection for maximum metabolic rates.
Parental care (Farmer 2000, Koteja 2000)	Endothermy evolved because it enabled parents to take care of precocial offspring. Higher body temperatures and activity levels increased the ability for parents to incubate their offspring while both feeding and defending them.

production via metabolism, ectotherms use "behavioral fever," actively seeking out warmer microclimates within their habitat (Vaughn et al. 1974, Covert and Reynolds 1977, Kluger 1979). The vast majority of species that have been investigated have shown a fever response (Elliot et al. 2002, Boltaña et al. 2013), consistent with the idea that immune function depends on temperature and has an evolutionarily constrained optimum that exceeds typical maintenance-level body temperatures. Fever is also adaptive; animals that are allowed to achieve behavioral fever under experimentally induced immune challenges have higher rates of survival and reproduction (Kluger et al. 1975, Covert and Reynolds 1977, Kluger 1979, Boorstein and Ewald 1987, Elliot et al. 2002, Gräns et al. 2012, Boltaña et al. 2013, Evans et al. 2015).

Historically, fever was assumed to help defend an organism against a pathogen by directly reducing the pathogen's growth and reproduction (Clint and Fessler 2016). Indeed, fungal pathogens in particular appear to have low thermal tolerance and often fail to grow under warm conditions. Basic evolutionary theory suggests that this is unlikely to be the primary purpose of fever, however, as pathogens typically evolve at much higher rates than their hosts (due to higher mutation rates, larger population sizes, and shorter generation times) (Woolhouse et al. 2002). Pathogens may therefore be capable of quickly evolving a thermal physiology that is tolerant of fever-range temperatures. So why do nearly all animals undergo fever when their immune systems are challenged? Growing evidence suggest that fever decreases the fitness of the pathogen indirectly by increasing the efficacy of the host's immune system. Although in certain cases fever-range temperatures do directly impact the fitness of pathogens (Casadevall 2005, Robert and Casadevall 2009, Berman and Casadevall 2010, Clint and Fessler 2016, Voyles et al. 2018), it now appears that the major role of fever is to push the organism to their thermal optimum for immune function by acting on the fundamental thermodynamic requirements of immune system components (Jiang et al. 2000, Chen et al. 2006, Evans et al. 2015). For example, fever increases the binding affinity of a number of immune system macromolecules, which increases lymphocyte trafficking to lymphoid organs, among other effects (Hanson 1997, Chen et al. 2006, Evans et al. 2015). Fever increases blood flow through vasodilation which speeds the transport of immune system cells to critical tissues (Hanson 1997, Chen et al. 2006, Evans et al. 2015), and it dramatically increases the proliferation, differentiation, phagocytic activity, and transport speed of macrophages and white blood cells (like neutrophils and T-cells) (Hanson 1997, Rosenspire et al. 2002, Chen et al. 2006, Mace et al. 2011, Sandmeier and Tracy 2014, Evans et al. 2015). Similarly, body temperatures below the range of the febrile response result in slower immune system response times (longer time delays to peak antibody levels) (Wright and Cooper 1981, Elliot et al. 2002, Sandmeier and Tracy 2014). Importantly, many of these effects have been demonstrated *in vitro* (Chen et al. 2006, Evans et al. 2015), suggesting that temperature directly impacts the performance of multiple immune system components independently of network interactions and signaling cascades. Clearly, fever is good for the immune system, and most animals strive to achieve higher body temperatures when they are infected with a pathogen.

Endotherm immune systems are 'primed'

Most biochemical processes, including those of the immune system, are highly temperature-sensitive (Angilletta 2009). The relationship between the rate of a biological process and temperature is called a "thermal performance curve" (TPC), and these curves almost always assume a stereotypical shape (Figure 1) (Angilletta 2009, Angilletta et al. 2010, Gunderson and Leal 2012, Phillips et al. 2014). They are described mathematically as left-skewed parabolic functions with an optimum that occurs very close to the point where the function drops to zero on the high end of the x-axis (Logan et al. 2014, Logan et al. 2018). Because ectotherms must behaviorally thermoregulate and are at the mercy of environmental fluctuations in time and

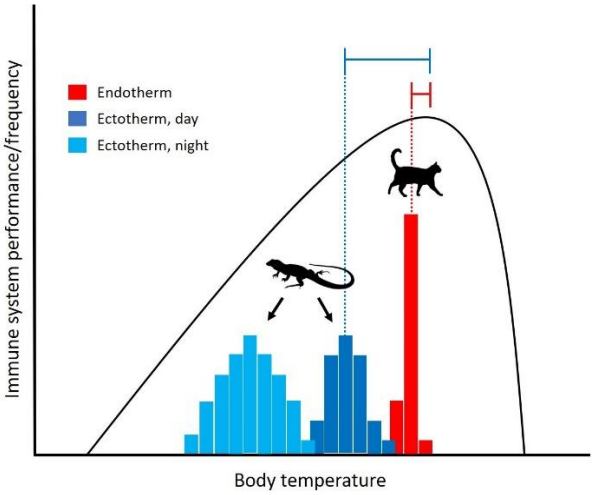

Figure 1. Endothermy effectively 'primes' the immune system for a rapid response to pathogens. Because many endotherms maintain stable internal body temperatures (red bars) via a metabolic thermostat, they can maintain high body temperatures that sit right on the precipice of the thermal optimum of the immune system. The black curve represents a hypothetical thermal performance curve for immune function, and the peak of this curve is the mean febrile temperature. In this way, endotherm immune systems can respond rapidly (red bracket) to an infection during both diurnal and nocturnal hours. By contrast, ectotherms typically have body temperatures that are significantly lower than the thermal optima for most physiological functions, including immune function, because behavioral thermoregulation is constrained by a variety of factors. During daytime hours (dark blue bars = diurnal body temperatures) ectotherms may experience a delay to peak immune performance while they search for optimal temperatures within their habitat (dark blue bracket). At night (light blue bars) behavioral thermoregulation is impossible and therefore ectotherms cannot achieve fever. Note that I assume for clarity of presentation that there is only one thermal performance curve for immune function for endothermic and ectothermic species living in a similar environment. While this is clearly a simplification, the relative benefits of precise thermoregulation do not change as long as the thermal optima of immune systems are generally higher and less variable than differences in mean body temperature among species.

space, their body temperatures have relatively high variance (Huey 1974, Huey and Slatkin 1976, Martin and Huey 2008, Gunderson and Leal 2016, Logan et al. 2016, Cox et al. 2018). At night, for example, thermal environments are spatially homogenous, and ectotherms are incapable of maintaining thermal homeostasis unless the thermal environment itself is temporally stable. A similar result occurs in diurnal environments when there is an abundance of cloud cover, or when ecological conditions prevent the free movement of individuals into preferred microclimates (Huey and Slatkin 1976, Hertz et al. 1993). On average, then, ectotherms achieve body temperatures that are below the thermal optimum for a given physiological function (Martin and Huey 2008, Logan et al. 2013).

Endotherms, on the other hand, have evolved a precise internal thermostat that increases or decreases metabolic rate to maintain the same body temperature as environmental temperature changes (Angilletta et al. 2010). Endothermy allows organisms to maintain their body temperatures very close to the thermal optimum for physiological functions, including immune function (Figure 1). Within minutes of detecting a pathogen, endotherms can increase their internal body temperatures to fever-range temperatures (Chen et al. 2006, Evans et al. 2015) while continuing, to at least some extent, with other important ecological tasks such as foraging. Ectotherms, on the other hand, must employ behavioral fever, physically moving to a suitable microclimate (Rakus et al. 2017). While both metabolic and behavioral fever have energetic costs, the latter may have more severe opportunity costs (an ectotherm focused on basking may struggle to forage or mate), may expose the animal to predation, and is highly constrained in thermally homogenous environments (Huey 1974, Huey and Slatkin 1976, Huey et al. 2009). It may take time, energy, and the confluence of ideal ecological circumstances for ectotherms to achieve the thermal optimum of their immune system. As such, behavioral fever is likely to be less effective at mounting a rapid immune response than the metabolic fever of mammals and birds.

Evolutionary arms race

My hypothesis is that endothermy is favored by pathogens because high, stable body temperatures prime the immune system for a rapid, effective response to infection. Because it invokes the role of body temperature in the evolution of endothermy, my hypothesis is closely related to the 'thermoregulation model' proposed by Crompton et al. (1978). One criticism of that previous model is that it is not clear how selection for marginally increased performance at warmer body temperatures could have been favored over the energy savings that ectothermy provides (Bennett and Ruben 1979). In principle, warmer, more stable body temperatures could benefit any number of physiological functions (locomotor performance, digestive efficiency, endurance, etc.), so what makes heightened performance of the immune system so special? The answer is that pathogens themselves evolve (often towards higher virulence), and

quite rapidly, and this could lead to an evolutionary arms race.

Assuming that several assumptions hold (see below), we would only need three starting conditions for host-pathogen co-evolution to result in the initial push towards endothermy. First, a population of ectotherms would need to live under ecological conditions that favor behavioral thermoregulation (e.g. a spatially heterogenous thermal environment). Second, this population would need to have heritable genetic variation in the capacity to thermoregulate precisely and at warmer body temperatures (e.g. some individuals maintain their body temperatures closer to the optimum for their immune system even when they are not infected). Finally, some exogenous force must select for either better thermoregulators or more virulent pathogens. An increase in pathogen virulence, for example, would select for those hosts that happen to thermoregulate at warmer, more stable body temperatures. As the speed and efficacy in which the host population can mount an immune response increases, selection would then favor a further increase in pathogen virulence, leading to a further increase in host thermoregulatory accuracy, and so on (Figure 2, top panel). At some point, the amount of time and energy spent thermoregulating at warm temperatures would become so costly that selection would favor an increase in endogenous heat production (Figure 2, bottom panel). At the physiological level, it is not difficult to imagine how this could occur, as ectotherms could achieve a rudimentary form of endothermy through a simple increase in mitochondrial volume and density (Grigg et al. 2004, Nespolo et al. 2011), perhaps in conjunction with morphological changes that enable heat retention (e.g. vascular shunting or insulation). Moreover, in the context of immune function, this process avoids some of the typical 'hurdles' associated with the thermoregulation model (see a discussion of these in Bennett and Ruben 1979) because even a small increase in body temperature could have resulted in a large increase in immune performance due to the extreme thermal sensitivity of several immune system components (Q_{10}s of lymphocyte proliferation and differentiation range from 100–1000; Hanson 1997). At any point during the evolution of endothermy, high aerobic scope, parental care, or a number of other sources of selection may have favored increasing metabolic heat production as well.

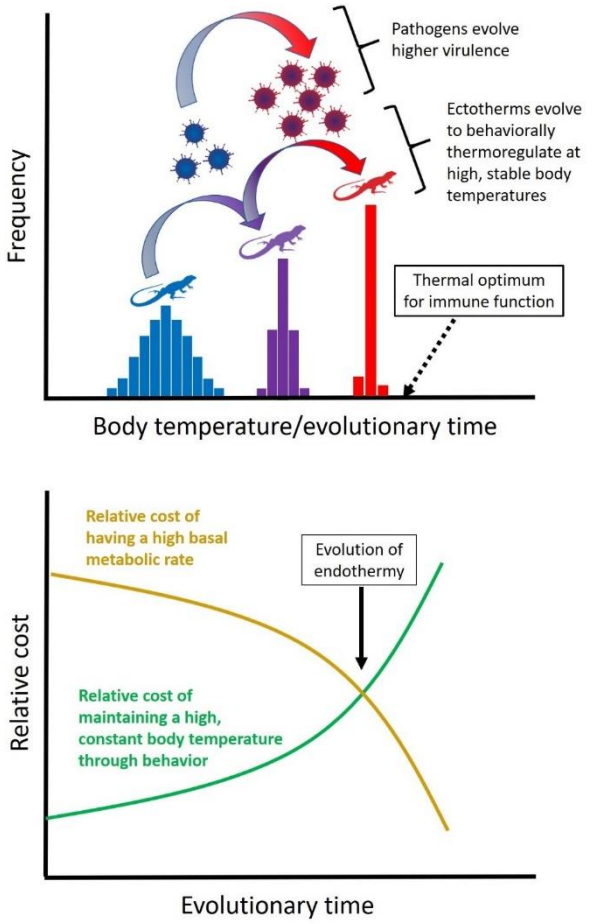

Figure 2. An evolutionary arms race between ancient pathogens and behaviorally thermoregulating ectotherms may have promoted the evolution of endothermy. An initial increase in either pathogen virulence or ectotherm thermoregulatory accuracy with respect to their immune system could have set off red queen dynamics whereby an increase in virulence or prevalence selects for those hosts that thermoregulate at warmer, more stable body temperatures (histograms show diurnal body temperature distributions, as thermoregulation during night time hours is difficult or impossible). Better host thermoregulation would then favor a further increase in pathogen virulence, which would in turn select for even better thermoregulators (top panel). Eventually, the cost of maintaining high, stable body temperatures through behavior would be greater than the cost of maintaining high metabolic rates, and metabolic thermogenesis would be favored by selection (bottom panel).

Testing the immune function model

I am not the first to recognize the possible importance of disease dynamics in the evolution of endothermy. Sandmeier and Tracy (2014) pointed out that the adaptive immune system likely benefits from an endotherm's capacity to rapidly increase body temperature in response to infection and may be part of the explanation for why it evolved. I build on this observation, suggesting that both the innate and adaptive components of the immune system benefit greatly from thermoregulation at high, stable body temperatures, and that simple red queen-like

dynamics could have triggered the initial progression towards endothermy in the stem groups of mammals and birds.

This immune-function model makes several testable predictions. First, the thermal optimum for immune performance should be higher than mean body temperature in virtually all vertebrates. Although some studies have explored the thermal sensitivity of immune system components (e.g. Butler et al. 2013), more are needed to establish which components of vertebrate immune systems are thermally sensitive and whether these features can be overcome by local adaptation (e.g. whether the thermal optimum for immune function can evolve to match mean body temperature). Nevertheless, the ubiquity of fever among animals strongly suggests that thermal optima for immune function vary less among species than do the optima for other physiological functions, and that thermal optima for immune function are typically higher than average maintenance body temperatures.

Second, the model makes predictions about host-pathogen dynamics. Endothermy and ectothermy represent ends of a continuum where substantial variation in the mean and variance of body temperature exists, even within endotherms (Florez-Duquet et al. 2001, Boily 2002, Geiser et al. 2002, Grigg et al. 2004, Kemp 2006, Lovegrove 2011). The model predicts that, all else remaining equal, the most virulent pathogens should be associated with the species that maintain the highest, most stable body temperature distributions, and an increase in pathogen prevalence or virulence (or the conditions favoring high pathogen prevalence or virulence like sociality and high population densities) should favor better thermoregulators. The reverse should also be true; a decrease in pathogen virulence or prevalence should select for a decrease in metabolic thermogenesis or a decrease in active behavioral thermoregulation. In principle, these predictions can be tested by comparing pathogen prevalence and virulence among ecologically similar species (or life stages within species) that vary in their use of endothermy. For example, the model predicts that mammal populations in torpor should experience higher rates of infection than ecologically similar populations that are metabolically active. In line with this prediction, bat populations are much more likely to experience high incidence of white-nose syndrome when they are in torpor relative to when they are metabolically active, and infection rates are better predicted by host physiology than by host density and contact rates (Blehert et al. 2009, Langwig et al. 2015). Moreover, infected bats are much more likely to emerge from torpor and increase their metabolic rates when infected (Reeder et al. 2012). Laboratory evolution experiments whereby ectotherms (such as lines of *Drosophila melanogaster*) are exposed to pathogens of varying degrees of virulence could be used to test whether heightened maintenance body temperatures and better thermal homeostasis are favored over evolutionary time.

Third, the model assumes that there is a substantial fitness cost to ectotherms of both behavioral fever and thermoregulation at high, stable body temperatures, and that this is more severe than the cost of endothermy in cases of high pathogen virulence or prevalence. This cost is likely mediated by 1) a time lag between when pathogens are identified by an ectotherm's immune system and when the ectotherm can achieve optimal body temperatures for immune function via behavior, 2) the lack of precision by which ectotherms can maintain a particular body temperature for a substantial length of time, 3) lost opportunities, and 4) exposure to predators. Many more studies of the fitness effects of behavioral thermo-regulation and behavioral fever in wild ectotherm populations experiencing pathogenic outbreaks are needed to verify these assumptions. Comparisons of thermoregulatory behavior between populations that are healthy versus ecologically similar populations that are experiencing disease outbreaks would be particularly valuable (e.g. Todd et al. 2016). Additionally, experimental manipulations of parasite and pathogen loads in the field could be used to confirm the effects of pathogens on ectotherm thermoregulatory behavior in nature. All these studies could be combined with mathematical models or computer simulations to test the macro-evolutionary hypothesis that host-parasite co-evolution could lead to a transition from ectothermy to obligate endothermy.

The above outstanding questions aside, evidence from comparative physiology and phylogenetics is broadly consistent with the potential importance of pathogens in the evolution and maintenance of obligate endothermy in mammals and birds. Fever is highly conserved over the evolutionary history of animals, suggesting that at a fundamental level the immune system benefits from high, stable body temperatures. Immunological studies show that most components of vertebrate immune systems are highly thermally sensitive and much more effective at high temperatures (Chen et al. 2006, Evans et al. 2015). Conversely, they become less effective at cooler temperatures. Most importantly, the vast majority of individuals across the vast majority of species encounter pathogens during their lifetime, and when these encounters result in infections they can be debilitating and fatal. Thus, pathogens represent an ever-present, strong source of selection that may have been required to justify the extreme energetic expense of endothermy.

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Referees

Michel E.B. Ohmer – m.e.ohmer@gmail.com
University of Pittsburgh

Alex R. Gunderson – agunderson@tulane.edu
Tulane University

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