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Heterothermy and antifungal responses in bats

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Hibernation, a period where bats have suppressed immunity and low body temperatures, provides the psychrophilic fungus *Pseudogymnoascus destructans* the opportunity to colonise bat skin, leading to severe disease in susceptible species. Innate immunity, which requires less energy and may remain more active during torpor, can control infections with local inflammation in some bat species that are resistant to infection. If infection is not controlled before emergence from hibernation, ineffective adaptive immune mechanisms are activated, including incomplete Th1, ineffective Th2, and variable Th17 responses. The Th17 and neutrophil responses, normally beneficial antifungal mechanisms, appear to be sources of immunopathology for susceptible bat species, because they are hyperactivated after return to homeothermy. Non-susceptible species show both well-balanced and suppressed immune responses both during and after hibernation.

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Introduction

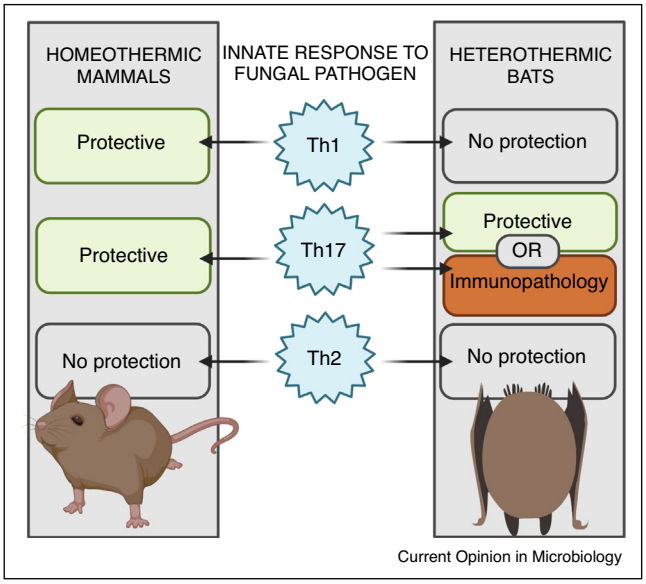
Mammalian immunity displays a specialised response to fungi over bacteria and viruses [1]. The antifungal response strikes a careful balance between allowing colonisation and limiting growth in a way that minimises both harm to the host and energy usage [2]. The host's sophisticated innate and adaptive immune systems, combined with high body temperatures, constitute two important barriers for fungi, preventing life-threatening diseases [3]. However, when individuals are immuno-compromised, fungal infections are not uncommon. The pathology associated with fungal diseases can either be predominantly driven by the fungal pathogen itself or by an overreaction of the host immune system [4]. Heterothermic mammals such as bats present unique characteristics regarding the interplay between thermoregulatory behaviour and the operation of their immune system. Many insectivorous bat species utilize prolonged hibernation (e.g. several weeks or months [5,6]), during which their immune system is mostly at a standstill [7], except during periodic arousals, lasting some hours, that interrupt their bouts of torpor. During torpor, the body temperature of the bat falls drastically to match the ambient temperature of their hibernaculum (e.g. 5–10°C [8]). These hibernating bats are prone to infection by the psychrophilic fungus, *Pseudogymnoascus destructans*, which causes white-nose disease (WND; the disease associated with white-nose syndrome, WNS [9]). The fungus grows on and into the exposed skin (i.e. wing) of hibernating bats but is cleared during their active season [10,11].

The host responses, which occur during *P. destructans* infection, provide an intriguing scenario for investigation on how thermoregulation modulates antifungal immunity in mammals. To add further interest, *P. destructans* infects several bat species. Some species are severely affected with common lethal outcomes (e.g. several Nearctic species, including *Myotis lucifugus*) while others are largely unaffected by the infection, such as species in the Palearctic (e.g. *Myotis myotis*), which likely co-evolved with the fungus [12–14]. Here, we review bat host responses to the fungal pathogen, and relate these to responses in normothermic mammals.

Innate immune system responses to mycosis

Upon colonization of the skin and penetration of the epithelial barrier, innate immune responses can be triggered [15]. If the innate response is not sufficient to restore a balanced host–microbe community, then the innate inflammatory response is intimately connected to the activation and amplification of adaptive immune responses [16,17]. Constitutively expressed pattern-recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs), allowing the innate immune system to respond quickly to invading pathogens. For

Figure 1



Outcomes of immune responses in homeothermic and heterothermic mammals. A Th-17 response can either be protective, or lead to immunopathology, depending on metabolic activity of the host. Created with BioRender.com.

fungal infections, these PAMPs are cell-wall components, recognized by PRRs such as Dectin and other members of the C-type lectin receptor (CLR) family and toll-like receptors (TLR) [18]. These receptors are expressed in epithelial tissues by keratinocytes, innate immune cells, and adaptive immune cells (Figures 1 and 2). The activation of these receptors, together with the sensing of damage-associated molecular patterns, initiates an inflammatory response that both limits the growth of the fungal invader and triggers a complex cascade of immune responses at both the local and systemic levels.

The response to fungal infection begins at the local site of infection, continues at a regional lymph node, and ultimately generates systemic responses. In a WND-susceptible species such as *M. lucifugus*, localized changes in gene expression indicate a robust innate inflammatory response to infection, but only once bats have aroused from torpor [19]. These local changes in gene expression include increased expression of inflammatory cytokines (such as *IL1B* and *IL6*), chemokines (like *CCL2*), and enzymes (like *PTSG2*), and also several CLRs and TLRs that would increase the ability to detect PAMPs. Corresponding effects are seen on both the regional [20] and systemic level [21]; aroused *M. lucifugus* with severe infection appear to have increased the expression of numerous cytokines, including interleukins and chemokines. However, a similar pattern of local gene expression changes is not triggered in *M. myotis* [22•], a Palearctic bat species that does not exhibit wide-spread mortality due to *P. destructans* infection [23]. Together, these studies of gene expression suggest the anti-fungal immune response triggered during *P. destructans* infection in severely affected species is similar to other mammals [24], but the effector mechanisms may be delayed by hibernation. However, more work is needed to understand innate mechanisms for anti-fungal immune responses and how they are affected by heterothermy, seeing as they may play a big part in evolution towards tolerance or resistance towards the pathogen [25,26•].

Adaptive immune system responses to mycosis

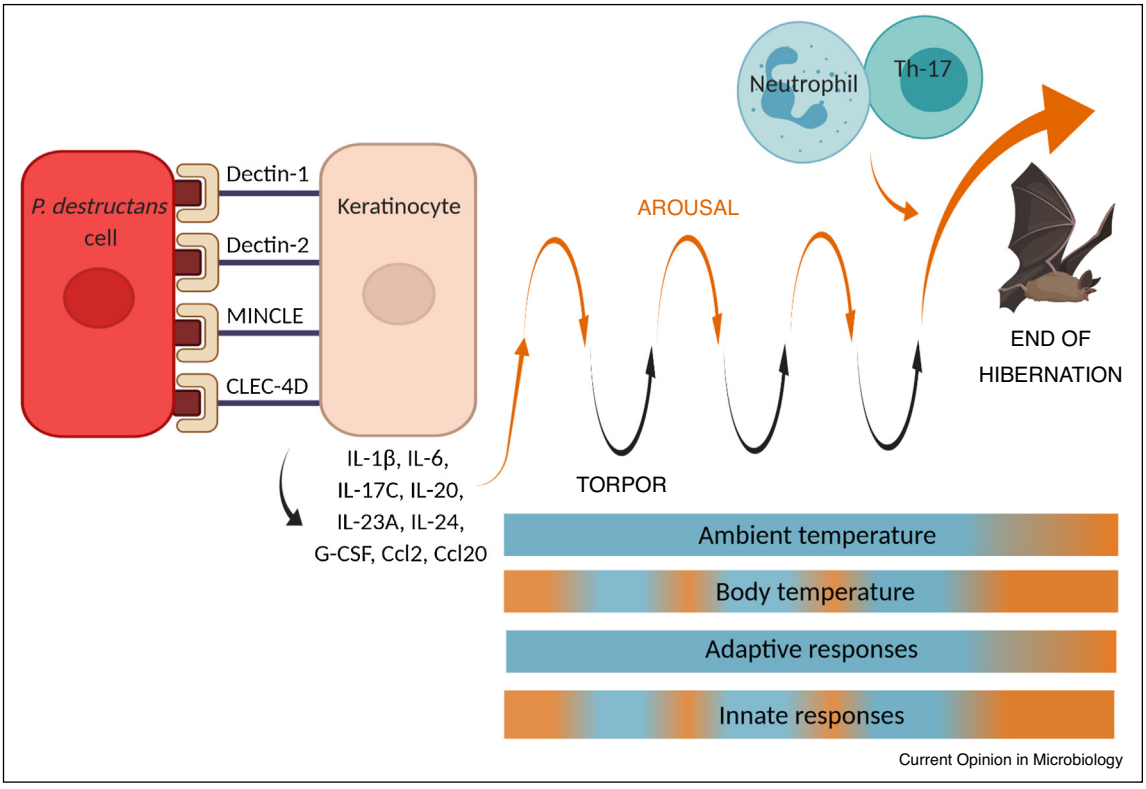
In normothermic mammals, peptide antigens from extracellular pathogens, such as *P. destructans*, are presented by MHC class-II molecules [27]. The response is then mediated by T-helper cells (Th-cells), which influence the specific adaptive immunity pathway taken, depending on the antigen of the invading pathogen and the cytokine environment presented by the innate immunity system [28]. Not all pathways can counter a fungal infection (Figure 1). The cellular Th1 pathway enhances the ability of macrophages and cytotoxic T cells against intracellular pathogens, whereas the humoral Th2 pathway advances an antibody response, stimulating mast cells, histamines, and eosinophils in response to extracellular pathogens [28]. The expression of IL-17 by innate pathways and the adaptive cellular Th17 pathway adds to the cascade of inflammatory responses leading to the activation of neutrophils [29]; the combined effector actions of Th17 cells and neutrophils lead to an effective response to fungal infections [1], at least in normothermic mammals. However, many of these adaptive pathways are energetically costly [30] and suppressed during torpor to conserve energy [7]. These response pathways have been investigated in association with *P. destructans* infection.

The Th1 response

The initial forays into investigating Th1-responses used proxies to deduce the involvement of the pathway during infection. For instance, the lower antioxidative ability measured in the blood of infected *M. lucifugus* [31] were associated with the function of the Th1 cytokine *IFN-γ*, which can trigger the release of oxidative free radicals to damage internal pathogens [32]. This is often reflected as lack of antioxidant ability [31], a response recently echoed in *M. myotis* [26•]. The involvement of this pathway was further enforced by the higher bactericidal ability seen in infected *M. lucifugus* blood [33] suggesting a Th1 response, due to the associated increase in leukocyte count [31].

Histopathology of infected wing tissue [34] and studies on transcriptional and translational activity in the wing tissue transcripts of *M. lucifugus* [19,21] showed that the Th1 response was incomplete. Despite the required

Figure 2



IL-17 response pathway in *M. lucifugus* leading to immunopathology by the end of the hibernation period. Created with BioRender.com.

chemokines being present, leukocytes are not recruited to the site of infection until after bats emerge from hibernation and shift to homeothermy, due to the severe reduction in their concentration during hibernation [19,34,35]. Furthermore, there is no evidence of an increase in translation of proteins that mitigate oxidative stress in infected *M. lucifugus* [36•]. The absence of a complete Th1 response [19] has been suggested to be due to the reduced energy availability that is a characteristic of hibernation [30] and also the absence of circulating leukocytes [37]. Heterothermy may modulate activating signals to effector phagocytes and the resulting inflammatory responses leading to adaptive immunity. For instance, a vaccine using highly immunogenic fungal antigens was found to provide some protection against *P. destructans* infection, but this protection was not strongly associated with either a Th1 (*IFN-γ*) or a Th17 (IL-17) response [38•]. Notably, this immunization was performed on bats housed at 21–24°C, where they would be expected to exhibit some heterothermy but would have been unable to fully enter torpor for energy conservation. Further study is needed to determine if this vaccine strategy would be more or less effective during the hibernation period or in fully homeothermic bats (i.e. housed at their thermoneutral zone).

The Th2 response

In general, an antibody-mediated response promoted by Th2 cells is not effective against fungal infections [2], and the promotion of this pathway dampens protective Th1 or Th17 responses. While *M. lucifugus* appears able to mount an antibody response to *P. destructans* [39], at least once they have emerged from hibernation, this response does not protect the bat host from subsequent infection [20]. In fact, it may actually prime the immune system for greater pathology in subsequent hibernation seasons, which may partially explain the higher observed mortality at hibernation sites in the second winter after the detection of the pathogen [40]. Thus, antibody-mediated immunity cannot explain survival of Palearctic bats infected with *P. destructans* and humoral responses are not a ubiquitous response among *Myotis* bats infected by this fungal pathogen (Figure 1).

Th17 response: the good, the bad and the ugly

The Th17 response can be an effective antifungal mechanism. Deficiencies in the Th17-pathway predispose humans and mice to fungal infections [41], and Dectin-1, a CLR involved in immune regulation, has been associated with this pathway [42]. However, a failure to regulate the Th17 response can lead to chronic

inflammation and failure to resolve the infection [43,44]. In mammals, the mechanisms linking inflammation to chronic infection have been associated with IL-17A, which effectively promotes neutrophil recruitment to a point where the inflammatory potential can no longer be impeded [45], all while directly promoting fungal virulence [46].

Infection by *P. destructans* initiates the Th17-pathway in *M. lucifugus* [20]. The role of cytokines associated with the pathway during the hibernation period have further been confirmed in a number of studies using transcriptomics [21,22•]. For instance, the upregulation of IL-23 is seen both at the site of infection [21] and in another tissue (lung) without infection [47]. IL-23 stimulates the maturation of Th17 cells, but has also been linked to chronic inflammation, and to intensifying the negative impact of a fungal *Aspergillus* infection [48]. Further Th17-associated cytokines IL-6 and IL-17C [49] were found to be upregulated in infected *M. lucifugus* in three separate transcriptomic studies [19,21,22•].

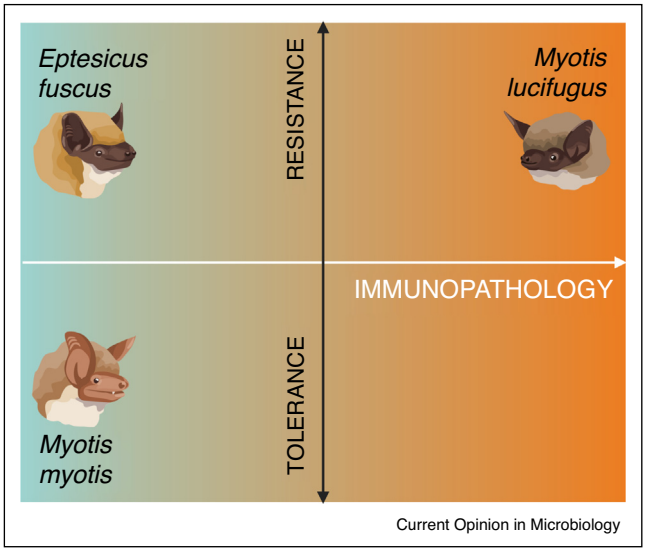
While the Th17 response can be beneficial, excessive expression of associated cytokines has been implicated in chronic inflammation [50]. Consistent with pathologic inflammatory responses, WND-susceptible species show very high levels of inflammatory cytokine transcripts, including IL-6 [21,22•], and a potential febrile response [51]. Torpor appears to limit the inflammatory effector pathways normally activated by Th17 pathways [20], setting up a pathological level of inflammation once bats emerge from hibernation. Increased levels of Th17 cells and the IL-6 cytokine have also been strongly associated with immune reconstitution inflammatory syndrome (IRIS) [52]. This syndrome is characterised by a rigorous response after the restoration of immune function after a period of suppressed immunity (e.g. during hibernation), which can exacerbate symptoms [7,53]. Three weeks after arousal and a return to elevated body temperature, the wing pathology of some *M. lucifugus* bats begins to increase [34,54•] and the metabolic rate remains elevated [55]. The Th17 pathway may therefore be amplified from an effective antifungal mechanism to a harmful immunopathological response during the arousals occurring during the hibernation period (Figure 2).

Resistance, tolerance and coevolution

Interestingly, local cytokine-mediated responses seem to be dampened in the apparently tolerant Palearctic species, *M. myotis*, but not in the resistant Nearctic species, *Eptesicus fuscus* (Figure 3). A comparison of the transcriptomes of infected and non-infected tissues of *M. lucifugus* and *M. myotis* revealed that the former had 1526 significantly differentially expressed transcripts, whereas the latter had a single downregulated transcript [22•]. This suggests euthermic, recently aroused *M. myotis* does not actively respond to the invasion of its tissues by *P. destructans* [26•]. This transcriptomic effect was echoed in a plasma proteome comparison between the same two species, where 11 out of the 157 proteins show significantly different abundance in infected *M. lucifugus*, compared to no difference in abundance in *M. myotis* [36•]. However, the apparently resistant *E. fuscus* show robust changes in gene expression in response to *P. destructans* infection, including IL6, IL1B, IL20, IL-23A, IL-24, G-CSF, CCL2, CCL20 and PTGS2, which are very similar to those seen in *M. lucifugus* [19,56•], yet with no signs of immunopathology [57]. Compared to the relatively unresponsive *M. myotis*, the susceptibility seen in *M. lucifugus* is suggested to be from an overstimulation of the immune system at a local level, which is ultimately ineffective in fighting off the infection. The difference between the effective response shown by *E. fuscus* and the ineffective response by *M. lucifugus* could be due to critical pathways that are differentially regulated, the timing of the responses, and/or the magnitude of the responses. Recent studies on *E. fuscus* also suggest the microbiome and cutaneous fatty acids could contribute to their resistance [58,59], in addition to their active immune response. Further investigation is needed for a better understanding of the net effect of each component in the observed resistance.

The differences in immune responses between the Nearctic and Palearctic *Myotis* species may be down to two factors: (1) whether the innate immune system can keep the infection in check during hibernation and (2) the strength and type of adaptive immune system pathways

Figure 3



An approximate overview in light of current knowledge on the effective response and the level of immunopathology caused by *P. destructans* infection in Nearctic *E. fuscus* and *M. lucifugus,* and in Palearctic *M. myotis*. Created with BioRender.com.

activated after emergence. The most cromulent explanation is whether the host attempts to resist or tolerate the pathogen. If they are unsuccessful in resisting pathogen colonization using innate mechanisms during hibernation, the resistance mechanisms meant to protect the host can result in harm instead [60], once the bat emerges from hibernation and hyper-inflammation is triggered. Tolerance can be derived from the host counteracting this immunopathology; in effect by not responding to the invading pathogen [61]. The severe impact of the disease on populations of *M. lucifugus* may be due to damage caused by an attempted immune response, while the root of tolerance in other species may be due to a combination of effective innate control of the pathogen and suppression of a damaging response after emergence.

The extensive coevolution between the bat host and the fungus in the Palearctic may have led to a commensal relationship [25,62]. So far, only *M. myotis* has been studied in detail with regards to *P. destructans* infection in the Palearctic. However, a number of other Palearctic species also show infection [10,12,63], that in some often results in either no damage or clinically inapparent damage to the host, fitting the description of commensalism [64]. Although many factors can contribute to this, such as hibernation site selection [65,66], hibernation behaviour [67], and resistance via the microbiome [68], the ability of the innate and adaptive immune system to recognize commensal and pathogenic fungi deserves more attention as a mechanism of tolerance [69].

Conclusions

Torpor allows bats to survive the winter, but allows colonisation by the psychrophilic fungal pathogen, *P. destructans*. In highly susceptible bat species, the reconstitution of the immune system upon emergence appears to result in immunopathology via a hyperinflammatory Th17 response. Two different strategies may allow survival of WND: a resistance strategy allowing an effective (innate) immune response that avoids excessive inflammation; or a tolerance strategy, where survival appears to be aided by a lack of a costly immune response. Understanding how torpor modulates responses to *P. destructans* infection is key to understanding disease severity. Further study in different species, in both torpid and aroused states, should be carried out to search for similarity in the responses of susceptible and tolerant bat species, as well as to understand the extent of the continuum leading to commensalism between the bat host and fungal pathogen.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Flora Whiting-Fawcett: Conceptualization, Writing - original draft. **Kenneth A Field:** Supervision, Writing - review & editing. **Sébastien J Puechmaille:** Writing - review & editing. **Anna S Blomberg:** Visualization, Writing - review & editing. **Thomas M Lilley:** Conceptualization, Supervision, Writing - original draft.

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