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Review

Reprint of "Review of Dscam-mediated immunity in shrimp and other arthropods" ☆

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ABSTRACT

Although true adaptive immunity is only found in vertebrates, there is increasing evidence that shrimp and other arthropods exhibit immune specificity and immune memory. The invertebrate immune response is now called "innate immunity with specificity" or "immune priming", and its underlying mechanisms are still unclear. However, while vertebrate antibodies have no invertebrate homolog, the Down syndrome cell adhesion molecule (Dscam), which is a hypervariable protein created by alternative splicing, can function as a pathogen-specific recognizing molecule in arthropods. Here we review our current understanding of the Dscam-mediated immune responses in arthropods, especially in shrimp, and show that Dscam may be involved in both general innate immunity and the pathogen-specific immune response.

Contents

1. Introduction

Classically, the two immune systems against invaders are innate immunity and adaptive immunity. Innate immunity is found in all animals, while adaptive immunity, which has the defining characteristics of antigen specificity and immunological memory, was thought to exist only in vertebrates (Cooper and Alder, 2006; Rowley

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and Powell, 2007). Recently, however, mounting evidence has suggested that invertebrates are also capable of exhibiting immune responses with specificity through antibody-independent mechanisms (Cooper and Alder, 2006; Chambers and Schneider, 2012). For example, arthropods can show highly-specific immune responses against specific pathogens after they have been immuno-primed by previous challenge with the same pathogen (Kurtz and Franz, 2003; Sadd and Schmid-Hempel, 2006; Pham et al., 2007; Powell et al., 2011). In addition, when shrimp are injected with antigens, these vaccine-like treatments somehow confer increased resistance/tolerance to the pathogen from which the antigen was originally derived (Johnson et al., 2008; Powell et al., 2011).

Penaeid shrimp aquaculture is a global market that continues to be greatly impacted by outbreaks of viral and bacterial diseases, and although shrimp have no classical adaptive immune system, some commercial shrimp farms nevertheless use a vaccination strategy to address this problem. Even though results are not always consistent, vaccination of the shrimp with pathogenic subunits and DNA plasmids carrying antigen genes is found to induce protective immunity against several pathogenic diseases. For example, when shrimp were vaccinated with DNA plasmids carrying a white spot syndrome virus (WSSV) envelope protein gene, such as *vp28* or *vp281*, this treatment protected the shrimp against WSSV infection starting from the first week and continuing through to the third week after immunization (Rout et al., 2007). Conversely, if shrimp were treated with DNA plasmids carrying only non-envelope protein genes, such as *vp15* and *icp35*, no WSSV-specific protective effect was triggered (Rout et al., 2007). Vaccination using WSSV envelope protein subunits or inactivated virion particles has also been shown to trigger shrimp protection against WSSV (Namikoshi et al., 2004; Witteveldt et al., 2004; Ha et al., 2008; Caipang et al., 2008; Zhu et al., 2009). All of these studies suggest that some kind of adaptive-like immune response must be present in shrimp. Further evidence of specific immune priming has also been provided by the protective specificity that is seen upon the second exposure to a pathogen in insects such as meal worm beetle, flour moth, bumblebee, fruit fly, and red flour beetle (Moret and Siva-Jothy, 2003; Rahman et al., 2004; Sadd and Schmid-Hempel, 2006; Pham et al., 2007; Roth et al., 2009). We note however, that even although immune response with specificity has been demonstrated in these arthropods, it is still not generally accepted that this implies the presence of immunological memory.

Although the mechanisms that underlie these phenomena are not yet well understood, if an invertebrate host is able to recognize a number of different pathogens with specificity, then a pathogen-specific receptor that is capable of high diversity is presumably required. In the last decade, germ-line-derived pattern-recognition receptors (PRRs) with an unexpected hypervariability have been found in a range of invertebrates, such as the 185/333 gene family in sea urchin (*Strongylocentrotus purpuratus*) and the fibrinogen-related proteins in snail (*Biomphalaria glabrata*) (Rast et al., 2006; Zhang et al., 2004). In arthropods, these characteristics are found in the Down syndrome cell adhesion molecule (Dscam), which exhibits extremely high variability generated from a single-copy gene through alternative splicing (Schmucker et al., 2000). However, if Dscam is to successfully emulate mammalian adaptive response, then the arthropod Dscam isoform population should be expected to shift in response to invading microorganisms and the Dscam isoforms must also function as pathogen-specific recognizing receptors. In this review, we focus on recent studies and observations that illuminate the possible regulation and immune function of this putative novel immune factor in arthropods, especially in shrimp.

2. Discovery of Dscam

2.1. DSCAM in vertebrates

DSCAM was first identified from the Down's syndrome critical region of human chromosome 21q22.2-22.3 (Yamakawa et al., 1998). It is a large protein (~220kDa), and it has more Ig domains than most other members of the immunoglobulin (Ig) superfamily (Human chromosome 11q23 contains another DSCAM-like molecule, DSCAML1, which has the same structure and is probably the result of gene duplication (Agarwala et al., 2001b), but this protein is not considered here). As Fig. 1 shows, the domain architecture of human DSCAM conforms to the following pattern: 9 Ig domains – 4 fibronectin type (FN) III domains – 1 Ig domain – 2 FNIII domains – transmembrane (TM) domain – cytoplasmic tail. In mammals, DSCAM is highly expressed in developing neurons of the CNS (central nervous system) and PNS (peripheral nervous system) (Fuerst et al., 2009; Schmucker and Chen, 2009). Vertebrate DSCAMs are involved in neuronal growth and development (Yamakawa et al., 1998; Fuerst et al., 2010), generation and differentiation (Agarwala et al., 2001a), axon guidance (Ly et al., 2008), self-recognition (Schmucker and Chen, 2009), and embryonic morphogenesis (Yimlamai et al., 2005). Mammalian DSCAM thus plays an important role in the correct formation of connections in neuronal networks (Yamagata

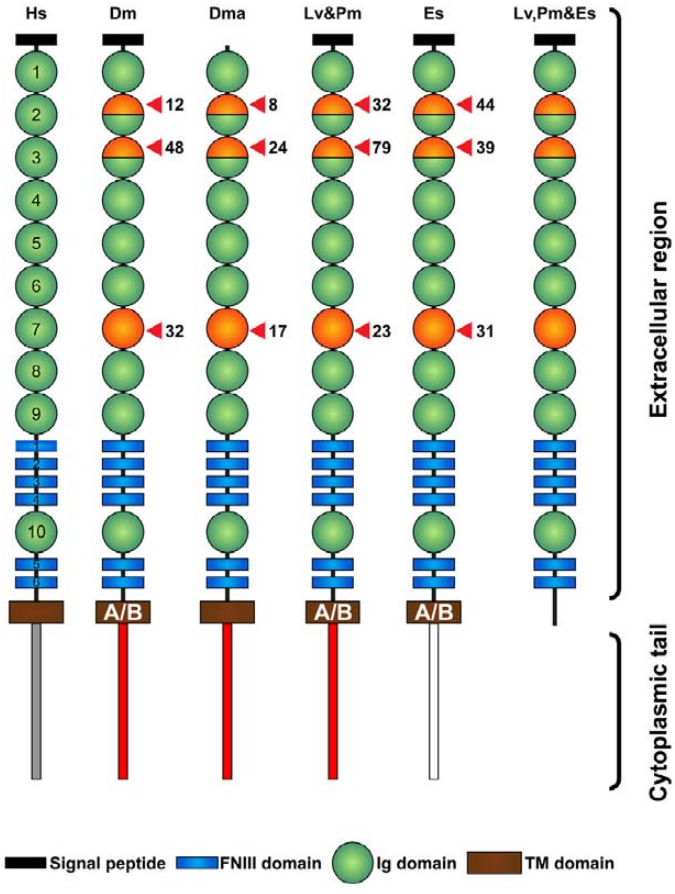

Fig. 1. Schematic comparing the Dscam domain architecture of several species and the locations of the alternatively spliced domains. Human DSCAM-like molecule and non-hypervariable arthropod Dscams are not included. *Homo sapiens* (Hs), *Drosophila melanogaster* (Dm), *Daphnia magna* (Dma), *Litopenaeus vannamei* (Lv), *Penaeus monodon* (Pm), and *Eriocheir sinensis* (Es). Variable Ig regions are colored orange, and the number of variants is indicated. Transmembrane (TM) domains that are labeled with A/B have two possible variants. Variable and invariable cytoplasmic tails are colored red and gray, respectively. The variability of the cytoplasmic tail of *E. sinensis* Dscam has not yet been investigated.