Insect Defense System and Immunosuppression Strategies of Entomopathogenic Nematodes - An Overview

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Abstract—Studies on host-parasite interaction and immune responses in insects will greatly benefit human health from biocontrol point of view. Role and relationships between insect hosts and entomopathogenic nematodes are elaborated where the efficacy of the entomopathogenic nematodes depends on the stability between the parasitic strategies and the immune response of the host. Entomopathogenic nematodes are potential biocontrol agent. The cellular and humoral responses are avoided by the nematode-bacterium complexes by producing immunodeficiency in insects. The review outlines the mechanisms of immune recognition and defense of insects as well as immune evasion strategies of Entomopathogenic nematodes (EPNs).

Keywords—Insect immune response, Entomopathogenic nematodes, Cellular and humoral immune response, Immunosuppression, evasion.

INTRODUCTION

Innate immunity is common to all metazoans and serves as first-line defense against foreign antigens. Insect possess a potent innate immune system by which they attempt to resist microbial infections and parasitic invasions. Host innate immunity plays a central role in detecting and eliminating microbial pathogenic infections in both vertebrate and invertebrate animals. Entomopathogenic nematodes (EPNs) are used as biological control agents against wide range of insect pests and vectors of pathogen. EPNs are classified into two genera: Steinernema and Heterorhabditis. The EPNs Steinernema spp. and Heterorhabditis spp. infective juvenile stage (IJ) harbors the symbiotic bacteria Xenorhabdus spp. and Photorhabdus spp., respectively in their intestine. Once IJs infect a host through natural openings such as the mouth, anus, and spiracles, they can release symbiotic bacteria into the haemocoel of the host, causing insect death within 24-48 h post infection. To survive within the insect and complete their life-cycle, EPNs use some tactics to suppress the host immune responses.

The suppression of the host immune system is essential for successful infection and the death of the host. Biological control agents may affect ecological fitness of the insects due to behavioral, morphological, and physiological changes (Girling et al., 2010; Kunc et al., 2017).

1.1. Behavioral resistance: Behavioral resistance occurs when the insect actively avoids or repels the nematode.

• Extremely active mosquito species had a lower prevalence of infection by the mermithid Romanomermis culicivorax than less active ones, Petersen (1975).

• A high defecation rate that reduces infection via the anus (scarab grub). Low CO$_2$ output or CO$_2$ released in bursts that minimize chemical cues (lepidopterous pupae and scarab grubs (Potter and Held, 2002)).

• Walling-off nematode killed individuals that avoid or reduce contamination tooher insects in a termites mound ; When nematodes are applied to termite colonies, the workers are able to recognize infected individuals and isolate them behind earthen barriers (Baimey et al., 2017).
1.3. Physiological resistance: Hemolymph of insects is a medium for several physiological processes like immune responses and intermediary metabolism. Enzymatic changes in infected larvae would envisage the metabolic stress of the insect experience during the development of pathogen. Insects exhibit cellular and humoral immune responses against various pathogens including microorganisms and multicellular parasites. Hillyer (2016) indicated that the insects have developed sensitive mechanisms for detecting the presence of microbial infections and activating signalling pathways that control the production of molecules with antimicrobial activity. Innate immune response of insects is traditionally divided into two main group factors including the following (i) humoral factors i.e., melanization , synthesis of antimicrobial peptides(AMPs) and (ii) cellular defense reactions (i.e., nodule formation, phagocytosis, or encapsulation by hemocytes) (Vilmos and Kurucz ,1998).

By recognition of non self (microorganisms or metazoans) and rapid effector mechanisms that involve several cell mediated and humoral processes. All the processes are triggered by free and membrane-bound Pattern Recognition Receptors (PRRs) capable of specifically binding to Pathogen Associated Molecular Patterns (PAMPs). PAMPs are molecules that are common to groups of pathogens and are recognized by free or cell associated receptors (PRRs) in all animal species. The prototypical PAMPs are the molecules secreted or derived from the surface of bacteria or fungi.

Host defenses and immune reactions in response to EPN infection have been studied only in a few EPN species-insect species combinations (Lewis and Clarke, 2012; Shapiro-Ilan et al., 2018).

The innate immune system in insects comprises two central and several peripheral tissues

A. The central tissues are:

1. The circulating fluid is called hemolymph which is freely distributed in an open circulatory system. The insect immune system consists of the fat body, which secretes effector molecules into the hemolymph and several classes of hemocytes, which reside in the hemolymph and of protective border epithelia. The main function of the fat body within the immune system is to release soluble factors into the hemolymph. Some of the factors are produced constitutively others only after immune stimulation. Humoral defences were also reported which includes the production of antimicrobial peptides (e.g., cecropins, attacins) (Lowenberger 2001; Manniello et al., 2021); the pattern recognition protein lysozyme , reactive intermediates of oxygen and nitrogen (Bogdan et al.,2000; Shrehan et al.,2020); activation of the prophenoloxidase cascade and phospholipase A2 (PLA2) (Hoffmann et al., 1996; Gillespie et al., 1997; Söderhall and Cerenius 1998; Kanost et al., 2004; Müller et al., 2007). Induction of their
transcription is achieved via the Toll and imd pathways which are located downstream of recognition molecules that bind microbial elicitors such as peptidoglycan and beta 1,3 glucan (Davis and Engstrom, 2012). Peptidoglycan recognition protein binds to its respective elicitor and results in the production of inactive prophenoloxidase (proPO). Phenoloxidase (PO) is one of the key enzymes activated via prophenoloxidase (PPO) cascade in the cuticle or the hemolymph of many insects in response to the immune challenge (Marmaras et al., 1996; Gillespie et al., 1997; Gillespie et al., 2000; Castillo et al., 2011). PO catalyzes the melanin coat around encapsulated pathogens and produces chemically reactive quinones that are toxic to microbial pathogens (González-SantoYo and Córdoba-Aguilar, 2012). Glutathione S-transferase (GST) and esterase (EST) are the major enzymes involved in detoxifying penetrating xenobiotics in insects (Fan et al., 2013). Dunphy and Halwani (1997) isolated two LPS-binding proteins (LBP-1 and LBP-2) in the hemolymph, that are specific for the bacterial surface and acts as endotoxin detoxifier, thus protecting hemocytes from damage in Galleria mellonella. Increased detoxifying enzyme activities against mycoses and other infections represent the insect’s response to bodily intoxication by metabolites or the host-tissue-degrading products of pathogens (Serebrov et al., 2001).

2. In insects, hemocytes freely circulate in the hemolymph, or are localized in specific regions of the body. The highly variable composition of hemocyte types amongst insect species reflects an adaption to their respective environment and its specific pathogens. Thus the prevalence of a particular set of immune cell types appears as an ecological trade-off indicating the necessity to allocate resources to the dominant immune challenges. Pro-hemocytes, granulocytes, plasmatocytes, spherulocytes and oenocytoids are common type of hemocytes in Lepidoptera. In Dipteran insect lamellocytes, cells with crystalline inclusions and plasmatocytes are present. In Drosophila, two prophenoloxidase (PPO1 and PPO2) are harbored by a specialized class of hemocytes (crystal cells) while a third one (PPO3) is produced by lamellocytes. Certain TEPs in D. melanogaster were shown to play a regulatory role of modulating phenoloxidase and melanization reactions responses by inducing humoral and cellular immune activities against Photorhabdus pathogens, these molecules also form a reliable indicator for their potential multipurpose involvement in linking host immunity and metabolism in the presence of pathogenic bacteria. Cellular immunity in D. melanogaster larvae and adult flies is controlled by the different types of hemocytes, which specialize in various immune activities that mainly include the detection, phagocytosis, and encapsulation of pathogens.

In S. exigua, the major haemocyte types reacting against bacteria include the granulocytes and plasmatocytes which respond to particulate antigens by phagocytosis and nodulation. Lavine and Strand (2002) reported plasmatocytes and granulocytes are known to be capable of recognize, adhere to and spread on foreign surface that are phagocytic in Lepidoptera. Six types of haemocytes were identified in G. mellonella by Boman and Hultmark (1987). Physiological defenses in chrysomelid beetles and mosquitoes frequently result in encapsulation and melanization of infective juveniles after penetrating the hemocoel. Haemocytes in presence of foreign targets are activated by the presence of PAMPs and/or endogenous soluble factors and initiate complex mechanisms such as intracellular signal transduction which activate the specific immune genes and initiates defense mechanisms such as phagocytosis, nodulation , encapsulation , synthesis of antimicrobial peptides and cell-mediated melanization (Chapman, 1998; Schmidt et al., 2001; Williams, 2007; Strand, 2008; Krzemien et al., 2011; Li et al., 2021).

Melanization also termed as humoral encapsulation is an efficacious defense mechanism in insect. Melanization is due to the activity of an oxidoreductase called phenoloxidase (Kanost and Gorman, 2008). This molecule is the terminal enzyme of a complex system of proteases (protease cascade), proteases inhibitors (serpins) and PRRs, constituting proPO-AS (Freitak et al., 2007; Castillo et al., 2011). ProPO-AS is the key element in the recognition of foreign bodies, an integral component of the insect immune system. Prophenoloxidase is converted into its active form by a limited proteolysis, and when activated phenoloxidase can oxidize phenols into quinines that in turn autocatalyze into melanin. S.feltiae infection in G.mellonella suppresses PO activity by interfering with LPS-mediated ProPO activation pathway in G.mellonella larvae (Brivio et al., 2002).

Phagocytosis is a process that can be envisioned as a specialized form of receptor-mediated endocytosis resulting in the internalization of foreign body. Apolipophorin III (apoLp-III), and Arylphorin, heat stable protein, isolated from the haemolymph of G.mellonella larvae enhances the phagocytic activity of isolated haemocytes(Gotz et al., 1997).

Nodulation: In the presence of many bacterial cells or fungi, hemocytes degranulate releasing humoral factors that form aggregates, called nodules, this process lead to the entrapping of foreign cells. Such nodular aggregates may adhere to host tissues and larger nodules may be encapsulated by the hemocytes.
Encapsulation: When the foreign invaders are too large to be phagocytized, they can be encapsulated by multiple layers of hemocytes. These hemocytes can produce a coat of melanin. The humoral PRRs are needed to stimulate the aggregation of plasmocytes on the surface of the target by formation of multicellular layered thick capsule that segregates the foreign organisms. The toxic effects of melanin, which is present inside the inner layers of the capsule, may contribute to kill the entrapped organism.

Cellular encapsulation and capsule melanization of EPNs in CPB is documented (Ebrahimi et al., 2011). Hemocytes from the Japanese beetle strongly encapsulated and melanized the *H. bacteriophora* HP88 strain, *S.glaseri* FL strain, *S.scarabaei* and *S.feltiae*. *H.bacteriophora* was intensively melanized in *E.orientalis*, *P.japonica* and *C.borealis*. *S.glaseri* NC strain suppressed the immune responses in *M.sexta*, *E.orientalis* and *P.japonica*, whereas as *S.glaseri* FL strain was less successful (Li et al., 2007). A *Heterorhabditis* species avoids encapsulation in tipulid larvae by exsheathing from the second-stage cuticle during host penetration (Peters et al., 1997). Peters and Ehlers (1997) examined the pathogenicity of *S.feltiae* and its symbiont *Xenorhabdus bovienii* to the crane fly (*Tipula oleracea*). *X.bovienii* is triggering the encapsulation response.

B. Peripheral tissues comprising the tracheae, the epidermis, the gonads, and the gut epithelium rely on the more locally restricted release of effectors such as prophenoloxidase and antimicrobial peptides and on the production of reactive oxygen species to varying extent.

**Immunosuppression strategies of Entomopathogenic nematodes:**

Entomopathogenic nematodes have developed strategies to avoid or suppress the insect immune system by preventing or disrupting the activation of immune responses to promote their survival in the host (Cooper and Eleftherianos, 2016). EPNs species shared immunosuppression strategies, mainly mediated by their symbiotic bacteria, but there are differences in mechanism of evasion and interference of the nematode with the insect host immune pathways. Once a host has been located, recognized, and penetrated, the nematode’s attack may still not succeed if the insect is able to respond with an effective immune response.

Penetration into the insect host is the first step of the EPN infection process. The infective juveniles have to penetrate through the cuticle (including the trachea) or gut to enter the hemocoel. To enter through the cuticle, the nematodes employ physical force such as body thrusting to rupture through the thin trachea or, as with *Heterorhabditis*, use an anterior tooth to penetrate directly. To enter through the gut, they use physical force and/or proteolytic secretions to digest the midgut tissues to gain access into the hemocoel (AbuHatab et al., 1993) EPNs produce bioactive molecules referred to as excreted/secreted products (ESPs). ESPs contain various products that have functions related to other biological processes, e.g., nematode development, social behavior and nematode communication. Some of the molecules described in *S. carpocapsae* play a role in the penetration of a host (e.g., aspartic protease Sc-asp113 and Sc-asp155). It has been reported that *S. carpocapsae* was able to suppress the immune response by secreting proteins, which may facilitate the release of their symbionts (Bowen et al., 1998; Elias et al., 2020). However, it was unknown whether similar proteins were produced by *Heterorhabditis* (Forst and Clarke, 2002). Different species of nematodes induce various immune responses in different insect hosts, which probably are correlated with the differences in surface coat proteins of the nematodes. *S. glaseri* is initially encapsulated by larvae of the Japanese beetle, *Popillia japonica*, but it escapes from the capsule and successfully infects its host (Wang et al., 1995) because the nematode has surface coat proteins (SCP) that suppress the host’s immune response and lyse the hemocytes (Wang and Gaugler, 1998). Once inside the host, IJs may overcome the host’s immune response by shedding of the second-stage–juvenile cuticle (sheath). Within the insect’s hemocoel, the nematodes and bacteria overcome the host’s immune response (Duphny and Thurston, 1990; Kaya and Gaugler, 1993) that involves interacting humoral and cellular factors. Infective juveniles of *S. carpocapsae* and *H. bacteriophora* release protease secretions which destroy the antibacterial factors of vaccinated *G. mellonella* larvae (Gotz et al., 1980). Balasubramanian et al. (2010) purified a trypsin-like secreted protease from *S. carpocapsae* that suppresses the prophenoloxidase (pro-PO) in *G. mellonella*. ESPs produced by *H. bacteriophora* have the ability to inhibit the melanization of *G. mellonella*. The enzymatic activity of ESPs remained the same regardless of nematode age. In *S. carpocapsae*, inhibitors of both humoral and cellular immune responses have been described. SCP protect *H. bacteriophora* from immune response in *Popillia japonica* and *Exomal orientalis* (Li et al., 2007) and some act as immune modulators (e.g., metalloprotease Sc-AST, chymotrypsin serine protease, BPTI-Kunitz family inhibitor and Sc-SP-3. Genes sc-asp113 and sc-asp155, encoding aspartic proteases, are up regulated at the beginning of the parasitic phase, and are probably involved in the disruption of the host tissue. Additionally, the astacin metalloprotease Sc-AST, could participate in the parasitic process of *S. carpocapsae*. Chymotrypsin serine protease, identified in the ESPs of *S. 
can inhibit prophenoloxidase and the subsequent encapsulation and activation of melanization of Galleria mellonella (Gulley et al., 2013; Veillard et al., 2016). Haemolysin activity was shown by both genera (Brillard et al., 2002). Similarly, the BPTI-Kunitz family of inhibitors (Sc-KU–4), not only causes inhibition of encapsulation, but also impairs the aggregation of hemocytes. Furthermore, some molecules produced by nematodes can contribute to virulence through their role in the regulation of development, e.g., lamanin, structurally diverse derivates of the 3,6-dideoxysugar ascarylose , acyl-CoA oxidases and the small pheromone molecule ascaroside C11 ethanolamide . The Mexican strain of Neoapectana carpocapsae help the bacteria X.nematophila by excreting an immune inhibitor that selectively destroys both forms of P9 and P5 immune protein of diapausing pupae of Hyalophora cecropia . ESPs produced by H. bacteriophora can inhibit PO-catalyzed melanization in G. mellonella larvae. H. bacteriophora produces a spectrum of ESPs with different functions, and some play a role in virulence.

Following host penetration, the release of bacteria by nematodes is usually delayed in the host by 30 min for Heterorhabdus species and several hours for Steinernema nematodes .There is thus a possibility for the insect to neutralize its parasite before the bacterial challenge. Many immune factors have been shown to vary in the hemolymph of the host following the entry of nematodes, including both humoral and cellular responses. Bacteria can then suppress immune attacks of insect hosts to protect themselves and their symbiotic nematodes. Under immunosuppressive conditions, these bacteria can multiply in the hemocoel and kill insects by septicemia or toxemia. Secretion of insect toxins, outer membrane proteins, other extracellular products, and the release of lipopolysaccharide (LPS) molecules from the bacterial envelope lead to the death of the host (Owuama,2001). Symbiotic bacterial toxins have been shown to cause actin polymerization, destabilizing the cytoskeleton architecture of haemocytes (Li et al., 2009). The decline in the density of all haemocyte types in Galleria mellonella Lineaus larvae resulted from the lipid A moiety of LPS was thought to be cytotoxic to haemocytes (Dunphy and Webster 1991). Photorhabdus used LPS modification to resist the action of the host-derived AMPs (Eleftherianos et al., 2006), but X. nematophila prevents induction of insect AMP expression altogether .

Subsequently, nematodes can develop and reproduce in the insect cadaver. To induce immunosuppression, symbiotic bacteria of EPNs can inhibit phospholipase A2 (PLA2) to shutdown eicosanoid biosynthesis of target insects (Stanley and Kim, 2018). Eicosanoids affecting aggregation of haemocytes, haemocyte migration, and release of prophenoloxidase from oenocytoids. The OMPs of X. nematophila and P. luminescens decreased PLA2 activity and probably prevented eicosanoid biosynthesis, since Anti microbial peptide (AMP) expression in S. exigua by eicosanoid pathway is inhibited by intact X. nematophila . Brivio et al. (2004) suggested that S.feltiae body surface plays an important role in the early parasitization phase. S.feltiae alone activated the enzyme, a GroEL-like toxin from Xenorhabdus budapestensis which activates PO in G. mellonella larvae. Yang et al., (2012) implies in H. armiger, X. nematophila complex to activate the enzyme. Yamanaka (1995) examined pathogenicity of several species and strains of Xenorhabdus spp. against Spodoptera litura. Pathogenicity varied depending on phase of the bacteria as well as production of biochemical exudates. Previous immunological studies of the X.nematophila- S.carpocapsae interaction have focused on their ability to jointly kill an insect (Goodrich-Blair and Clarke, 2007). Specifically, X.nematophila produces compound, rhaddbuscin which inhibits phenoloxidase and benzylidene acetone, which suppresses antimicrobial peptide production in insects (Hwang et al., 2013). Reproduction of entomopathogenic nematodes requires that they escape recognition by a host’s immune system or that they have mechanisms to escape encapsulation and melanization. In pathogenic bacteria, some OMPs have been identified as virulence factors overcoming host immune activities (Darsouei et al., 2019). Inducible OMPs in Xenorhabdus and Photorhabdus were identified, including the stress response proteins skp in P. temperata . X. nematophila produces Opns, an inducible protein of provide growth advantage in insect hemolymph. Several bacterial insecticidal factors characterized in X. nematophila and P. luminescens (Txp40 toxin, Tc toxin, 17-kDa pilin protein) have important roles bacterial virulence and hence EPNs efficacy(Bowen et al., 1998). The toxin complex a (Tca) purified by Blackburn et al., (1998) from P. luminescens has specific effect on the midgut epithelium of the insect Manduca sexta. Barbieri et
al., (2002) have showed that bacteria have evolved numerous toxins and delivered type III effector molecules which can interfere with the actin cytoskeleton and inhibit phagocytosis.

The insect cadaver becomes deep red but does not putrefy, apparently because of an antibiotic(s) produced by the bacteria (Webster et al., 2002) viz., stilbene antibiotic, 3,5-dihydroxy-4-isopropylstilbene. Anthraquinones are metabolites of bacteria and only 1,3,8-trihydroxy-9,10-anthaquinone and two of its monomethyl ether derivatives, 1,8-dihydroxy-3-methoxy-9,10-anthaquinone and 3,8-dihydroxy-1-methoxy-9,10-anthaquinone, have been recorded from P. luminescens. These pigments have antimicrobial activities; function as antagonistic agents against colonization from other microorganisms in the insect cadaver.

Dowds and Peters (2002) reported that the bacteria and nematodes cooperate with each other to overwhelm the host’s immune response, permitting the bacteria to multiply vegetatively. Binda-Rossetti et al., (2016) demonstrated in their experiments with S. carpocapsae and X. nematophila that infection with live nematodes and bacteria can suppress the antibacterial peptide immune response of red palm weevil Rhynchophorus ferrugineus, but the inhibitory effect was not present when insects were injected with dead microorganisms. ESPs of H. bacteriophora suppress the expression of the Dipter cin gene in D. melanogaster. This suppression could help the symbiotic bacteria P. luminescens to survive and overcome the insect immune defenses.

Secondary metabolites produced from symbiotic bacteria result in the activity of insect PO and generation of reactive oxygen species (ROS). These free radicals are highly reactive and result in harmful effects on cells and tissues in organisms. For example, in Manduca sexta, P. luminescens cells secreted an antiphagocytic factor that permitted the bacterial cells to obstruct their own phagocytosis (Silva et al., 2002), whereas in S. exigua, X. nematophila cells were able to hamper nodule formation (Park and Kim 2000; Park et al., 2003). Additionally in S. exigua and M. sexta, X. nematophila inhibits transcription of insect genes encoding antimicrobial peptides (Ji and Kim 2004; Park et al., 2007). The transcriptome resource of insect exposure to nematode challenge will help to support studies on host-parasite interactions.

CONCLUSION

The characterization of specific molecules produced by nematodes could offer new possibilities for EPNs in field applications, as well as in improved efficacy of the previously used nematode-based pesticides. Accumulating knowledge on host-parasite relationships will lead to the discovery of novel nematode-bacterial strategies for targeting specific host immune-related components as well as host defense systems (Akhurst and Dunphy, 1993; Brivio and Mastore, 2018) designed to oppose deadly attacks by entomopathogens.

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