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# **A Novel Mechanism of Immune Memory Unveiled at the Invertebrate–Parasite Interface**

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**Pinaud et al. recently provided the first global investigation of the molecular processes underlying innate immune memory in an invertebrate species. They showed that the memory response of the snail *Biomphalaria glabrata* to *Schistosoma mansoni* infection is associated with a shift from cellular to humoral mechanisms.**

Specificity and memory of immune systems are important traits with strong implications for the evolution of host–parasite interactions, the dynamics of infectious diseases, and potential strategies for the prevention and control of infections of economically valuable species. The classical view that immune memory is restricted to the adaptive immune systems of vertebrates is challenged by an increasing number of studies reporting immune memory traits from both vertebrate and invertebrate innate immune systems [1,2]. However, the existence of immune memory processes in invertebrates (also referred to as immune priming) remains controversial because it is still largely unexplained at the cellular and molecular levels (but see [3]).

In their recent work on the immune response of the snail *Biomphalaria glabrata* to infection by the human blood fluke *Schistosoma mansoni*, Pinaud et al. [4] demonstrated that the observed heightened response to a secondary infection was associated with a shift from cellular to humoral processes. While a classical cellular encapsulation occurs during the first infection, secondarily infecting parasites are killed without encapsulation. Using experimental transfer of plasma, they inferred that the soluble fraction of the snail blood caused the parasite death. This result was unexpected for two reasons. First, previous studies on innate immune memory mostly showed that cellular rather than humoral processes play a role, especially when the immune memory involves specificity [5,6]. Moreover, the memory response of the mosquito *Anopheles gambiae* to *Plasmodium* infection is based on a sustained hemocyte differentiation protecting mosquitoes from secondary infections [3]. Second, until now, invertebrate immune memory was believed to rely either on a sustained response, involving the long-lasting upregulation of the same immune effectors after the initial immune challenge (Figure 1A), or a recalled response, leading to a faster and stronger defense (Figure 1B). Both processes implicitly involve the same immune effector systems during the primary and the secondary immune responses. By contrast, the work of Pinaud et al. reveals that the primary and secondary immune responses, developed against the same parasite, involve different immune effector systems resulting in a shift from a cellular to a humoral response (Figure 1C).

A first insight into the molecular mechanisms associated with this immune shift was provided by a comparison of whole-snail transcriptome at various times after a first infection and after a secondary exposure to the parasite. A substantial set of differentially expressed transcripts was over- or under-represented exclusively following the secondary challenge. Among the overexpressed candidates were transcripts coding for various fibrinogen-related proteins (FREPs). FREPs are complex pattern recognition proteins undergoing somatic rearrangement [7]. They are known to interact with the highly polymorphic mucins (SmPoMucs) from *S. mansoni* and to participate in *Biomphalaria* immune responses (for review, see [8]). Experimentally reduced expression of three of the major FREP members via RNA interference resulted in a partial loss of protection, demonstrating that FREPs are involved in the memory response. Other transcripts over-represented during the secondary response included cytotoxic and cytolytic molecules such as lipopolysaccharide-binding protein/bactericidal/permeability-increasing protein (LBP/BPI) and biomphalysin. Analysis of primed plasma proteomes revealed that a number of proteins, consistent with the transcriptomic approach, were specifically present in the plasma after a secondary challenge. Altogether, these results showed that the primary and secondary challenges result in the expression of different sets of genes and in the presence of different plasmatic proteins, further supporting the initial histological observation of a shift in immune responses.

The precise mechanisms determining this immune shift should be further characterized. In particular, it is important to distinguish the immune memory response from (i) the effects that are potentially mediated by the parasites themselves, and from (ii) immune responses resulting from a constant stimulation by parasites. It would further be interesting to see whether the form of memory observed here is primarily based on receptor, signaling, or effector molecules. Intriguingly, FREPs could serve as both receptor and effector, just like vertebrate antibodies. In this context, it is noteworthy that the vertebrate immune response entails a shift from cellular (innate, granulocyte-based responses) to humoral (antibody-based) and back to cellular (memory B and T cells) responses. While such details of the immune responses of the snail still need to be uncovered, the obvious complexity of the induced responses led the authors to support views that question the artificial dichotomy between innate and adaptive immunity [1]. Recently, elucidation of mechanisms determining memory processes from the vertebrate innate immune system led vertebrate immunologists to propose the concept of ‘trained immunity’ [2]. It refers to an immune response that (i) is induced after a primary infection or vaccination; (ii) increases resistance to reinfection, in a more or less specific manner; and (iii) is independent

of the vertebrate-acquired immune system. These criteria are met by the memory type responses of invertebrates and plants, emphasizing that this concept has rather large evolutionary implications. Furthermore, while the concept of trained immunity has been proposed for the development of innate immune memory within the individual, it may also include transgenerational effects in which the immunological experience of parents could be used to reprogram the immune system of the offspring in both animals and plants [9].

In conclusion, a major achievement of this work is to provide molecular evidence for a so-far unreported process of memory type immune response in invertebrates, further highlighting the diversity of invertebrate immune processes. Indeed, it seems unlikely that FREPs, here shown to be involved in the snail immune memory response, also determine immune memory responses in phyla such as insects or sea urchins, where immune recognition relies on other pattern recognition proteins. More generally, while major immune signaling pathways (i.e., Imd, Toll, JAK/STAT) are well conserved across invertebrate phyla, non-self-recognition molecules such as FREPs or Down syndrome cell adhesion molecule (Dscam) are highly diversified [10]. Invertebrate immune systems may be viewed as a mosaic of evolutionary conserved processes and independent immune innovations. Deciphering the cellular and molecular basis of invertebrate immune responses from an increasing variety of phylogenetically distant models will shed light on the nature and origin of these evolutionary innovations, including immune memory type novelties.

## References

1. Kurtz, J. (2004) Memory in the innate and the adaptive immune systems. *Microbes Infect.* 6, 1410–1417.
2. Netea, M.G. et al. (2011) Trained immunity: a memory for innate host defense. *Cell Host Microbe* 9, 355–361.
3. Rodrigues, J. et al. (2010) Hemocyte differentiation mediates innate immune memory in *Anopheles gambiae* mosquitoes. *Science* 329, 1353–1355.
4. Pinaud, S. et al. (2016) A shift from cellular to humoral responses contributes to innate immune memory in the vector snail *Biomphalaria glabrata*. *PLoS Pathog.* 12, e1005361.
5. Pham, L.N. et al. (2007) A specific primed immune response in *Drosophila* is dependent on phagocytes. *PLoS Pathog.* 3, e26.

6. Roth, O. and Kurtz, J. (2009) Phagocytosis mediates specificity in the immune defence of an invertebrate, the woodlouse *Porcellio scaber* (Crustacea: Isopoda). *Dev. Comp. Immunol.* 33, 1151–1155.
7. Zhang, S.M. et al. (2004) Diversification of Ig superfamily genes in an invertebrate. *Science* 305, 251–254.
8. Coustau, C. et al. (2015) Advances in gastropod immunity from the study of the interaction between the snail *Biomphalaria glabrata* and its parasites: a review of research progress over the last decade. *Fish Shellfish Immunol.* 46, 5–16.
9. Moret, Y. and Schmid-Hempel, P. (2001) Entomology – immune defence in bumblebee offspring. *Nature* 414, 506.
10. Cerenius, L. and Söderhäll, K. (2013) Variable immune molecules in invertebrates. *J. Exp. Biol.* 216, 4313–4319.

**Figure 1. Basic Models of Immune Memory Responses in Invertebrates.** In response to a primary infection (black arrows), a cellular response (blue line) is mounted and may either (A) be sustained in a long-lasting upregulation of immune effectors protecting from a secondary infection (blue arrow); (B) be recalled in a faster and stronger manner after a secondary infection (blue arrow); or (C) result in a shift to a humoral response (broken red line) upon secondary infection (blue arrow).

