Comparative Immunology Reports 8 (2025) 200206

Contents lists available at ScienceDirect

Comparative Immunology Reports

journal homepage: www.sciencedirect.com/journal/comparative-immunology-reports

Behavioral fever enhances T-cell responses in fish providing insights into the evolutionary integration of fever and adaptive immunity

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ARTICLE INFO

Keywords:
Behavioral fever
T cell immunity, Lower vertebrates

ABSTRACT

Recently, Yang *et al.* published a study in *Proceedings of the National Academy of Sciences* showing how in tilapia, behavioral fever helps optimizing antimicrobial immunity by alleviating T-cell apoptosis. The current manuscript is a short commentary on this landmark study.

Commentary

Life is inherently tied to temperature. The origin of life depended on suitable environmental conditions, and temperature fluctuations have continuously influenced evolutionary history. During evolution, different organisms have evolved different strategies to harness temperature as a means of enhancing survival and reproductive success. Among these strategies fever, defined as a status during which the body temperature exceeds the normal physiological range, stands out as a means of anti-infection defense mechanism.

Fever is an adaptive response molded by natural selection and provides a survival advantage during pathogenic infections by raising the core body temperature. Both homeothermic (warm-blooded) and poikilothermic (cold-blooded) animals employ fever as a defensive strategy, although their mechanisms differ. Warm-blooded animals regulate temperature via neuroendocrine and metabolic pathways, while cold-blooded animals depend on behavioral adjustments to generate fever [1]. For example, studies on behavioral fever in common carp infected with CyHV-3 as a homologous virus-host model demonstrated the universal importance of particular cytokines to mediate fever. By demonstrating the ability of this virus to alter the behavioral fever response of the host through the expression of a single gene, tumor necrosis factor-α was confirmed central to drive fever [2]. Evidence suggests that fever enhances both innate and adaptive immunity in warm-blooded animals, while behavioral fever in cold-blooded animals predominantly bolsters innate immunity [3]. From an evolutionary perspective, innate immunity, and behavorial fever in invertebrates (e.g. [4]), may predate adaptive immunity. The complex integration of fever with adaptive immunity could be a unique adaptation of warm-blooded animals, or not. Potential, as-yet-undiscovered benefits of fever continue to be an open question.

Recently, Professor Jialong Yang and colleagues from East China Normal University published an article in *Proceedings of the National Academy of Sciences* titled "Cold-blooded vertebrate utilizes behavioral fever to alleviate T-cell apoptosis and optimize antimicrobial immunity" [5]. Focusing on Nile tilapia, the authors presented compelling data highlighting the effect of behavioral fever on T-cell immunity in fish and regulatory mechanisms involved, providing valuable insights for developing disease management strategies in aquaculture. This new study unquestionably marks a landmark contribution to the field of fish immunology.

Fish, as cold-blooded vertebrates whose body temperature is easily modulated by environmental conditions, provide an ideal model for studying the integration of fever and immunity. Comparable with the experimental set-up for the study of behavioral fever in common carp infected with CyHV-3 [2], Yang *et al.* set the temperatures of three interconnected aquariums to either a constant 28–28–28 °C (normal group) or 28–31–34 °C (behavioral fever group), and tracked the movement of infected fish within these tanks, here *Edwardsiella piscicida*-infected Nile tilapia. Again, comparable to the infected carp, infected tilapia preferentially sought the warmest (34 °C) zone, and this behavior-driven fever accelerated pathogen clearance and improved survival rates. Conversely, inhibiting the fever response during infection led to increased mortality. Very different from the study in carp, however, the authors investigated the role of T cells and revealed that the survival advantage conferred by behavioral fever was linked to T-cell immunity. Unlike in mammals, fever did not affect T-cell activation or proliferation in tilapia; however, it did enhance cytokine production (including but not exclusively expression of TNF-α) and cytotoxic activity. The authors conclude this suggests that the optimization of T-cell

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https://doi.org/10.1016/j.cirep.2025.200206
Received 23 December 2024; Received in revised form 31 January 2025; Accepted 1 February 2025
Available online 6 February 2025

immunity through fever is an evolutionarily conserved survival strategy predating the emergence of warm-blooded vertebrates. Most certainly, this novel finding provides the first description that behavioral fever regulates T-cell immunity in cold-blooded vertebrates, offering valuable new insights into the evolutionary relationship between fever and adaptive immunity.

Another significant finding of this study is the identification of a previously unknown benefit of fever: its role in alleviating T-cell apoptosis. Following pathogen infection, T cells undergo rapid proliferation and differentiate into effector T cells to exert cytotoxic functions [6]. Yang *et al.* demonstrate that fever mitigates T-cell apoptosis during the early stages of the primary immune response, thereby optimizing anti-infection immunity by preserving the T-cell pool. This effect appears closely linked to enhanced HSP70 and ERK1/2 activity, which prevents the activation of Caspase-8 and Caspase-3, thereby inhibiting apoptosis in T cells. Notably, during the later stages of the immune response, fever no longer suppresses T-cell apoptosis, allowing T cells to transition into the contraction phase, which is crucial for maintaining immune homeostasis. Thus, the dynamic fever-induced modulation of T-cell survival versus apoptosis as described in this publication, provides a critical time window for fish to either mount an effective immune response against pathogens or maintain immune balance. To the best of our knowledge, this is the first study to demonstrate that fever promotes T-cell survival, supporting investigations of new avenues for developing potential strategies for disease therapy such as induced artificial hyperthermia.

Infection is accompanied by a range of sickness behaviors, including anorexia, fever, lethargy and pain. Once thought to serve little function, these behaviors are now recognized as highly coordinated responses that help combat infection and enhance host survival [7]. Exploring the precise relationship between sickness behaviors and immune responses in non-mammalian models can shed light on the adaptive significance of these responses. In fish, T cells appear to be especially responsive to sickness behaviors; beyond behaviorally induced fever, Yang *et al.* also demonstrated that anorexia can trigger T-cell autophagy, thereby enhancing antibacterial immunity in tilapia [8]. These findings suggest that these T cells have been actively modulated by environmental and behavioral cues, underscoring the flexibility and complexity of T-cell immunity in fish.

In conclusion, this specific article by Yang et al. identifies mitigation of T-cell apoptosis as a previously-unrecognized benefit of fever enhancing anti-infective immunity in cold-blooded vertebrates. This finding offers a new perspective for a further understanding of the relation between fever and immunity through an evolutionary lens. Of course, several intriguing questions remain open for further investigation. For example, how does fever differentially regulate various T-cell subpopulations in fish? How intertwined exactly are T-cell regulation and the production of endogenous pyrogenic cytokines such as TNF-α? Could fever similarly mitigate T-cell apoptosis in mammals? And last but not least, from an applied perspective, how in aquaculture might we dynamically simulate and control the fever response to advance the development of preventive or therapeutic strategies for disease management?

CRediT authorship contribution statement

Geert F. Wiegertjes: Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] M.F. Flajnik, A cold-blooded view of adaptive immunity, Nat. Rev. Immunol. 18 (7) (2018) 438–453.
[2] K. Rakus, M. Ronsmans, M. Forlenza, M. Boutier, M.C. Piazzon, J. Jazowiecka-Rakus, D. Gatherer, A. thanasiadis, F. Farnir, A.J. Davison, P. Boudinot, T. Michiels, G.F. Wiegertjes, A. Vanderplasschen, Conserved fever pathways across vertebrates: a herpesvirus expressed decoy TNF-α receptor delays behavioral fever in fish, Cell Host. Microbe 21 (2017) 244–253.
[3] S.S. Evans, E.A. Repasky, D.T. Fisher, Fever and the thermal regulation of immunity: the immune system feels the heat, Nat. Rev. Immunol. 15 (6) (2015) 335–349.
[4] M.E. Casterlin, W.W. Reynolds, Fever induced in marine arthropods by prostaglandin E1, Life Sci 25 (1979) 1601–1603.
[5] H. Gao, X. Wei, K. Li, Y. Cao, W. Rao, J. Zhang, D. Wang, J. Yang, Cold-blooded vertebrate utilizes behavioral fever to alleviate T cell apoptosis and optimize antimicrobial immunity, Proc. Natl. Acad. Sci. USA 121 (52) (2024 Dec 24) e2408969121.
[6] L. Sun, Y. Su, A. Jiao, X. Wang, B. Zhang, T cells in health and disease, Signal. Transduct. Target. Ther. 8 (1) (2023) 235.
[7] P.C. Lopes, S.S. French, D.C. Woodhams, S.A. Binning, Sickness behaviors across vertebrate taxa: proximate and ultimate mechanisms, J. Exp. Biol. 224 (9) (2021).
[8] K. Li, X. Wei, K. Li, Q. Zhang, J. Zhang, D. Wang, J. Yang, Dietary restriction to optimize T cell immunity is an ancient survival strategy conserved in vertebrate evolution, Cell Mol. Life Sci. 80 (8) (2023) 219.