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REVIEW

SPECIAL ISSUE

DEVELOPMENTAL PLASTICITY: FROM MECHANISMS TO EVOLUTIONARY PROCESSES

The plasticity of immune memory in invertebrates

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ABSTRACT

Whether specific immune protection after initial pathogen exposure (immune memory) occurs in invertebrates has long been uncertain. The absence of antibodies, B-cells and T-cells, and the short lifespans of invertebrates led to the hypothesis that immune memory does not occur in these organisms. However, research in the past two decades has supported the existence of immune memory in several invertebrate groups, including Ctenophora, Cnidaria, Nematoda, Mollusca and Arthropoda. Interestingly, some studies have demonstrated immune memory that is specific to the parasite strain. Nonetheless, other work does not provide support for immune memory in invertebrates or offers only partial support. Moreover, the expected biphasic immune response, a characteristic of adaptive immune memory in vertebrates, varies within and between invertebrate species. This variation may be attributed to the influence of biotic or abiotic factors, particularly parasites, on the outcome of immune memory. Despite its critical importance for survival, the role of phenotypic plasticity in immune memory has not been systematically examined in the past two decades. Additionally, the features of immune responses occurring in diverse environments have yet to be fully characterized.

KEY WORDS: Host–parasite relationship, Phenotypic plasticity, Ecoimmunology, Immune response, Trained immunity

Introduction

Phenotypic plasticity is the ability of a specific genotype to generate distinct phenotypes in response to different environmental conditions during an organism's development (Pigliucci, 2005). For example, the immune response constitutes an intricate network of molecules and cells regulated by genes, exhibiting a plastic nature rather than a fixed one, which is influenced by factors such as age, sex, temperature and reproduction (Demas and Nelson, 2012). The plasticity of the immune response can be illustrated through 'reaction norms', which describe graphically how the phenotype – in this case, the immune response – which is controlled by genes, changes across varying environments (Martin et al., 2021). In a host–parasite interaction, parasites act as a selective force on their hosts, while the hosts, in turn, affect parasite evolution (we use the term 'parasite' to refer to the parasitic strategy that encompasses parasites, pathogens and viruses; Gómez-Díaz et al., 2012; Adamo, 2022). This mutual interaction can drive plasticity in both host and parasite traits. For instance, as parasites evolve to better exploit their hosts, hosts develop strategies to resist or tolerate parasitism (Lazzaro and Rolff, 2011; Parker et al., 2011; Lazzaro and Clark, 2012; Louie et al., 2016; Gorbunova et al., 2020; Vrtílek and Bolnick, 2021). Meanwhile, the parasites evolve strategies to more successfully invade their hosts (Altizer et al., 2003; Adamo, 2019; Bobardt et al., 2020; Schmid-Hempel, 2021). Immune memory can be plastic and can vary depending on parasite virulence (see Glossary). Immune memory can be very broad: after an initial immune response, subsequent responses may not discriminate, for example, Gram-positive from Gram-negative bacteria or fungus from bacteria (this is called cross-protection, as exposure to a pathogen of one type provides protection against other pathogens of the same type). However, immune memory can also be very specific. The term 'specific memory' describes the enhanced protection resulting from a previous encounter with a specific pathogen or parasite (Kurtz, 2005). Upon a subsequent immune challenge with the same parasite, this protection results in better survival, an enhanced immune response and improved parasite clearance compared with the initial immune challenge (Little et al., 2005). The experimental design used to assess immune memory includes both homologous (similar) and heterologous (different) immune challenges (see Glossary; Kurtz and Franz, 2003; Little et al., 2005) and, when testing for immune specificity, homologous and heterologous challenges should be carried out with different parasites and/or pathogen species or strains (Contreras-Garduño et al., 2016). In this context, we define 'immune memory' as better protection observed in homologous challenges compared to heterologous challenges, and we refer to the memory as 'specific' when the immune protection manifests at the level of parasite species or strain (see Glossary; Table S1).

In this Review, we examine immune memory in invertebrates within generations (for specific memory across generations, see Tetreau et al., 2019; Vilcinskas, 2021; Rutkowski et al., 2023). We begin by providing some background on the discovery of immune memory in invertebrates. We will then: (1) discuss general methods to test immune memory, which is sometimes confounded with immune enhancement (Kurtz, 2005; Contreras-Garduño et al., 2016); (2) explore potential scenarios that may promote plasticity of immune memory; (3) review the plasticity in the kinetics of immune memory; and (4) suggest future research that is needed to understand the plasticity of immune memory.

The discovery of immune memory in invertebrates

Given that parasites are ubiquitous and infect all organisms (Schmid-Hempel, 2021), immune memory might be found in a wide variety of species, including vertebrates, invertebrates and plants, and might not necessarily be linked to factors such as life span, size and specific immune mechanisms (e.g. immunoglobulins or B-cells; Contreras-Garduño et al., 2016). Organisms exposed to a constant parasitic environment may be more likely to evolve

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Glossary

Encapsulation response
The formation of a protective barrier of melanin or melanized cells around a foreign object, typically a pathogen or a non-self substance.

Graft recognition
Ability of the immune system to distinguish between the body's own tissues (self) and foreign tissues (non-self) introduced through transplantation or grafting procedures.

Heterologous challenge
Involves exposing an organism to a sub-lethal dose of one pathogenic organism or strain, followed by a subsequent repetition of the challenge using a lethal dose of a different pathogenic organism or strain.

Homologous challenge
Involves exposing an organism to a sub-lethal dose of, for instance, a pathogen (utilized to prime the immune response) and subsequently subjecting the organism to a follow-up challenge with a lethal dose of the same pathogenic species or strain.

Priming or immune priming
Involves initial exposure of the immune system to induce an immune response, which may or not result in specific protection during subsequent homologous or heterologous challenges. Importantly, immune priming is often confused with immune specific memory in invertebrates.

Innate immune response
A rapid mechanism of defense against infections, present from birth.

Specific immune memory and adaptive memory
Immune protection and improvement of survival after a subsequent encounter with the same parasite or pathogen species or strain. Functionally, specific immune memory in invertebrates is similar to the adaptive immune memory of vertebrates.

Virulence
A measure of the pathogen's ability to cause harm to its host. For example, a highly virulent pathogen is more capable of causing death, whereas a less virulent one may cause milder symptoms.

immune memory (Lui, 2000). Furthermore, parasites may be able to avoid specific memory by rapidly changing their structures to evade recognition by the host, as seen in the recent pandemic caused by SARS-CoV-2 (Markov et al., 2023). These scenarios highlight the importance of parasites in the occurrence of immune memory. Immune memory in invertebrates has long been a topic of interest among scientists. For a long time, classical immunologists focused predominantly on the molecular and physiological responses of adaptive immunity in vertebrates. The prevailing assumption was that the absence of antibodies and graft recognition (see Glossary) in invertebrates was evidence of a lack of immune memory in these organisms. In a pioneer study, McKay and Jenkin (1969), immune memory was termed 'adaptive memory' in invertebrates. From the late 1960s to the early 1990s, it was thought that this phenomenon occurred in flies, cockroaches and crayfishes (McKay and Jenkin, 1969, 1970a,b; Hartmann and Karp, 1989; Karp, 1990; Faulhaber and Karp, 1992). Then, in 2000, a mathematical model suggested that the evolution of immune memory should be favored by the constant selective pressure exerted by parasites on their hosts, instead of being selected for as a result of a long life span, as was generally accepted (Lui, 2000). This model suggested that immune memory should not only be present in vertebrates but also in invertebrates. However, the occurrence of specific immune memory in invertebrates was largely hidden until 20 years ago, when it was demonstrated in the crustacean *Macrocyclop salbidus*, in response to infection by the cestode worm *Schistocephalus solidus* (Kurtz and Franz, 2003). Subsequently, evidence supporting or refuting the existence of specific memory has accumulated in different invertebrate groups (Fig. 1). Hexapoda has been the most widely studied, followed by Crustacea and Mollusca, whereas studies on Nematoda, Cnidaria and Ctenophora have been scarce (Fig. 1). Further research is needed to investigate whether specific immune memory occurs in a broader range of invertebrates, such as tardigrades, onychophores, placozoos, lophophorates and rotifers.

Interestingly, some studies have failed to support the occurrence of immune memory in invertebrates (Fig. 1), raising the question about which factors may influence its variation. In the mealworm *Tenebrio molitor*, some evidence supports the occurrence of non-specific immune protection: in this species, bacterial cell wall components (lipopolysaccharide) promote resistance against a fungus (Moret and Siva-Jothy, 2003). However, other work in *T. molitor* has demonstrated specific immune memory against fungus and against particular bacterial species (Medina-Gómez et al., 2018a).

Immune memory in invertebrates

Immune memory is thought to have five dimensions: strength, speed, extinction, duration and specificity (Pradue and Du Pasquier, 2018). These dimensions are key to understanding the plasticity of immune memory. However, to the best of our knowledge, there are no studies that test all five dimensions at the same time in invertebrates. In this section, we will discuss the two of these five features that have been most studied: (1) specific immune protection and (2) long-lasting protection (duration).

Specific immune memory

As outlined in Table S1, immune priming (see Glossary) has undergone more extensive testing in invertebrates compared with specific immune memory. A straightforward protocol for assessing immune priming is exemplified in the following scenario. Individuals of the shrimp *Litopenaeus vannamei*, were injected either with inactivated *Vibrio harveyi* (a Gram-negative bacterium) or with saline (Pope et al., 2011), followed by treatment with a lethal *Vibrio harveyi*, 7 days later. Those individuals that received the inactivated bacterium (i.e. the pre-challenge) had higher phagocytic activity than controls (Pope et al., 2011). This suggests that some protection is derived from priming the shrimps with parasites but does not provide evidence for specific immune memory. Specificity has been tested in the red flour beetle *Tribolium castaneum* because this insect survived better when confronted with homologous challenge at the strain level compared with heterologous challenges with different strains or species of bacteria (Roth et al., 2009). There have only been a handful of studies that have demonstrated that parasite recognition in invertebrates is highly specific (i.e. Kurtz and Franz, 2003; Roth et al., 2009). Since these publications, little interest has been paid to test the immune memory specificity at the strain level. Further investigations are warranted and should consider different species, strains and the associated underlying mechanisms. In the absence of evidence supporting the existence of specific immune memory, it is crucial to explore the potential role of parasites on the immune memory outcome. It is possible that parasites can either evade specific immune memory or be so virulent that it is ineffective against them (Contreras-Garduño et al., 2016).

Long-lasting protection

The long-lasting nature of the protection provided by specific immune memory means that invertebrates should be protected against a given parasite for most of their lifetime, in the same way that vaccines protect us from the neonatal stage to adulthood. For example, in an experiment conducted by Thomas and Rudolf (2010), larvae of *T. castaneum* were exposed to oocysts of the

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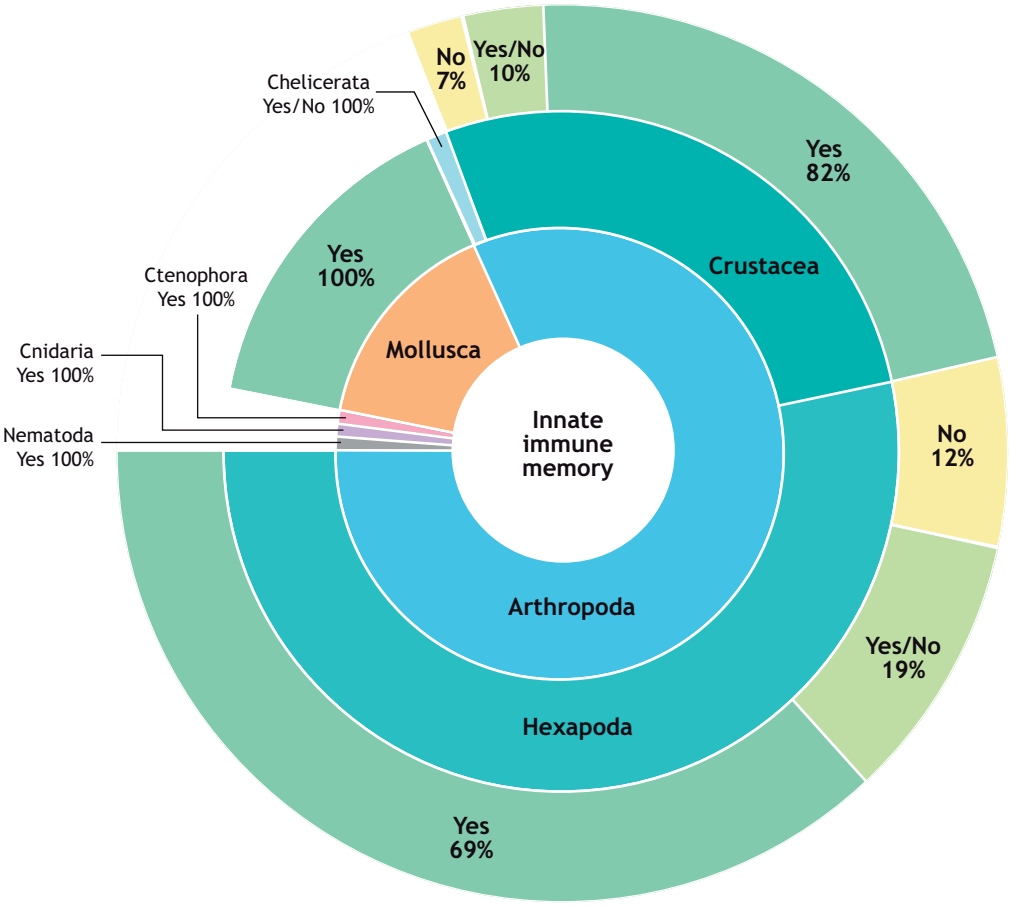

Fig. 1. Studies of specific immune memory within generations in invertebrates according to their taxonomic classification. The figure shows the percentage of papers that support (Yes), that do not support (No) or that partially support (Yes/No) the occurrence of immune memory in invertebrates. It is important to note that few of these studies have tested the specific immune memory at the level of strain such as Kurtz and Franz (2003) and more studies like this are needed to know how specific immune memory is in invertebrates. Further details and a full list of the studies is provided in Table S1.

parasite *Gregarina minuta*, and then later re-infected at the adult stage. The control group consisted of adults who were only exposed to the parasites at the adult stage. The parasite load was lower in adults that had previously been infected as larvae compared with those that were not infected during the larval stage (Thomas and Rudolf, 2010). In another study, researchers tested whether *Aedes aegypti* mosquitoes could develop immune protection against the Dengue virus across different life stages (Vargas et al., 2020). Female mosquitoes fed with rabbit blood infected with Dengue virus show lower viral loads if they were primed with virus as larvae than controls (not primed with virus), suggesting that immune priming provides long-lasting protection to mosquitoes against the Dengue virus (Vargas et al., 2020). However, it should be noted that this work did not investigate the specificity of immune memory. Another study in *Anopheles gambiae* suggests that there is an increase in immune response across life stages (Brown et al., 2019) but does not support the idea of long-lasting protection due to specific memory. Adult *An. gambiae* are more resistant to *Escherichia coli* infection if they are infected with bacteria as larvae (both live and inactivated *E. coli* were used, as well as live *Enterobacter* sp.), compared with those that were not exposed to bacteria in the larval stage (Brown et al., 2019). Finally, long-lasting specific immune memory has been tested in the crayfish *Astacus astacus* (Gruber et al., 2014). In this work, crayfish were immune challenged with a nylon implant and subsequently challenged with a novel nylon implant at 2, 3 or 4 months after the first. There was no significant difference in the encapsulation response (see Glossary) against the nylon implant between the control (which did not receive the initial implant) and the other groups. However, note that this research did not test for the specific immune memory, but for the role of immune priming on subsequent protection, which may be part of immune memory but not of specific immune memory.

The fact that the studies discussed above present conflicting findings could be explained by the nature of the immune challenge. Natural enemies were used against *T. castaneum* and *A. aegypti*, whereas *An. gambiae* and *A. astacus* (which did not show specific immune memory) were challenged with unnatural immunological agents. Roth et al. (2009) found that specific memory was supported against natural pathogens at the infection strain level with *Bacillus thuringiensis*, but not against *E. coli*. In addition, *Anopheles albimanus* showed specific memory against *Plasmodium berghei* (Contreras-Garduño et al., 2014, 2015) but not against *E. coli* (Moreno-García et al., 2015). *T. castaneum* showed specific memory against a strain of *B. thuringiensis* that infects this insect, but not against novel bacteria (Milutinović et al., 2014). Taken together, it is therefore plausible that the host immune response exhibits plasticity, activating specific memory in response to actual harm but not in the face of innocuous challenges. Investigating the distinct mechanisms underlying immune responses in these two scenarios could reveal differences in the plasticity of recognition and the plasticity in effector responses when encountering novel parasites versus natural ones. Moreover, it is crucial to explore the existence of a threshold that must be exceeded for the activation of the immune response. Considering that the immune response is costly, this threshold may serve to prevent unnecessary immune activation in response to pathogens of low virulence and allow the immune system to

respond only when genuine damage is occurring. This suggests plasticity of immune memory depending on the intensity of infection and the risk of dying.

Potential factors that may affect the plasticity of immune priming or specific memory

The immune response undoubtedly has a strong hereditary component; however, it can also vary with respect to the environment (Brodin et al., 2015). It is now acknowledged that the immune response, in general, is variable, and some sources of variation have been identified (Schmid-Hempel, 2005; Demas and Nelson, 2012). For instance, it varies with age, gender, temperature, reproduction, or the virulence of parasites or pathogens. Nevertheless, the reasons for and the mechanisms behind the variation in immune memory in invertebrates are less understood. In this section, we pinpoint potential sources of variation in immune memory, summarizing the factors that might affect the expression of immune memory. Subsequently, we propose how further investigation of the effect of these elements on immune memory might contribute to our understanding of whether such variation stems from phenotypic plasticity.

The impact of parasite infection has been shown to be affected by the temperature experienced by the infected insect host (Adamo and Lovett, 2011). Additionally, temperature alone is an important factor that determines invertebrate resistance after parasite exposure (see review by Sheehan et al., 2020). For example, in the crayfish *Parachaeraps bicariyatus*, the temperature and the priming dose have a strong effect on the level of protection (McKay and Jenkin, 1969, 1970b): at 19°C, the vaccinated groups exhibit a more persistent immune response compared to the control group, while no significant differences are observed at 14°C (McKay and Jenkin, 1969). Hence, the role of seasonality in the development of specific immune memory deserves further research, as does whether changing temperatures during different seasons favor a plastic specific immune memory outcome (Gruber et al., 2014). Furthermore, the influence of the abiotic environment on the occurrence of specific immune memory remains poorly tested. In general, the impact of environmental variation on immune memory, at the individual or population level, should be investigated further (Tate and Rudolf, 2012).

Another factor that may affect the plasticity of specific immune memory is the developmental stage. Immune response decreases with age (Adamo et al., 2001; Nikolich-Žugich and Čičin-Šain, 2010; Mackenzie et al., 2011; League et al., 2017; Amaro-Sánchez et al., 2023) and with reproduction (Adamo et al., 2001; Leman et al., 2009; Gershman et al., 2010). We predict that plastic specific immune memory is more likely to be found in larvae than in adults. No studies have specifically tested this question, but studies in ants might provide some support: in the ant *Formica selysi*, there is no evidence supporting specific memory in adults confronted with the fungus *Beauveria bassiana* (Reber and Chapuisat, 2012), but larvae of *Camponotus amponotus pennsylvanicus* confronted with *Serratia marcescens* supported the specific memory (Rosengaus et al., 2013). However, the expression of immune memory in ants (and other social insects) may be particularly complex; for example, ant queens do not show a trade-off between immunity and reproduction (Pamminger et al., 2016), including the expression of immune priming (Gálvez and Chapuisat, 2014). Therefore, investigating larvae and queens may shed some light on the plasticity of specific immune memory in social insects. Moreover, if immune memory is present in adult workers of social insects, the social context may elicit phenotypic plasticity in the immune function (Ruiz-Gónzalez et al., 2009) as well as the task performed (Bocher et al., 2007), possibly influencing the detection of immune memory. Overall, solitary species may provide the best systems in which to study reproductive trade-offs.

If we are to learn more about phenotypic plasticity in immune memory it would be fruitful to consider the development of the host. The occurrence of specific immune memory during the larval stage may vary within a species and is influenced by factors such as cost (Contreras-Garduño et al., 2019), parasite strain (Carmona-Peña et al., 2022; Khan et al., 2019), the parasite's route of infection (Futo et al., 2016; Milutinović and Kurtz, 2016) and population variation (Tate and Graham, 2015; Khan et al., 2016, 2019). Regarding cost, in *An. albimanus* infected with *P. berghei*, females from the 'memory' group pay a cost in terms of reproduction compared with the control group: Females in the memory group experienced reduced hatching success, and those who opted for immune memory exhibited a lower egg production in their ovarioles (Contreras-Garduño et al., 2014). However, in *T. castaneum*, the memory group exposed to *B. thuringiensis* demonstrated an enhancement in reproduction compared with the control group (Khan et al., 2019). The former study suggests that there is a trade-off between reproduction and specific immune memory (Contreras-Garduño et al., 2014, 2016; Khan et al., 2019), whereas the latter may be explained because the memory groups invested in reproduction at the expense of survival, as a form of terminal investment (Khan et al., 2019). Future research is needed to define the situations that favor investment in immune memory at the expense of reproduction or vice versa.

Some studies suggest that immune memory is associated with variation in developmental rate within a species. In *T. molitor*, individuals challenged with the fungus *Metarhizium brunneum* exhibit a lower rate of development from larva to pupa and show an increase in CO_2 production, suggesting a cost of memory (Contreras-Garduño et al., 2019). However, the opposite is observed in the developmental rate from pupa to the adult stage, suggesting a plastic response and a potential compensation in development to reduce the cost of the slower larval stage development (Contreras-Garduño et al., 2019). Invertebrates are known to accelerate development to evade infections from fungi and bacteria (Vey and Fargues, 1977; Roth and Kurtz, 2008; Moret and Moreau, 2012; Milutinović et al., 2014), but the role of this accelerated development in specific immune memory remains unknown. Both acceleration and retardation of development have been reported to coincide with the establishment of immune memory, but the underlying mechanisms remain unclear. One possibility is that accelerated development is an adaptive strategy under stressful conditions. In this scenario, ecdysis, or the shedding of the old cuticle, during specific immune memory may occur when the subsequent developmental stage is less susceptible to parasite invasion or if parasites remain attached to the previous cuticle (see, for example, Roth and Kurtz, 2008; Moret and Moreau, 2012; Carmona-Peña et al., 2022). Alternatively, the acceleration of ecdysis could be a strategy to enhance reproduction if the organism is close to the reproductive stage, such as during the last larval developmental stage or the pupae. An alternative hypothesis is suggested by the fact that pupation or developmental stages nearing pupation may require more resources and be costlier than earlier stages. Consequently, it may be more energetically demanding to establish specific immune memory close to pupation or adulthood compared with earlier developmental stages. Interestingly, in vertebrates, it has been shown that neonates are more successful in establishing specific immune memory compared with elderly individuals (Domínguez-Andrés

et al., 2023). Further research is required to determine whether there is an optimal developmental stage that favors the establishment of specific immune memory.

A biotic factor that may influence the phenotypic plasticity of immune memory is mutualism, as exemplified by the antiviral role of *Wolbachia* in insects (Pimentel et al., 2021). For instance, insertion of several *Wolbachia* strains in *A. aegypti* interferes with replication of the dengue virus, apparently through immune priming (Bian et al., 2010; Rancès et al., 2012). However, the coevolutionary history of the specific host and *Wolbachia* strain may influence the expression of some immune genes. For example, in *Aedes fluviatilis*, infection with *Plasmodium gallinaceum* is actually enhanced by the presence of the native *w*Flu *Wolbachia* strain (Caragata et al., 2017). Therefore, the role that *Wolbachia* plays in the activation of the immune system across insects is not necessarily universal.

When testing specific immune memory, it is crucial to consider a variety of immune response parameters because not all parameters may decline in the same way over time post-infection, which is consistent with what is observed in the overall immune response: some increase, others decrease or remain stable (Schmid-Hempel, 2005; Trauer and Hilker, 2013). Consistently, Table S1 shows that some immune parameters correlate with specific memory (such as hemocyte activity and load), but others do not. Interestingly, hemocytes and their activity (i.e. phagocytosis) seem to be very important to our understanding of specific memory and in the development of invertebrate vaccines (Yang et al., 2021). Considering various immune parameters may uncover plasticity not solely attributable to a gradient of biotic and abiotic environments but also potentially revealing a concurrent correlation between the immune response and the environment.

An interesting observation arises from the fact that not all populations of *T. castaneum* develop specific memory against *B. thuringiensis* (Khan et al., 2016, 2019). Across most populations, there are no discernible differences in the developmental rates between control and memory groups. However, it is noteworthy that in one population, development is accelerated in the memory group, whereas in another, it is retarded compared with the control group (Khan et al., 2019). These variations could potentially be attributed to factors such as genetic drift, variable life-history costs associated with the immune response, and differing susceptibility to pathogens (Khan et al., 2016). Among these hypotheses, an intriguing avenue of exploration involves investigating the plasticity in parasite populations and the concurrent development of specific memory by the host (Khan et al., 2019). In line with these considerations, a noteworthy finding is the evolution of specific immune memory against host-specialized bacteria after 14 generations of selection (Ferro et al., 2019). It is also interesting to note that, after 11 generations, specific immune memory is more likely to evolve against heat-killed bacteria (less harmful) than against high doses of live bacteria (Khan et al., 2017). This implies that natural selection, acting on both parasites and hosts, could be a driving force in the evolution of immune memory.

The studies discussed above reveal that immune memory or specific immune memory are not inflexible strategies to combat parasites, but that the biotic and the abiotic environment sculpt their effectiveness and plasticity. In a laboratory setting, researchers operate under controlled conditions to manage sources of variation in the immune response (Martin et al., 2021). However, to assess phenotypic plasticity and reaction norms, it is essential to create gradients of environmental conditions in the laboratory (Martin et al., 2021). A similar approach can be applied to the study of immune memory, providing insights into its degree of plasticity.

The plasticity of the immune response during specific immune memory

Textbooks often depict the kinetics of adaptive memory as biphasic (Murphy and Weaver, 2016). This means that after the initial exposure, the immune response increases and then returns to basal levels. Upon a subsequent challenge, the response increases to a greater extent before returning to basal levels. This biphasic immune response is predicted in invertebrates (Kurtz, 2005; Brehélin and Roch, 2008; Contreras-Garduño et al., 2016; Schmid-Hempel, 2021; Fig. 2A). The first evidence for a biphasic response in specific immune memory in invertebrates was reported in *An. albimanus* (Contreras-Garduño et al., 2015). When *An. albimanus* is exposed to *P. berghei*, the homologous challenge, compared with the heterologous challenge, shows a biphasic immune response involving three peptides that combat *Plasmodium*: Gambicin, Cecropin and Attacin. Interestingly, gene expression analysis reveals that there are higher levels of mRNA encoding Gambicin and Cecropin in the second challenge compared to the first, whereas *Attacin* gene expression is lower in the second challenge (Contreras-Garduño et al., 2015). Since then, this biphasic response has been observed in Insecta (Vargas et al., 2016; Li et al., 2022), Malacostraca (Wang et al., 2019; Yang et al., 2020; Zhu et al., 2023) and Bivalvia (Lafont et al., 2020; Wang et al., 2020). However, the kinetics of the immune response can take different forms (Melillo et al., 2018; Prigot-Maurice et al., 2022). Other studies have reported a decrease (Contreras-Garduño et al., 2015; Wang et al., 2019; Rey-Campos et al., 2019; Lafont et al., 2020; Zhang et al., 2022a,b; Tang et al., 2022; Burciaga et al., 2023; Fig. 2C), enhancement or increase (Wang et al., 2019; Lafont et al., 2020; Yang et al., 2020; Li et al., 2022; Tang et al., 2022; Burciaga et al., 2023; Fig. 2E) or a shift (Pinaud et al., 2016; Fig. 2G) in the immune response from the first to the second challenge, or an increase in some immune parameters and a decrease in others (Contreras-Garduño et al., 2015). Interestingly, the innate immune response (see Glossary) in vertebrates also exhibits a plastic component when exposed to heterologous activators, just as occurs in the vertebrate adaptive immune system (Liu et al., 2016; Fig. 2). Therefore, it is crucial to investigate whether the kinetics of the immune response differ in heterologous challenges compared with homologous challenges. It is expected that the kinetics of the immune response during specific immune memory exhibit specialized responses, whereas nonspecific responses are predicted during heterologous challenges. Another prediction is that a biphasic response should occur in specific immune memory and a sustained or diminished response should occur during heterologous challenges. This is supported in the work discussed above in which *An. albimanus* was infected with *P. berghei* (Contreras-Garduño et al., 2015). This improvement in immune response after the second exposure, may explain why the mosquitoes' survival was better in homologous compared with heterologous challenges (Contreras-Garduño et al., 2014). To more comprehensively understand the adaptability in the dynamics of specific immune memory, it is imperative to connect these studies with assessments of both survival (Milutinović and Kurtz, 2016) and reproductive outcomes (Contreras-Garduño et al., 2014, 2019). This is crucial to allow us to discern the impact of specific immune memory on evolutionary fitness.

Further research is necessary to fully understand the plasticity of the immune response scenarios during immune memory and specific immune memory. One possible explanation is that different immune response parameters are traded-off, meaning that not all parameters may increase simultaneously after the second

Journal of Experimental Biology (2024) 227, jeb246158. doi:10.1242/jeb.246158

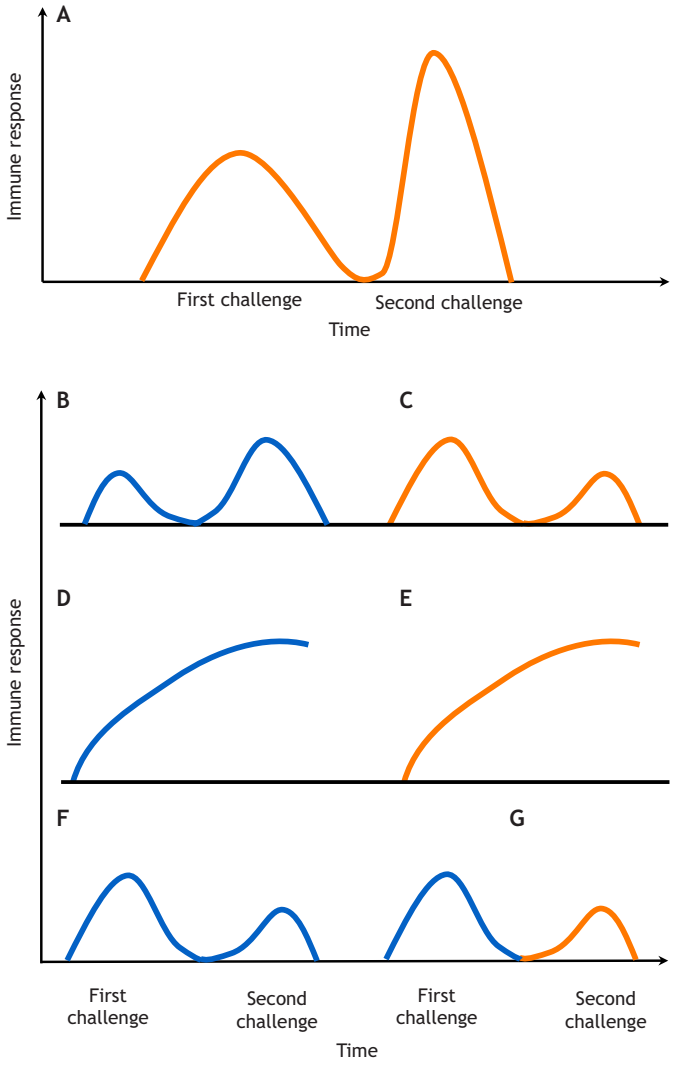

Fig. 2. Plasticity in the immune response. (A) The classical scenario in adaptive immunity involves a biphasic immune response, characterized by a higher and faster response during the second challenge compared with the first challenge. (B,D,F) Scenarios showing heterologous challenges. (C,E,G) Expected scenario with homologous challenge (memory). (B) A biphasic immune response is expected in heterologous challenges, but in this case, a generalized, non-specific immune response is predicted instead of the specificity observed in specific immune memory. (C) In specific immune memory, a reduction in the immune response has been observed, suggesting tolerance to infection. However, it remains unknown whether the mechanisms involved in the immune response during homologous challenges are the same as those in heterologous challenges. (D,E) Immune enhancement has also been described in specific immune memory, where the immune response is initially activated and remains high for an extended period, effectively eliminating parasites during the second challenge. Nevertheless, potential differences between sustained immune responses in heterologous (D) versus homologous (E) immune challenges have yet to be explored. (F,G) Finally, it is also possible that specific immune memory activates similar levels of immune responses in both heterologous challenges (F) and homologous challenges (G). In both cases, the mechanisms involved might be comparable in terms of the intensity of the immune response. However, during specific immune memory, the first challenge might induce mechanisms that favor specific memory, and in the second challenge, a shift in immune mechanisms is expected. This may involve a specific immune response against parasites. The blue color refers to an unspecific immune response, and the orange color shows a mechanism of specific immune memory. G shows a mechanism of specific immune memory after the first challenge (blue) and a shift to new specific mechanisms different from the first challenge but only involved in memory (orange). The references that support each scenario (A,C,E,G) are provided in Table S1 and in the text.

challenge. This trade-off hypothesis suggests that certain aspects of the immune response may be prioritized over others because expression of all components of the immune response may be costly (Contreras-Garduño et al., 2015); the immune response should not be uniformly enhanced during subsequent exposures, but should be optimized (Viney et al., 2005; Adamo, 2004). An alternative explanation is the concept of immune response tolerance following the second challenge. This hypothesis proposes that the immune system may display a muted or diminished response to prevent excessive damage (Vargas et al., 2016). Specifically, if the parasite load increases and the host incurs damage, a transition from tolerance to an augmented immune response is predicted (Lazzaro and Rolff, 2011). Consequently, immune tolerance is expected in the case of low-virulence parasites causing minimal damage. However, a biphasic response or a shift in the immune response is predicted when dealing with more damaging parasites. A third explanation is that the immune response undergoes a reconfiguration to achieve an optimal response. This idea comes from a general proposal that the immune system adjusts its strategies and mechanisms to defend the host against parasites without incurring a cost for the host (Adamo, 2017; Adamo et al., 2017). It is also possible that a combination of these scenarios occurs, depending on the immune response parameter in question. The kinetics of the various immune response parameters may depend on the specificity with which the immune system recognizes and eliminates the parasites, as well as the level of harm inflicted by the parasite. Further investigation is required to unravel the plasticity of the immune response and the intricacies of the underlying mechanisms. Given that specific immune memory is influenced by both biotic and abiotic factors (as demonstrated in the previous section), it would be intriguing to investigate how the environment contributes to the plasticity in the kinetics of the immune response.

Finally, there are three genetic bases that underlie plastic responses: overdominance, pleiotropy and epistasis (Scheiner, 1993; Pigliucci, 2005). Understanding these mechanisms may help to offer insights into their respective contributions to the plasticity of specific immune memory.

Conclusion and future research

It is an open question as to when specific immune memory evolved (Kasahara et al., 2004; Flajnik and Du Pasquier, 2004). The lack of antibodies and the absence of diversification of immunoglobulins in invertebrates may lead immunologists to reject the possibility that they possess specific immune memory. Indeed, the proposal of specific immune memory in invertebrates has raised strong skepticism (Hauton and Smith, 2007). However, growing evidence in support of specific immune memory in invertebrates has now attracted attention to the underlying molecular mechanisms to analyze how this protection is achieved and could even support vaccination in economically important invertebrate species (Melillo et al., 2018; Yang et al., 2021; Lanz-Mendoza and Contreras-Garduño, 2022). Unfortunately, the molecular mechanisms involved are still descriptive: we only have information about effectors of the immune response and not yet about how specific recognition is achieved, and how the immune memory is stored and

recalled during subsequent immune challenges (Lanz-Mendoza and Contreras-Garduño, 2022). Achieving a mechanistic understanding will not be an easy task because the mechanisms of specific immune memory are likely to be plastic and might be as diverse as the invertebrates themselves (Milutinović and Kurtz, 2016).

Studies that provide no support or only partial support for the idea of specific immune memory may be important to help us to understand the potential causes of plasticity of the specific immune memory outcome and the contribution of biotic and abiotic factors to such memory (Contreras-Garduño et al., 2016). These factors encompass both biotic elements (such as mate partners, predation, parasitic virulence, encounters with novel versus natural parasites and microbiota) and abiotic elements (such as temperature), as well as intrinsic organismal factors such as developmental rate and developmental stage. In this Review, we have considered potential sources of variation including parasites, temperature, developmental rate, developmental stage and evolutionary cost. If we fail to consider these sources of variation it is possible that specific immune memory in invertebrates may remain hidden to immunology. The same rationale applies for intergenerational immune memory (also referred to as transgenerational immune memory or immune memory across generations). For example, does the developmental stage at which parents and their offspring are immunologically challenged affect specific immune memory? In other words, if the parents are challenged during the larval, pupal or adult stages, does it impact their offspring if they are challenged during the larval, pupal or adult stages as well?

Understanding the limits between tolerance and immune response in invertebrates is fundamental and will yield valuable insights into plastic responses. Exploring how invertebrates activate or deactivate specific immune memory is important to understanding environmental influences on the plasticity of immune memory. To date, only a limited number of studies have examined molecules associated with signaling, tissue damage and the regulation of the immune response. Salt (1970) pointed out that the nature of the insect immune reaction must be determined principally by its effect on parasites, particularly those that endanger the life of the host. It will be necessary to study the antigens, pathogens and parasites that induce an immune response, tolerance or immune memory in invertebrates. Exploring the mechanical attributes of the damage generated during pathogen–invertebrate interactions could offer valuable insights into the activation and efficiency of the immune response under natural conditions. This exploration would shed light on the extent of plasticity in these responses.

Going forwards, techniques such as single-cell RNA sequencing (Yang et al., 2021), transcriptomics (Fuse et al., 2022), ATAC-seq (assay for transposase-accessible chromatin using sequencing; Lau et al., 2018), metabolomics (Zang et al., 2022), proteomics (Zhai et al., 2021) and single-cell sequencing to determine cell identity (Lambert et al., 2021) will be helpful to compare differential mechanisms underlying the various kinetics of the immune response during specific immune memory. Techniques like this, comparing heterologous and homologous immune challenges, will provide valuable information to establish fundamental differences between specific immune memory and the non-specific immune activation with heterologous immune challenge. In addition, studying parasites with different degrees of virulence while controlling for host species will help to reveal the contribution of parasites to the kinetics and plasticity of the immune response.

Despite two decades having passed since the formal discovery of specific immune memory in invertebrates as an adaptive-like immune response, this field of research remains in its early stages of development. More work is needed to allow us to uncover the mechanisms used to generate specific immune memory, and to reveal how both biotic and abiotic factors – as well as intrinsic changes in an organism – favor plasticity of the immune memory in both invertebrates and vertebrates.

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