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Insect immunity: evolutionary roots of the mammalian innate immune system

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Abstract

The innate immune system of vertebrates was considered as a survival of ancient antimicrobial systems that have become obsolescent by the emergence of adaptive immunity. Despite the fact that innate immunity lacks the elegance of genetic recombination mechanism to produce trillions of specific clones of immune cells and shows no memory, that view is out of date. Today, the innate immune system is rather regarded to be essential to the function of adaptive immunity by dictating the conduct of the acquired immune response [1] with the help of cytokines, complement, lectin receptors, antigen-reactive T-lymphocytes and B7.1, B7.2 proteins on B cells [2]. This review focuses on recent studies of insect immunology and summarises the currently known similarities between the innate immune system in insects and in vertebrates.

Keywords: Review; Insect immunity; Evolutionary roots; Mammalian innate immune system

1. Introduction

Evidences for the power and wisdom of innate immunity emerged from studies of the ancient defence system of insects. Insects represent one of the most successful groups of evolution accounting for nearly one million species and 10^{18} individuals, and except for the seas they colonise all ecological niches. Consequently they cope with an extremely large variety of pathogens. During evolution insects developed a complex and effective innate immune system, which apparently differs from the adaptive immune system of vertebrates. However there is no evidence for clonal selection mechanisms in insects and their immune response shows no memory, their defence mechanisms are rapid, lasting up to a few days, and offering a particularly powerful resistance to microbial infections. It is appreciated that the host defence mechanisms of insects share many fundamental characteristics with the innate immune system of vertebrates [3–5].

2. Pathogens of insects

The pathogenic effect of bacteria and the antibacterial defence reactions have been investigated in insects [6], but infections caused by viruses [7–10], fungi [11,12], protozoa [13], nematodes [14], and multicellular parasites [15] became the object of recent interest.

3. The immune system of insects

Insects exhibit a particular resistance to infections. This resistance is due to the cuticle that forms a mechanical barrier effectively safeguarding against microbial invasion and to the innate immune reactions.

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The innate immune system of insects consists of organs composed of different types of cells plus a variety of cells circulating free in the hemolymph. To our present knowledge all the components of the insect immune system: the fat body, the lymph gland and the hemocytes originate from the mesoderm [16–18]. The fat body is made up of adipose tissue attached to the internal surface of the cuticle and distributed in all segments of the animal. It is a large biosynthetic organ, functional analogue of the mammalian liver [19] and responsible for the synthesis of antimicrobial peptides [20,21]. The lymph gland is composed of a few paired pericardial lobules, lying on the anterior end of the dorsal vessel and it is supposed to form hemocytes of larval and adult life [22]. The hemocytes are actively trafficking cells and thought to be involved in all defence mechanisms. The insect hemocytes have been classified by morphological criteria [23] but there is an increasing number of reports to characterise them by serological means using mAbs [24–29] or enhancer trap lines [30].

4. Immune reactions

It was understood in the early 1930s that the immune response of insects is manifested both as cellular and humoral reactions. In humoral defence processes three immediate reactions are triggered: melanisation, clotting of the hemolymph and the synthesis of antimicrobial peptides. In cellular reactions the microorganisms or the apoptotic cells are phagocytosed, entrapped by nodule formation, or encapsulated by hemocytes.

4.1. Humoral reactions

4.1.1. Melanisation

The formation of the black pigment, melanin is catalysed by the enzyme phenoloxidase, which is converted to its active form by a serine protease cascade (reviewed by Ashida et al. [31].) The inactive proenzyme, prophenoloxidase is synthesized in the hemocytes and after releasing by cell rupture it is either actively transported into the cuticle [32], or deposited around wounds and encapsulated parasites [12]. Prophenoloxidase has been purified and subsequently characterized from the hemolymph of a range of insect species [33–37]. Several recent investigations report the cloning of insect prophenoloxidases [38–40] and of the activating enzyme of the *Drosophila* prophenoloxidase [41]. The insect prophenoloxidase enzyme contains a sequence with similarity to the thiol-ester region of the vertebrate complement component proteins C3 and C4 [39].

4.1.2. Hemolymph clotting

In insects, two types of clotting mechanisms have been identified. One of them was described in the cockroach (*Leucophaea maderae*) [42] and the locust (*Locusta migratoria*) [43], where the polymerisation of clottable proteins is catalysed by a Ca^{2+} dependent transglutaminase released from the hemocytes. The clottable proteins are lipophorin [44] and vitellogenin-like proteins [45]. The latter contains a region homologous to the 'D' domains of the von Willebrand factor tangentially involved in the vertebrate blood clotting. The other type of coagulation has been best studied in horseshoe crab (*Lymulus polyphemus*), another arthropod, and there are suggestions for the existence of the same system in *Drosophila* [46,47]. In horseshoe crab, the LPS or the (1-3)-β-D-glucan mediated coagulation is activated by a three step serine protease cascade. The components of this reaction have been thoroughly characterised and found to contain complement-related domains, C-type lectin domain, epidermal growth factor-like domain [48], and structural similarity to the nerve growth factor [49]. The structural homology between the hemolymph clotting enzymes, the complement system and blood clotting of mammals raises the possibility of a common origin of all these proteolytic cascades. In addition, the serine protease cascades of insects play a dual role, since the intermediate components of hemolymph clotting (factor B and proclotting enzymes with defensin-like domains) [48] and melanin formation (quinones and superoxid anions) [50] are toxic to microorganisms.

4.1.3. Immune-proteins

The third humoral reaction to infection is the rapid de novo synthesis of a battery of antimicrobial peptides (reviewed by Boman [51] and Hetru et al. [52]). The principal site of synthesis is the fat body [19], but also the hemocytes [53], the cuticular epithelial cells [54], the gut [55], the salivary gland [56], and the reproductive tract [57,58] are able to produce antimicrobial factors. In the last decade the field of antimicrobial peptide research has grown considerably, today near to 60 peptide antibiotics have been described in insects. Although these peptides are diverse in structure, all mature peptides are amphipatic, basic molecules acting at membranes and thereby killing the target cell eventually by lysis [59,60]. In response to the infection insects synthesize a combination of their antibacterial peptides and they act in synergy by attacking different components of the bacterial envelope [61]. The insect antimicrobial proteins are grouped into families, based on structural and sequence similarities and their proposed target in the bacterial cell wall.

The attacin-like bacteria inducible proteins have been identified in butterflies [62,63] and in *Drosophila* [64]. These proteins are active only against Gram-negative

organisms, where they affect cell division mechanisms by inhibiting the synthesis of outer membrane proteins [65]. The family of these factors includes glycine-rich peptides (20–28 kDa) characterised by the presence of one or more copies of the G domain [4].

Lysozyme hydrolyses β-(1,4)-glycosidic bounds in peptidoglucan of bacterial cell wall. Insect lysozymes are proteins (14 kDa) with sequence similarity to vertebrate lysozymes. The lysozyme genes or cDNAs have been cloned in several insect species [56,66,67]. In *Drosophila*, the lysozymes are encoded by at least seven genes and expressed in different parts of the digestive tract and at different stages of development [55] (reviewed by Hultmark [68]).

Cecropins have antibacterial activity against both Gram-positive and Gram-negative bacteria since they interact with lipid membranes forming voltage-dependent ion channels [69]. The cecropins (4 kDa) are devoid of cystein, and exhibit a structure of two α-helices joined by a hinge-region [70]. Families of cecropin genes with some sequence differences have been found in butterfly species [71–73], in the flesh fly (*Sarcophaga peregrina*) [74] and in *Drosophila* [75]. A mammalian cecropin was identified in pig intestine [76] and bovine adrenal glands [77] which implies that cecropins may be widespread in the animal kingdom.

In contrast to the attacin-like antibacterial peptides, defensins attack mainly Gram-positive bacteria. They act on the cytoplasmic membrane and lyse the cells by formation of membrane channels [58]. Insect defensins are cationic peptides (4 kDa) containing six conserved cystein residues engaged in three disulphide bridges. They posses three distinct domains: an amino-terminal loop, an α-helix, and an antiparallel β-sheet [78]. About thirty defensins have been characterized in various insect species [79–84]. Although numerous defensins have been isolated from mammalians [85,86] and from plants [87], further analyses revealed that they are not homologous to the defensins of insects [88].

The proline-rich antimicrobial peptides lyse Gram-negative bacteria by increasing the membrane permeability [89]. They are peptides with molecular mass of 2–4 kDa, lacking cystein and containing at least 25% proline. The *O*-glycosylation at the threonin residues is essential for their biological activity. Apaedicins [90] and abaecin [91] from honey-bee, drosocin [92] and metchnikowin [93] from *Drosophila*, pyrrhocoricin [82], lebocin [89,94] and metalnikowin [95] belong to this family. Also the pig intestine [96] and bovine leukocytes [97] have been shown to produce proline-rich antibacterial peptides, although these peptides do not share sequence homology to the proline-rich peptides of insects.

Diptericins have so far been described only in dipteran species [98–100]. They are 9-kDa peptides containing both an attacin-like G domain, a C-terminal glycine-rich residue and a short N-terminal proline-rich region containing a consensus site for *O*-glycosylation [101]. Diptericins are lytic for Gram-negative bacteria which may be due to a way of action similar to that of attacins.

Other inducible antibacterial proteins have been isolated from insects not fitting into the groups described above. Coleoptericin [79], holotricin-2 [102], hemiptericin [82], and gallysin-1 [103] act on Gram-negative bacteria, while moricin [104], thanatin (homologous to frog-skin antimicrobial peptides of the brevinine family) [105], and hymenoptaecin [106] can lyse both Gram-negative and Gram-positive bacteria.

Recently, inducible peptide antibiotics against fungi have been discovered in insects. The peptides named AFP [107], tenecin-3 [108], and holotricin-3 [109] share sequence similarities while drosomycin [110] shows a significant homology with a family of plant antifungal peptides. Furthermore, the antibacterial peptides metchnikowin and thanatin have antifungal activity [93,105].

During the past few years it has become apparent, that the humoral immune response of insects parallels the mammalian acute phase response. The acute phase response of mammals is stimulated by tissue injury or bacterial challenge and characterized by the immediate synthesis of acute phase proteins mainly in the liver and in cells of the innate immune system. The synthesized proteins act as opsonins, blood clotting and wound healing factors. In insects, the rapid humoral immune reactions are also triggered by wound or microbial infection. They involve proteolytic cascades leading to hemolymph clotting and the rapid de novo synthesis of antimicrobial peptides by the fat body, the functional analogue of the mammalian liver, and the hemocytes.

The immune genes coding for insect immune proteins have been found to contain regulatory sequences similar to the binding site for the mammalian member of the Rel family of transcription factors, NF-κB [80,111–114], which is an enhancer for genes participating in inflammatory and acute phase response [115] (reviewed by Hultmark [4], Meister et al. [116] and Engström [117]). In insects, the transcription factors homologous to NF-κB are: the cecropia immunoresponsive factor (CIF) of the giant silk moth (*Hyalophora cecropia*) [118], Dorsal [119], Dorsal-related immune factor (Dif) [120], and Relish [121] found in *Drosophila*, and Gambif-1 [122] a Dorsal homologue of the malaria vector mosquito (*Anopheles gambiae*). In addition to the NF-κB element, the upstream region of the diptericin gene exhibits sequence similarities to the mammalian NF-IL6 response element and to a core motif (GAAANN) of the interferon-sensitive response element of mammals [123]. The protein binding to the GAAANN motif was identified in *Drosophila* and serological similarity was found between the insect DNA-

binding factor and mammalian IRF-1 which recognizes the GAAANN motif [124].

In *Drosophila*, the three Rel proteins binding to NF-κB-like regulatory sequences have been found to activate different antibacterial genes [125–127]. Dorsal can heterodimerize with Dif in vitro [127] and can be converted from an activator to repressor [128]. In addition, an immune-deficient mutation (imd) has been characterized in *Drosophila* and causes reduced level of transcription of antibacterial genes, whereas the expression of the antifungal protein, drosomycin is not affected [129]. These data reveal the complexity of the regulatory system of insect immune proteins and the possible existence of more than one signalling pathways. The latter provides additional similarity to the mammalian acute phase response which is induced by at least two cytokines, IL-1 and IL-6 [130].

The homology between insect humoral immune reactions and vertebrate innate immune system is supported further by the existence of various antimicrobial peptides isolated recently from amphibian skin [131], avian and mammalian leukocytes [132,133], bovine epithelia [134], human blood [135], bone marrow and testis [136] (reviewed by Martin et al. [85]).

4.2. Cellular reactions

4.2.1. Phagocytosis

Unlike the mechanism of phagocytosis in vertebrates [137], little data is available regarding the molecular aspect of phagocytosis in insects. Cells with phagocytic activity usually represent a subpopulation of insect hemocytes. Both granular cells and plasmatocytes are supposed to be primarily responsible for phagocytosis [138].

The cell surface molecules described on phagocytic hemocytes exhibit striking similarities to the receptors found on mammalian phagocytic cells. Insect proteins Malvolio [139] and dSR-CI [140] show homology to mouse natural resistance-associated macrophage protein-1 (NRAMP-1) and mammalian class-A macrophage specific scavenger receptors, respectively, and croquemort [141] is a member of the CD36 superfamily. Similarly to CD36, croquemort mediates the recognition of apoptotic cells. In *Drosophila*, another protein named peroxidasin is supposed to participate in the phagocytic breakdown of apoptotic cells [142]. Peroxidasin is homologous to mammalian macrophage peroxidases and contains four immunoglobulin-like C2 domains including a single IgA1 hinge region.

All these homologies suggest that phagocytic cell types arise from a common ancestor with a strict conservation of important molecules [139], and elucidate the basic importance of phagocytosis. This view is supported further by a recent finding that human B-1 lymphocytes are able to transform into phagocytic macrophage cells [143]. Thus, B-1 cells represent prelymphocytes combining the specificity of the adaptive immune system with an innate defence mechanism—phagocytosis [144].

4.2.2. Nodule formation

During nodule formation insect hemocytes aggregate to entrap bacteria. Nodules can attach to tissues or may be encapsulated. An insect lectin, named scolexin was found to be involved in the formation of nodules in the tobacco hornworm (*Manduca sexta*). Scolexin is produced by epidermal and midgut cells upon wounding or bacterial infection [145]. In the medfly (*Ceratitis capitata*), a protein with molecular mass of 47 kDa is secreted by hemocytes after LPS stimulation and aggregates *E. coli* cells by the presence of tyrosine and tyrosinase [146].

4.2.3. Encapsulation

Encapsulation is a multicellular defence mechanism where a capsule of overlapping layers of hemocytes is formed around protozoans, nematodes and eggs or larvae of parasitic insects. Encapsulation does not induce the expression of antimicrobial genes [147] but it may associate with melanisation which contributes to the killing of the invader [50,148].

It is still unclear whether the reaction is mediated by a given subset of hemocytes or through an interaction between different subpopulations of immune cells [149–151]. In both cases adhesion molecules are essential to the capsule formation. By analogy to vertebrates, the existence of various integrins in *Drosophila* [152] raises the possibility that these molecules can participate in the cellular reactions of insects. Moreover, the encapsulation response of the moth *Pseudoplusia includens* was found to involve an RGD (Arg-Gly-Asp)-dependent cell adhesion mechanism which is typical for integrins [153].

Parasites have developed various mechanisms to circumvent the encapsulation reaction of host insect. During oviposition endoparasitic wasps inject polydnaviruses which suppress the immune system of the host, thus ensuring successful development of the immature endoparasite [154] (reviewed by Summers et al. [155] and Beckage [156]). In the genom of mosquitoes, quantitative trait loci (QTLs) involved in encapsulation process have been localised [157,158].

In many mutations in *Drosophila*, melanotic tumors can be observed as black masses of tissues [159]. These mutations may or may not show overgrowth phenotype and can associate with hemocyte overproduction and the overgrowth of the lymph gland [160,161]. During the tumor development the hemocytes form a capsule around the self tissue and deposit melanin in it. In this case the encapsulation is directed against the organism itself (reviewed by Gateff [162] and Watson et al. [163]).

5. Signals and receptors

The innate immune processes of insects are triggered by a great variety of signals. Microbia, microbial substances, mitogens (arachidonic acid, phorbol esters and phytohemagglutinin [164]) and the injury of the cuticle are exogen factors leading to the activation of both humoral and cellular defence mechanisms. Among microbial substances, LPS [165], laminarin [166], (1-3)-β-D-glucans [167], peptidoglucan [168], zymosan [169], and flagellin [170] have been found to induce immune reactions in insects.

The endogenous factors regulating the cellular immune reactions in insects are poorly known. Hormones are best candidates for being the main modulators of these processes, although the only evidence supporting this idea is the finding that 20-hydroxyecdysone enhances phagocytic activity of *Drosophila melanogaster* hemocytes in vitro [171]. *Drosophila* hemocytes synthesize the glycoprotein DS47 which is homologous to mammalian secretory proteins produced by activated macrophages [172]. The hemocytes of the silkworm release LPS during phagocytosis which leads to the activation of genes coding for antibacterial proteins [173]. Similarly to vertebrates, biogenic amines [174,175], cytokine-like factors (hemokines) [176,177], eicosanoids [178,179], and H_2O_2 [164] can modulate insect cellular immune responses (reviewed by Gillespie et al. [180]).

Soluble receptors for bacteria, LPS or (1-3)-β-D-glucan have been shown to activate both humoral and cellular defence reactions. These findings point to the existence of opsonisation mediated recognition mechanisms in insects. The hemocytes and fat body of the giant silk moth secrete a protein named hemolin that binds to the surface of bacteria and hemocytes [181,182] and subsequently activates a signalling pathway involving protein kinase C and protein tyrosine phosphorylation [183]. Hemolin is a member of the immunoglobulin superfamily and participates in a protein complex formation on the bacterial surface that is likely to initiate phagocytosis. The Gram-negative bacteria binding protein (GNBP) of insects [184,185] shows serological cross-reaction and sequence similarity to the mammalian LPS receptor, CD14. In insects, LPS binding proteins have been isolated from the hemolymph of the American cockroach [186] and of medfly [146]. The LPS binding protein of cockroach contains a carbohydrate-recognition domain of C-type animal lectins [187] and acts as an opsonin [188]. Another protein, hemocytin identified in the silkworm (*Bombyx mori*) contains several repeated sequences similar to the repeated regions of von Willebrand factor, and a lectin domain homologous to mammalian mannose-binding protein [189]. Some other lectins binding various oligosaccharides have also been purified from insect species [190–193].

The cell surface receptors participating in innate immune response of insects are non-clonally distributed on the immune cells and recognise not only a specific antigenic determinant, but also certain characteristics or patterns common on infectious agents, but absent from the host [194]. The receptors, hemomucin [195] and FKBP39 [196] of *Drosophila* bind *Helix pomatia* lectin (activator of T-lymphocytes) and the immunosuppressive drug FK506, respectively. The membrane bound receptors for 5-hydroxytryptamine [197] and LPS [198] activate signal transduction events through adenylate cyclase and tyrosine phosphorylation, respectively. The receptors involved in phagocytosis (malvolio, dSR-CI, croquemort) and their homology to mammalian innate immune receptors is mentioned above. The homology between malvolio and NRAMP-1 suggests that the nitric oxide pathway of mammalian macrophages may exist in insect hemocytes.

The most impressive homology to a signal transduction pathway of the mammalian immune system was described in *Drosophila*. The transmembrane protein, Toll controls the dorsal-ventral patterning in *Drosophila* embryos [199] and upon binding its ligand Spätzle activates genes of antimicrobial proteins through the Toll-Dorsal signalling pathway [200–202]. Spätzle shows homology to the coagulogen, the clotting protein from Horseshoe crab [49] suggesting the possible link between different humoral processes of insects. The signalling through Toll parallels the signalling pathway induced by the IL-1 Receptor (IL-1R) in mammalian cells. All the members of the Toll-Dorsal pathway have been found to exhibit apparent homology to its known counterpart of the mammalian IL-1R–NF-κB signalling pathway [203–207] (reviewed by Hoffmann et al. [3], Medzhitov et al. [5] and Hultmark [208]). In addition, the Toll receptor is related to the *Drosophila* 18-wheeler, a transmembrane protein involved in antibacterial gene regulation [209,210], to the mammalian macrophage differentiation marker MyD88 [211], and to the Tobacco Mosaic Virus resistance gene N of tobacco [212]. The human homologue of the Toll protein (hToll) have recently been cloned in human and found to be involved in the production of inflammatory cytokines as well as the costimulatory molecule B7.1 [213].

6. Summary

The sophisticated genetics and cytogenetics of insects help us to obtain deeper insight into the ancient innate immune defence mechanisms. They offer unique opportunities to get closer to the roots of the mammalian innate immunity. As a result of the precise description of the innate immune system we will understand what makes an antigen immunogenic, both dangerous and

not dangerous. This will permit the development of more effective vaccines and therapies for autoimmunity, tumors and infectious diseases in the future.

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