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Progress and Prospect of Dscam Gene in Drosophila Immunity

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Abstract: The cell adhesion molecule (*Dscam*) gene in Down syndrome is an extraordinary example of diversity: by combining alternative splicing exons, thousands of subtypes can be generated from just one gene. So far, this diversity of the gene has only been found in insects and crustaceans, and the basic part of neural connections has been well characterized as *Drosophila melanogaster*. More than a decade ago, evidence from *Drosophila melanogaster* indicated that the *Dscam* gene is involved in insect immune defense. However, we are still far from fully understanding the functions of *Dscam* in parasites and pathogens, as well as its full correlation with the immune system. In this article, we first briefly introduce the immune mechanism of fruit flies and the current research status of *Dscam*. Finally, the future research prospects of *Dscam* are summarized and proposed, with the aim of providing a multi perspective perspective to further study the relationship between this gene and immune defense in detail.

Keywords: *Drosophila*; Drosophila Immunity; *Dscam* Gene.

1. Introduction

The universality, low cost, short life cycle, clear genomic characteristics, and feasibility of genetic manipulation of fruit flies make them an indispensable model organism for basic research. The *Dscam* gene is a member of the immunoglobulin (Ig) superfamily. In *Drosophila melanogaster,* it plays a crucial role in neuronal wiring: it is an axon guiding receptor that ensures olfactory receptor neurons synapse at the correct target. Subsequently, the importance of subtype diversity in neuronal circuits and self-recognition was discovered. In 2005, Watson [2] and his colleagues discovered that depletion of *Dscam* protein could impair the ability of *Drosophila melanogaster* blood cells to phagocytose bacteria, prompting research on its potential immune effects in Drosophila and other crustaceans. It is speculated that the diversity of subtypes of Dscam protein can provide specificity for antigen recognition. The *Dscam* gene is particularly interesting because it encodes highly diverse and multifunctional, as well as because the neural and immune systems may exert different selection pressures on the gene. Since the discovery of the *Dscam* gene as a highly variable axon guiding receptor on the cell surface of *Drosophila melanogaster,* our understanding of its function in the nervous system and its evolution in arthropods has been widely expanded. However, we still have a far from complete understanding of the *Dscam* gene's function in the immune system [3,4]. Therefore, this article mainly reviews the research progress prospects of *Dscam* genes in fruit fly immunity by understanding the immune mechanism of fruit flies and the immune function of *Dscam* genes, with the aim of providing a detailed understanding of this gene from another perspective.

2. Organization of the Text

2.1. Innate Immunity in Drosophila

2.1.1. Humoral Immunity

The humoral innate immune responses in Drosophila mainly include the production of AMP and anti-pathogenic factors through the Toll, IMD, and JAK / STAT signaling pathways. The main role of the Toll pathway is to participate in Drosophila embryonic development. In 1995, Hultmark (Rosetto et al., 1995) [5] introduced in Toll (Toll-1) as a potent immune activator in Drosophila cell lines. Since then, the Toll pathway has been shown to be associated with immune defenses against a range of pathogens. Similar to the Toll pathway, the Drosophila IMD pathway mainly targets Gram-negative pathogens and plays an important role in humoral immunity through AMP production and pathogen clearance. The JAK / STAT signaling pathway controls various biological processes and tissue hemostasis in mammals and invertebrates, and also contributes to host humoral immunity. It is primarily activated upon microbial infection and / or cellular damage resulting from a stress response / pathogen infection, and ultimately produces regulatory molecules, and antiviral agents, and antimicrobial agents, including AMP [6].

2.1.2. Cellular Immunity

In addition to humoral immunity, cellular immunity is an important component of the innate immune system in Drosophila. As an important organ of Drosophila immunity, in which plasma cells (Plasmatocytes) and thin-layer cells (Lamellocytes) can exercise immune function through phagocytosis and capsule action. Phagocytosis involved in the uptake of apoptotic debris and the destruction of foreign pathogens by blood cells (plasma cells, crystal cells and sheet cells) represents the basic means of maintaining tissue homeostasis (Lemaitre and Hoffmann, 2007) [7]. Phagocyte surface recognition receptors are important for regulating phagocytosis, and multiple recognition receptors have been found in Drosophila, responsible for the recognition of different types of pathogens. They mainly include type I scavenger receptor (dSr-CI), CD36 family scavenger receptors (Peste and Croquemort), Nimrod family proteins (Eater, Drapper, and NimC 1), immunoglobulin superfamily proteins Dscam, thioester-containing TEPs (TEP 2-4 and TEP 6), and PGRP-LC [8]. Wnt signaling in Drosophila is also able to mediate phagocytosis, and Jumu, a member of the Fox

protein family, can regulate the occurrence of cell phagocytosis by mediating the expression of NimC 1 and the remodeling of the cytoskeleton. Encapsulation is another cellular response that aims to eliminate pathogens by forming blood cell capsules around the foreign body.[9]. Melanization is another immune response in insects characterized by melanin synthesis and phagocytosis of deposits around the microorganism. Melanization is also involved in wound healing, phagocytosis, blood coagulation, and AMP expression in arthropods [10].

2.2. Dscam Findings and Research

2.2.1. The Diversity of the Dscam Proteins

Dscam is a transmembrane protein on the cell surface. They are members of the immunoglobulin superfamily and consists of an extracellular domain, transmembrane domain, and cytoplasmic tails. The extracellular domain consists of 10 Ig domains and six FNIII domains. The diversity of Dscam proteins is mainly due to its variable domains [11]. The *Dscam* gene locus contains 115 exons, of which 95 are arranged in four clusters, namely, exons 4,6,9, and 17, consisting of 12,48,33, and 2 variable exons, respectively. Variable exons within each cluster are spliced in a mutually exclusive manner, potentially generating up to 19 008 isoforms encoding different classes of immunoglobulin domains (exons 4,6 and 9 clusters) with different adhesion properties and two different transmembrane domains (exon 17 cluster) [12]. Few genes encoding have such extreme molecular diversity, however, in species other than *Drosophila melanogaster,* direct homologous exon clusters sometimes have different numbers (e. g., exons 4,6 and 10 in Anopheles gambiae) [13], alternatively spliced exons across species encode the N terminus of Ig2 and Ig3 and the entire Ig7. These Ig domains are located in the extracellular portion of the protein. The mutually exclusive alternative splicing of exons encoding the extracellular region may result in the production of 124833 = 19,008 isoforms [14]. If exons 17 and exons 19 and 23 are included in the subtype diversity calculation, the estimates increase to slightly below 150,000 gene subtypes. This is an incredible diversity, expressed by only one gene [15].

2.2.2. Role of Dscam Proteins in Drosophila Immunity

The elucidation of the protein structure of *Drosophila* melanogaster Dscam suggests how a protein might function in the nervous system and the immune system, implying that there may be selective pressure from both systems. In the immune system, Dscam has been proposed for heterophilic binding to the parasites, and if it is involved in host-parasite interactions, then the selective pressure exerted by the parasite on genes may mean that the individual diversity of each alternatively spliced exon may be important, in contrast to the nervous system. The link between Dscam and crustacean immunity has been extensively reviewed over the past few years, and early studies in Drosophila melanogaster hypothesized that it may function as a signaling receptor or coreceptor during phagocytosis and possibly as an opsonin (i. e., binding to the pathogen surface to facilitate its phagocytosis) [16]. Over the past decade, the study of Dscam proteins in other arthropods such as Drosophila, mosquitoes have identified them as a highly variable pattern recognition receptor (PRR) essential to the innate immune system, mainly contributed by extraordinary splicing forms at the molecular level. As noted by many reviews in recent articles, the immune mechanism of Dscam is still unclear, with both advantages and disadvantages [17,18].

role as a phagocytic receptor; (4) signaling patterns indicated by the composition of its cytoplasmic segments. It is clear that Dscam is involved in immune defense in certain insects and crustaceans [19]. What can be determined is that Dscam binds the pathogen surface in Drosophila immunity to promote its phagocytosis, but whether there are other immunological effects remains to be investigated, and these studies can reveal the conditions under which Dscam responds or does not respond in an immunological context.

2.2.3. Research Prospects of Dscam in Immunity

Even in terms of the general nature of *Dscam,* many parts of the *Dscam*-mediated immunity puzzle are still missing. We still do not have intact Dscam responding to one or multiple stimuli with various immunostimulants at the mRNA level and protein level. As for the immune diversity of *Dscam*, the main question to be addressed is what are the factors involved in *Dscam* alternative splicing and which mechanisms support the production and maintenance of specific *Dscam* isoforms after pathogen challenge. Meanwhile, regarding the immune specificity of *Dscam*, we should not focus only on a specific highly expressed exonic variant, but rather investigate how the whole Ig2 / Ig3 / Ig7 combination participates in specific binding to the corresponding pathogen and other rest of the Dscam protein to the corresponding pathogen [20]. Other outstanding questions include: Which cell types can act as immunological memory cells? Are the specific *Dscam* isoforms expressed after pathogen stimulation generated only by specific cells? We still go a long way from answering these questions. The study of *Dscam*-mediated immunity also has practical significance. The clear understanding of *Dscam*-mediated immunity mechanism is the theoretical basis and scientific basis for the study of *Dscam* gene and other species immunity [21]. As an extension of the previous point, *Dscam* is peptide sequenced after infection with a pathogen or parasites to test the variability of alternate splice sequences at the protein level; to determine how long the protein lasts in the hematolymph (especially related to knockdown studies); to test whether *Dscam* is involved in changing primary and secondary pathogen / parasites with *Dscam* knock down before primary and / or second pathogen / parasites exposure [22]; further characterizing the effect of *Dscam* on the microbiota may be interesting. Therefore, we believe that further investigation of *Dscam* in Drosophila immunity has great potential and should be very encouraged.

3. Conclusion

In the above article, we first briefly introduced the immune mechanism of Drosophila, described the diversity of *Dscam* and the role of *Dscam* in Drosophila immunity, and finally summarized the future research prospects of *Dscam*, put forward part of different views and different research trends, in the hope that the conditions of *Dscam* to respond or not respond in the immunological background by further studying the role of *Dscam* in Drosophila immunity. It can also provide reference value for other aspects of research.

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