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The Role of Innate Immune System: A Crosstalk between Invertebrates and Humans

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Abstract

Innate immunity is the oldest form in evolution and is present in all multicellular organisms, including vertebrates and invertebrates. Although humans are the most recent evolutionary phylum, there is abundant evidence of a genetic inheritance shared between invertebrates and humans. There is correspondence between molecular pathways associated with the recognition systems of pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) and Peptidoglycan recognition proteins (PGRPs). From a molecular point of view, intimate associations occur in key components of the molecular signaling process such as signal transducer and activator of transcription (STAT), Janus kinase (JAK), c-Jun N-terminal kinase (JNK), Toll-like receptor (TLR). Using these parallels is essential for a better understanding and conservation of living organisms, establishing essential biotechnological strategies for the progress of the understanding of the immune system.

Keywords: Innate immunity, Invertebrates, Humans

Abbreviation: PRRs: Pattern Recognition Receptors; PAMPs: Pathogen-Associated Molecular Patterns; TLRs: Toll-Like Receptors; NLRs: Nucleotide-Binding Oligomerization Domain Receptors; ROS: Reactive Oxygen Species; PGRPs: Peptidoglycan Recognition Proteins; AMPs: Antimicrobial Peptides

Introduction

The immune system has multiple pathways of action, and these pathways are divided into two major blocks: innate immunity, which is intrinsic to animals, and adaptive immunity. Innate immunity represents the first line of defense against pathogens in animals and it is characterized by its nonspecific nature. This form of immunity is the oldest form in evolution and is present in all multicellular organisms, including vertebrates and invertebrates [1]. Unlike adaptive immunity, which depends on specific recognition of pathogens and involves a memory component, innate immunity acts immediately after infection and does not require prior exposure to a pathogen, being a more immediate response pathway than adaptive immunity [2].

Innate immune system employs a variety of mechanisms to identify and respond to pathogens. At the heart of this process are pattern recognition receptors (PRRs), which recognize conserved molecular patterns associated with pathogens, known as pathogen-associated molecular patterns (PAMPs) [3]. These receptors include Toll-like receptors (TLRs), which play a critical role in initiating immune responses by detecting microbial components and activating signaling pathways that lead to the production of inflammatory cytokines and antimicrobial peptides (AMPs) [4]. Innate immune responses can be modulated by several factors, including environmental cues and the presence of other immune cells, which can either enhance or suppress the overall immune response [5].

With studies being conducted modulating the action of innate immunity, the concept of "learned immunity" has been highlighted, focusing mainly on clades of animals that only have innate immunity as a form of immune response. Learned immunity occurs when innate immune cells exhibit enhanced responses after re-exposure to pathogens, suggesting a form of immunological memory that was previously considered exclusive to adaptive immunity [6]. Studies such as these are able to highlight the need to better understand how innate immunity works in the body and in animal cells. For this reason, the present work aims to highlight the importance of innate immunity through a review of what is known about innate immunity as a form of response within the evolution of taxa, addressing the theme from more basal animals to mammals.

The Foundation of Immunity: Basal Animals as Evolutionary Evidence

Innate immunity in basal animals, such as poriferans (sponges) and cnidarians (i.e. sea anemones and corals), represents a fundamental aspect of their biological defense mechanisms against pathogens. This first form of defense is characterized by its reliance on germline-encoded receptors and immediate responses to microbial threats, distinguishing it from the adaptive immune responses seen in more complex organisms.

In poriferans, innate immunity is primarily mediated by PRRs, which recognize PAMPs. Previous studies have shown that sponges express TLRs, which play a crucial role in initiating immune responses by triggering signaling pathways that lead to the production of AMPs and inflammatory cytokines [7,8]. The sponge *Amphimedon queenslandica* [9] has been highlighted for its complex repertoire of nucleotide-binding oligomerization domain receptors (NLRs), which are integral to the innate immune response and can initiate pyroptosis and apoptosis in response to infections [10]. This indicates that, even at this early stage of metazoan evolution, sponges possess sophisticated mechanisms for detecting and responding to pathogens.

Furthermore, sponges already utilize several immune signaling pathways, including MyD88-dependent pathways, which are essential for their defense against bacterial infections [8], and these receptors can be induced upon exposure to microbe-associated molecular patterns, demonstrating their ability to recognize and respond to environmental microbial threats [11]. With evolution, it is possible to see some gains but also similarities between animals, with the innate immunity of Cnidaria being similarly characterized by the presence of TLRs and other immune receptors that facilitate the detection of pathogens. The TLR in sea anemones is involved not only in the detection of pathogens, but also in developmental processes, indicating a dual role in both immunity and growth [12].

Innate immune responses in cnidarians are also marked by the activation of signaling pathways that lead to the expression of immune-related genes, which help in the fight against infections [13]. The evolutionary conservation of innate immune genes among these basal taxa highlights the fundamental nature of these immune mechanisms in early-diverging metazoans [14]. For cnidarians, there is also an important relationship that highlights the effectiveness of their innate immunity, indicating that cnidarians have a diverse repertoire of PRRs, which allows them to recognize both microbial threats and their symbiotic partners, such as photosynthetic microalgae that play an important role in obtaining energy for corals (i.e. zooxanthellae) [3]. This immunological specificity is particularly important to maintain the balance between tolerance and defense, as the host must distinguish between beneficial symbionts and harmful pathogens [15]. Innate immune responses in corals can be modulated to support the symbiotic relationship with zooxanthellae, while providing defense against potential pathogens [16].

In taxa lacking an adaptive immune system, the presence of innate immunity in basal metazoans (such as cnidarians and poriferans) provides essential defense mechanisms that enable these organisms to survive despite environmental stressors. In corals, innate immunity plays a pivotal role in maintaining health by regulating the balance between beneficial and harmful microbial communities. Environmental changes, including rising temperatures and salinity fluctuations driven by climate change, can disrupt this balance, leading to a shift from symbiotic to pathogenic microbiota. This dysbiosis can compromise the health and resilience of Cnidaria. However, the innate immune system contributes to the taxon's ability to manage such microbial shifts, offering a degree of protection against disease and environmental perturbations [17].

The Role of Modern Invertebrates

Similar to poriferans and cnidarians, molluscs have a robust innate immune system, with specialized hemocytes that play a crucial role in defense against pathogens in both freshwater and marine environments. Hemocytes are the main immune cells in molluscs, analogous to mammalian phagocytes such as neutrophils and macrophages. They are involved in several immunological functions, including phagocytosis, encapsulation, and release of antimicrobial substances [18,19]. These cells circulate in the hemolymph of molluscs of all classes and are recruited to sites of infection, where they can recognize and eliminate pathogens through phagocytosis [20,21]. The ability of hemocytes to produce reactive oxygen species (ROS) and other cytotoxic molecules is critical for the destruction of engulfed pathogens [19].

Snails do not have an adaptive immune system, meaning that their immune responses are not specific or anticipatory. Instead, they rely on a diverse array of innate immune mechanisms that include the recognition of PAMPs via PRRs

[22]. Peptidoglycan recognition proteins (PGRPs), for example, are important components of the molluscan immune response, facilitating the detection of bacterial infections and triggering downstream immune signaling pathways [23].

The arthropod immune system, particularly in the model organism *Drosophila melanogaster*, is characterized by a highly efficient innate immune response that plays a crucial role in defense against pathogens, a trait that can be traced back to molluscs. This immune response is mediated primarily by two major signaling pathways: the Toll pathway and the immunodeficiency (Imd) pathway. Both pathways are activated by PRRs that detect PAMPs, leading to the production of AMPs and other immune effectors [24,25]. Upon recognition of PAMPs, such as peptidoglycan from bacterial cell walls or β-glucans from fungal cell walls, the Toll receptor activates a signaling cascade that ultimately leads to the activation of the transcription factor NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), which promotes the expression of several AMPs [26,27].

Recent studies have highlighted the role of specific Toll receptors, such as Toll-7, in the recognition of viral infections and in the activation of autophagy as a defense mechanism [26]. This indicates that the Toll pathway is not only involved in the response to fungal pathogens, but also plays a significant role in antiviral immunity, showing the versatility of this immune signaling pathway. The innate immune mechanisms observed in *Drosophila* are remarkably conserved among arthropods, indicating a common evolutionary origin. Comparative genomics has revealed that many immune genes are shared among different arthropod species, highlighting the importance of innate immunity in this diverse group [28]. The evolutionary conservation of the Toll and Imd pathways highlights their fundamental roles in host defense against infections.

Finally, among invertebrates, and their last link before they have adaptive immunity, are the Echinoderms. Like arthropods, echinoderms use a variety of cellular and humoral mechanisms to defend themselves against pathogens. Coelomocytes are specialized immune cells that play a crucial role in the innate immune response of echinoderms. They are produced in the axial organ and circulate within the coelomic fluid, where they can respond rapidly to infections or injuries [29,30]. There are several types of coelomocytes, including phagocytes, spherulocytes, and amoebocytes, each with distinct functions in immune defense [31,32]. Phagocytes are particularly important as they are responsible for the process of phagocytosis, where they engulf and digest pathogens such as bacteria and viruses [32,33]. The ability of coelomocytes to recognize and eliminate foreign materials is critical for maintaining the health of echinoderms in their marine environments, as the coelomocytes of the sea cucumber *Apostichopus japonicus* can effectively phagocytose *Vibrio splendidus*, a common marine pathogen [32].

AMPs are an essential component of the echinoderm immune system. These peptides are produced by coelomocytes and play a crucial role in the direct targeting and neutralization of pathogens [31,34]. The diversity of AMPs in echinoderms is remarkable, with some species exhibiting a wide range of antimicrobial activities against various pathogens [34]. Furthermore, echinoderms possess a complement-like system that enhances their immune responses. For example, the purple sea urchin *Strongylocentrotus purpuratus* has been shown to express a complement homologue, SpC3, in its coelomocytes, which is involved in pathogen recognition and elimination [35].

The immune system in invertebrates (**Figure 1**) carries functions and pathways that can also be seen in vertebrates, and is the precursor to many of the adaptive immunity

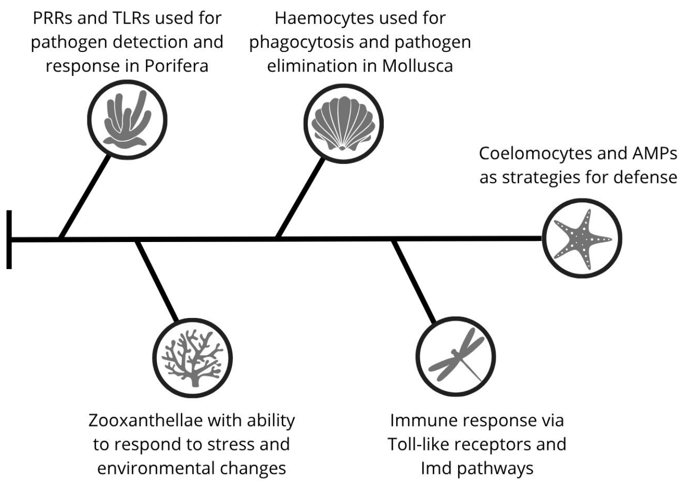

Figure 1. Evolutionary progression of innate immune components and response strategies in invertebrates. From basal Porifera to the more derived Echinodermata.

pathways that vertebrates have evolved to adopt. What can be concluded in relation to these animals is that, although invertebrates do not have adaptive immunity, there are different and common cellular means and functions among all of them that can explain part of how adaptive immunity works and intensified in vertebrate animals.

Molecular Genetics Implication of Immune System in Invertebrates in Relationship to Humans

Although humans are the most recent evolutionary phylum, there is abundant evidence of a genetic inheritance shared between invertebrates and humans. Similarities are essential for the use of model organisms that aid in the understanding of immunological processes, identifying key components that can be used as a biotechnological tool.

Thinking about homology is an extremely interesting intellectual exercise when one aims at sharing evolutionary inheritance. Examples in this sense can be found for signaling systems that make up the innate immune response, such as members of the Janus kinase (JAK) (hopscotch in *Drosophila melanogaster*), signal transducer and activator of transcription (STAT) (Stat92E/marelle in *Drosophila*), c-Jun N-terminal kinase (JNK) (basket in *Drosophila melanogaster*) and p38 (p38b in *Drosophila melanogaster*) signaling protein family [36–39]. Porifera have shown intrinsic similarities with the JNK proteins of humans. According to the work of Müller and collaborators [40], there is an important process of selective pressure in the presence of introns in genes related to the *JNK* gene, and an expansion can be observed in humans. In cnidarians, it is also possible to find homologies related to signaling proteins associated with the aforementioned molecular pathways, such as Wnt, Transforming growth factor beta (TGF-β), and Fibroblast growth factor (FGF) [41].

One of the most intriguing homologies concerns the components of the TLR molecular pathway. The association of the human proteins NF-κB, inhibitor of nuclear factor kappa B (IκB), brain-derived neurotrophic factor (BDNF), interleukin-1 receptor-associated kinase 1 (IRAK-1), IκB kinase (IKK) with the proteins dorsal, cactus, spätzle, pelle and kenny in *Drosophila melanogaster* has already been described [37,42–47]. Other invertebrates such as poriferans [48], ctenophores [49,50] and echinodermatans [51] show similarities with NK-κB and IκB signaling, as well as IRAK1 [52,53].

In this paper, we can observe that it is possible to establish parallels of important molecular pathways between invertebrates and vertebrates, revealing a broad field of scientific application. Thus, the present work has shown that it is possible and, in addition, it can serve as an important starting point as a biotechnological tool. Thus, we believe that the use of these parallels is essential for a better understanding and conservation of living organisms.

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