



Review

Immune memory in invertebrates

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ABSTRACT

Evidence for innate immune memory (or 'priming') in invertebrates has been accumulating over the last years. We here provide an in-depth review of the current state of evidence for immune memory in invertebrates, and in particular take a phylogenetic viewpoint. Invertebrates are a very heterogeneous group of animals and accordingly, evidence for the phenomenon of immune memory as well as the hypothesized molecular underpinnings differ largely for the diverse invertebrate taxa. The majority of research currently focuses on Arthropods, while evidence from many other groups of invertebrates is fragmentary or even lacking. We here concentrate on immune memory that is induced by pathogenic challenges, but also extend our view to a non-pathogenic context, i.e. allograft rejection, which can also show forms of memory and can inform us about general principles of specific self-nonself recognition. We discuss definitions of immune memory and a number of relevant aspects such as the type of antigens used, the route of exposure, and the kinetics of reactions following priming.

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1. Introduction

Numerous studies have recently demonstrated diverse forms of immune memory in a number of taxa, in particular invertebrate species (for review see [1–4]). Since invertebrates lack the machinery of adaptive immunity in the narrow sense (i.e. lymphocytes and antibodies), such forms of memory have been denoted as innate immune memory [5] or immune priming [6]. In this review, we will provide an overview of examples for such innate immune memory in invertebrates. We will use a phylogenetic approach, and include taxa where currently merely phenomenological evidence is available, as well as those where the mechanistic underpinnings are being elucidated. However, the available evidence for innate immune memory appears to be quite heterogeneous, and also the terminology used is rather inconsistent. Let us therefore first try to disentangle the different forms of immune memory.

1.1. An attempt to define immune memory

Rather broad definitions of immune memory are prevailing in the recent literature, while earlier definitions sometimes restricted the use of this term to the adaptive immune system of vertebrates and basically denied the possibility of other forms of memory (e.g., [7–9]). We propose that we should separate the definition of immune memory from the mechanisms that provide memory [5]. Immune memory could then be defined as the ability of an immune system to store or simply use the information on a previously encountered antigen or parasite, upon secondary exposure [10,11]. Note that we use a broad definition of a ‘parasite’ that focuses on the antagonicity of the interaction and includes microparasites such as bacteria and viruses. In a stricter sense (and also from the vertebrate viewpoint), memory would exclude cases where an immune trait that is induced upon primary contact remains active until secondary exposure. However, in the following, we will discuss that such induced, lasting defenses do not necessarily need to be disregarded as memory, especially if the responses activated are qualitatively different than unprimed responses ([12], Greenwood, 2016, in prep). This would suggest an anticipatory response and the utilization of the primary information. The mechanisms behind both modes of priming could be fairly different, however, the experiments that simply test resistance upon re-exposure would be unable to discriminate this, from a reaction that vanishes and rises again upon re-exposure. Also because of this inability, the term ‘priming’ instead of memory is often used, in particular in the invertebrate literature. Note as well that whereas in most cases, memory will lead to enhanced resistance upon a secondary encounter, other consequences such as increased tolerance [13] could also be possible, but are rarely studied.

Another somewhat controversial aspect is the specificity of the response. Specificity measures the degree to which the immune system differentiates between different antigens, and is the opposite of degeneracy or cross-reactivity [11]. While also non-induced immune reactions can be specific (i.e. genetic specificities in host-parasite interactions), specificity is often considered as an important aspect of memory [10]. Indeed, if an immune response is completely unspecific, it makes little sense to speak of memory, since the immune system is not really ‘remembering’ any specific characteristic [5]. In any case, it appears useful to discriminate the dimensions of inducibility and specificity of a memory reaction [14].

These considerations show how delicate it is to come up with a universal definition of memory. Likewise, the definition of innate and adaptive (mostly used in synonymy with ‘acquired’) immunity is not straightforward. A broad definition of adaptive immunity would comprise all reactions that enable the host to adapt to parasites during its lifetime. Adaptation here means that the immune mechanisms are tuned towards specific characteristics of the pathogen. This process of adaptation occurs within an individual, and not through the Darwinian process of selection over generations. It enables hosts with often relatively long generation times to keep pace with parasites that might evolve fast. Again, a more narrow definition basically restricts the term adaptive immunity to the type of immune system that vertebrates have evolved (i.e. based on lymphocytes and antibodies). However, the elucidation of a second type of adaptive immunity in the jawless vertebrates [15] shows that this definition is hard to hold, even for vertebrates.

A potentially useful distinction between innate and adaptive immunity focuses on whether or not the involved immune receptors are somatically diversified [7,16]. In this view, an innate immune system makes use of antigen receptors that are expressed as they are encoded in the germ line, while an adaptive immune system takes advantage of somatic diversification processes to expand the receptor repertoire beyond the boundaries set by the limited number of genes in the germ line. Basically, the degree of individualization of the receptor repertoire is in focus here. However, it is as of yet unclear, where a useful boundary could be set: would e.g., alternative splicing of an immune receptor with only a few splice variants already be sufficient to denote this an adaptive immune receptor or not? Essentially, the seemingly clear distinction between innate and adaptive immunity is increasingly blurred by the recent examples that emphasize the diversity of forms of memory and the potentially underlying molecular mechanisms in the immune systems of vertebrates and invertebrates.

According to the definition chosen, we could thus either say that there is evidence that invertebrates possess forms of ‘innate immune memory’ or that they seem to have ‘alternative’ forms of adaptive immunity. In the following, we are going to review such available evidence.

1.2. Phenomena of immune memory in invertebrates

The studies on immune memory in invertebrates vary considerably regarding their experimental design, but often use a repeated challenge (or ‘priming’ followed by ‘challenge’) approach [6,17,18]. It is important to note that in some studies live parasites were used for priming or previous infection [17], sometimes at a low dose that does not lead to any obvious infection (e.g. [19]). However, in such cases, it is normally not possible to fully exclude the possibility of latent infections that might directly affect challenge and such possibility preferably needs to be eliminated [20,21]. Other studies have used inactivated, e.g. heat-killed or otherwise non-infective agents for priming (e.g. [22]). The time span between priming and challenge varies considerably across studies, but is often rather short. A few studies have addressed the time course more directly and studied resistance at different time points after priming [23–25].

Priming itself can be achieved by different ways of exposure. A large number of studies used septic priming, for example by pricking with a bacteria-contaminated needle (e.g. [20]) or injection of bacteria (e.g. [26]) and an increasing number of studies uses oral exposure to achieve priming (e.g. [19,27,28]). However,

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