

Review Article

Venom of the Endoparasitoid Wasp *Pteromalus puparum*: An Overview

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Parasitoid venom is a focal research point in the biological control area, which aims to explore its physiological functions and nature. *Pteromalus puparum* is a gregarious pupal endoparasitoid wasp which has evolved unique means to adopt the host's immune system, as no other parasitoid-associated factors other than venom are injected into its hosts during oviposition. It represents an excellent model for research of parasitoid venom. In this paper, information was gathered on outcomes of *P. puparum* venom. We first began this paper by examining its functional properties. Next, we reviewed the nature of this parasitoid's venom components. Even great achievements have been made, further research is required to uncover the sophisticated bioactivity of the venom and isolate more novel toxic peptides/proteins.

1. Introduction

Parasitoids are important as diverse biological agents, which spend part of their life in the body or on the body surface of other invertebrates [1, 2]. To overcome intrusion, insect hosts have evolved highly efficient innate immune system comprising an array of cellular and humoral immune responses [3]. Parasitic wasps introduce or secrete various factors into host's body upon parasitization to create suitable host environment for the needs of the immature parasitoids to ensure successful development of their progeny [4]. These factors include venom, polydnviruses (PDVs), virus-like particles (VLPs), teratocytes, and ovarian proteins [5]. Parasitoid venoms are notably known to induce paralysis, to disrupt the host's development or to interfere with its immune response, alone or in combination with other factors [4, 6, 7]. They are biochemically, pharmacologically, and physiologically complex mixture of proteinaceous as well as nonproteinaceous components with promising applications in biomedical sector and developing novel, environmentally safe insect control agents. Over the past several decades, studies have focused on the physiological functions and bioactive compounds of parasitoid venoms [8].

Pteromalus puparum (Hymenoptera: Pteromalidae) is a gregarious pupal endoparasitoid with a wide host range that repeatedly prefers to parasitize the pupae of certain papilionid and pieridid butterfly species [9, 10]. It is the most predominant pupal parasitoid of the small white butterfly, *Pieris rapae* (Lepidoptera: Pieridae), with a parasitism rate that can be greater than 90% in fields of cruciferous vegetables in China [11]. It has evolved a unique means to manipulate its hosts, as no parasitoid-associated factors other than venom are found in the female reproductive organ [12]. Over the past 15 years, we have investigated the parasitoid-host interactions using *P. puparum* as a model. Herein, we provide a brief overview of our outcomes.

2. Venom Functions

2.1. Cellular Immunity. The insect immune reactions involve two types of responses, namely, humoral and cellular ones, whereby the overall immunity results from a complex interplay of the two systems [13]. In view of the cellular immune response, parasitoid venom has various effects on host hemocytes depending on the host-parasitoid system. These include alterations in total (THC) and differential hemocyte

counts (DHCs), modifications in hemocyte morphology and ultrastructure, induction of hemocyte death, and inhibition of hemocyte spreading and encapsulation [8, 14–17].

Parasitism by *P. puparum* resulted in a significant increase in the THC of the host, and the percentage of the host plasmatocytes and granulocytes decreased and increased, respectively, [18, 19]. Similar increases in THC of hosts were observed in some parasitoid-host systems, while opposite results were also observed in some other cases [20]. The results observed were also similar to that of THC for the effect of parasitism on the proportions of hemocyte types [21]. Obviously no general picture emerges from these observations. To interpret the underlying reason, it would be that each parasitoid-host system is unique [13, 22]. As to why the hemocyte population is changed after parasitization, it could be due to parasitoid maternal factors which directly affect host's hematopoiesis in the hematopoietic organs and produce active factors to change the cell cycle. Thus, the circulating hemocytes in the host were changed. The concentration of circulating hemocytes in *Drosophila melanogaster* larvae was changed by the parasitism of *Asobara citri* (Hymenoptera: Braconidae) with severe disruption of the hematopoietic anterior lobes [23].

Envenomated by *P. puparum* venom, a rounded appearance without pseudopods, condensed chromatin and loss of mitochondria were observed in plasmatocytes, and breakdown of plasma membranes and “clumping” of chromatin were obvious in granulocytes in *P. rapae* [24]. However, there was no obvious alteration of the cytoskeleton in either cell type. It is different from that of *Campoletis sonorensis* (Hymenoptera: Ichneumonidae) and *Cotesia rubecula* (Hymenoptera: Braconidae). After being parasitized by these two parasitoid wasps, their hosts hemocytes cytoskeleton was disrupted by the active PDV proteins [25–27]. However, RT-PCR (reverse transcription polymerase chain reaction) analysis showed that the transcription of actin, actin depolymerization factor, and tubulin genes of *P. rapae* were all downregulated by *P. puparum* parasitization [28], which suggests that there would be active protein present in the venom of *P. puparum* with the ability to regulate hemocytes cytoskeleton genes expression.

After *P. puparum* parasitization, hemocyte mortality in parasitized host pupae was noticeably higher [18]. Similarly, injecting the venom to the host significantly reduced the viability of host plasmatocytes and granulocytes [29]. The cytotoxic effects of parasitoid venom would be achieved by producing cytotoxic molecules. Several such substances correlated to parasitism have been identified [16].

Hemocyte spreading and encapsulation responses were inhibited both by parasitization and venom microinjection [18, 29, 30]. In *in vitro* assay, venom of *P. puparum* also displayed low activity to inhibit the spreading and viability of nonnatural hosts such as *Spodoptera litura* (Lepidoptera: Noctuidae), *Musca domestica* (Diptera: Muscidae), and *Sarcophaga peregrina* (Lepidoptera: Noctuidae), high ability to block the spreading of Tn-5B1-4 cells derived from *Trichoplusia ni* (Lepidoptera: Noctuidae), and high cytotoxicity to Ha cells derived from *Helicoverpa armigera* (Lepidoptera: Noctuidae) [31]. But the *P. rapae* hemocytes

were significantly more sensitive to venom by comparison with that of nonhosts. This is in agreement with *Euplectrus plathypenae*, *Bracon hebetor*, *Nasonia vitripennis* and *Pimpla hypochondriaca* venoms, which were toxic to defined specific range of species [32–35].

Up to now, the molecular mechanisms responsible for these cellular immune effects of *P. puparum* venom have been unclear. Using suppression subtractive hybridization technique, host genes encoding proteins involved in the insect cellular immune response and/or nonself recognition such as lectin, gram negative binding protein, calreticulin, and scavenger receptor were changed in response to *P. puparum* venom injection [30, 36]. This indicates that regulation of the *P. rapae* cellular immune related genes might be one of the molecular mechanisms of *P. puparum* venom inhibiting hosts cellular immune response.

2.2. Humoral Immunity. Insect humoral immune responses include enzymatic cascades that regulate melanization and coagulation of hemolymph, the syntheses of antimicrobial peptides, and the production of reactive oxygen species and reactive nitrogen species [37]. It is well known that activated prophenoloxidase plays an important role in hemolymph melanization for invading microorganisms and eukaryotic parasites [38]. Endoparasitoids must spend their immature stages inside the hemocoel of their hosts, and are therefore susceptible to humoral immune responses including phenoloxidase-dependent melanization. Decreased phenoloxidase activity is frequently observed in host insects parasitized by hymenopteran wasps [39, 40]. Parasitization by *P. puparum* was followed by inhibition of melanization capability of hemolymph from *P. rapae* and *P. xuthus* pupae [30, 41]. Asgari et al. [42] reported that *Cotesia rubecula* used a venom protein (Vn50, a serine proteinase homolog) to block the melanization reaction in *P. rapae* hosts by interfering with prophenoloxidase activation through an interaction with either this enzyme or PPO-activating proteinase. We found that *P. puparum* venom could downregulate the prophenoloxidase cascade system by directly interfering with transcription levels of genes encoding proteins such as prophenoloxidase activating enzymes, hemolymph proteinases and serpin. But the exact inhibitory mechanism still remains to be uncovered. In a conventional immunity concept, microbial cells are considered to be disease-causing agents that host cells need to eliminate through antimicrobial innate immunity [43]. From this point of view, parasitization caused wounds on the host body would be extremely dangerous. Obviously, it is disadvantageous for the survival and development of the parasites. However, endoparasitoids have evolved the effective means to deal with this problem. For example, the expression of antibacterial peptides or antifungal peptide in *Drosophila* were induced following infection by larval and pupal parasitoids [44]. Plasma lysozyme activity in *Heliothis virescens* (Lepidoptera: Noctuidae) was reduced in *Campoletis sonorensis* (Hymenoptera: Ichneumonidae) parasitized larvae [45]. After parasitism by *P. puparum*, antibacterial activity of parasitized host's hemolymph became stronger

compared to that of nonparasitized one [46]. The transcription level of several potential antimicrobial molecules including cecropin, lysozyme, attacin, lebecin, proline-rich AMP, cysteine-rich peptide, gallerimycin, and immune inducible peptide decreased in hemocytes or fat body of hosts injected with *P. puparum* venom, and the activity of host lysozyme is downregulated by parasitization [30]. Moreover, higher hemagglutination activity of *P. puparum* parasitized host hemolymph than that of wounded and nonparasitized ones was also observed [46]. These data indicated that *P. puparum* parasitization induces a full humoral immune response regulation.

2.3. Endocrine Regulation. Endoparasitoids and their hosts display remarkable developmental synchrony [47, 48]. The host's growth, development, reproduction, and immune defense reactions are manipulated by combined actions of juvenile hormone (JH), juvenile hormone esterase (JHE), ecdysteroids, and prothoracicotropic hormone [49]. Thus, hosts hormones should coordinate with the development of immature parasitoid. Alterations of endocrine levels in parasitized hosts have been extensively documented in many parasitoid-host systems [50]. Parasitism by *P. puparum* or its venom-microinjection resulted in an increase of JH III titer, and ecdysteroid titer and JHE activity decreased in *P. rapae* pupae hemolymph [51]. This demonstrated that venom alone of this parasitoid wasp actively disrupts its host's normal endocrine program which is one of the strategies used by this parasitoid to achieve successful development in their host.

2.4. Metabolism. Parasitoids quantitatively and qualitatively regulate the level of the host's nutrient (carbohydrates, proteins, lipids, etc.) metabolism to obtain nutritional requirements from host [52, 53]. Many studies have reported that host's metabolism can be regulated by parasitoid wasp maternal factors. The metabolic alterations of hosts protein, lipid, and amino acid were caused by *P. puparum* parasitization and venom [54]. The levels of hemolymph soluble proteins in the *P. puparum* venom injected *P. rapae* and *P. xuthus* pupae increased significantly, while levels of soluble proteins in the fat body decreased after parasitization or venom injection. The total lipid levels in hemolymph of parasitized and venom injected pupae decreased significantly, whereas it did not change in the fat body. *P. puparum* parasitization induced the decreasing of the titer of total amino acid in the *P. rapae* pupae hemolymph, especially for aliphatic amino acid. We found that the transcriptional level of arylphorin-type storage protein mRNA in *P. rapae* pupae fat body was inducible response to parasitism by *P. puparum* [55]. It may result in alternating arylphorin titer in *P. rapae* hemolymph after parasitization. After parasitization by *P. puparum*, some proteins associated with energy metabolism in the plasma of hosts were differentially expressed, and their transcript levels were inducible in response to the parasitism [41, 56]. These results provide an understanding of the toxic properties of how this parasitoid venom regulates the metabolism of its host.

3. Venom Constituents

3.1. Biochemical Property. Parasitoid venom was a complex mixture, which has been characterized in more than 20 species. These studies revealed that parasitoid venoms are mostly acidic containing not only proteins of low molecular masses (less than 5 kDa) but also proteins of high molecular masses (over 100 kDa) [8, 57]. Although all the parasitoid venoms analyzed to date exhibit high molecular proteins, some species lacked low molecular proteins such as *Chelonus* sp. near *curvimaculatus* (Hymenoptera: Braconidae), *Bracon hebetor* (Hymenoptera: Braconidae), and *Apanteles glomeratus* (Hymenoptera: Braconidae) lacking venom proteins with molecular masses lesser than 30, 20, and 18 kDa, respectively [6]. The abundant proteins composition of *P. puparum* venom ranges from 14.4 kDa to 116.0 kDa, and numerous polypeptides lower than 14.4 kDa and few proteins higher than 116.0 kDa are present [12, 31]. On two-dimensional gels, majority of the venom proteins of this parasitoid range from 4 to 7 demonstrating predominant acidic nature, which are similar to the counterparts of other parasitic wasps [58].

3.2. Enzyme. There are a variety of enzymes present in parasitoid venom [6, 8, 57, 59]. In *P. puparum* venom, acid phosphatase, alkaline phosphatase, phosphodiesterase, phospholipase, esterase, protease, serine protease, arginine kinase, aminotransferase-like venom protein, and serine protease homolog were detected [36]. Among these, acid phosphatase had the optimal pH and temperature of 4.8 and 45°C, respectively [60]. Alkaline phosphatase was found to be temperature dependent with bivalent cation effects [61]. The full lengths of acid phosphatase, alkaline phosphatase, and arginine kinase were cloned. They were shared high identity to their counterparts from other insects. In addition, their transcriptions appeared to be development related, suggesting that these three venom enzymes may be associated with female reproduction [58, 60, 61]. All the functions of them were not investigated in detail. We speculated that they might be with the similar biological activity to the counterparts reported in other parasitoid venom or other insect's organs. Beside the venom enzymes described above, a lot of others such as phenoloxidase, metalloprotease, aspartylglucosaminidase, γ -glutamyl transpeptidase, and chitinase have been reported from other parasitoid venoms [62–72]. Some of them would be present in venom of *P. puparum*, but some may not exist. The diversity of enzymes present in the venom might be a reflection as well as specificity and the role they play in each host-parasitoid interaction as well as venom metabolism in the parasitoid [57].

3.3. Venom Peptide/Protein. In addition to enzymes, an increasing number of original peptides and proteins have been reported in the venoms from parasitic Hymenoptera. In *Pimpla hypochondriaca* (Hymenoptera: Ichneumonidae) venom, Cys-rich venom protein 1, 2, 4, and 6 as protease inhibitors, Cys-rich venom protein 3 and 5 similar to conotoxins, pimplin with lethal paralysis, and VPr3 known

to antihemocyte aggregation were isolated [73–75]. Vn1.5 necessary to the expression of PDVs genes in host hemocytes, Vn4.6 and Vn50 interfered with host prophenoloxidase activating cascade to inhibit melanization, and calreticulin preventing encapsulation of the developing parasitoid were contained in venom of *Cotesia rubecula* (Hymenoptera: Braconidae) [42, 76–78]. P4 protein with immune suppressive functions and a serpin (LbSPNy) that inhibited the PO cascade in the hemolymph were reported from the venom of *Leptopilina boulandi* (Hymenoptera: Figitidae) [79, 80]. In venom of *Microctonus aethiopoulos* (Hymenoptera: Braconidae) and *M. hyperodae* (Hymenoptera: Braconidae), calreticulin, heat-shock protein, icarapin, tetraspanin, ferritin, TEGT, VG3, and VG10 were identified [72]. Many known and unknown proteins such as calreticulin, chitin binding protein-like venom protein, antigen 5-like protein, C1q-like venom protein, general odorant-binding protein-like venom protein, low-density lipoprotein receptor-like venom protein, and venom protein D to Z were present in venom of *Nasonia vitripennis* (Hymenoptera: Pteromalidae) [81]. In *P. puparum*, the venom proteins of calreticulin and heat shock protein 70 were identified [58]. Even we have not investigated the physiological functions of calreticulin in venom of *P. puparum*, we considered it as candidates for antihemocyte activity like that present in venom of *C. rubecula* [78]. Hsp70 as molecular chaperones acts in many aspects of cell biology. The exact function of Hsp70 in parasitoid venom is not understood. In addition, Vn.11 venom protein with 24.1 kDa in size was isolated in *P. puparum*, which is able to inhibit the spreading behavior and encapsulation ability of host hemocytes [82].

3.4. Antibacterial Peptide. Numerous antibacterial agents have been searched and characterized from snake, honeybee, bumblebee, ant, spider, and scorpion venoms [83, 84]. Recently, the venoms of *P. hypochondriaca* and *Diadromus collaris* (Hymenoptera: Ichneumonidae) were found to be with antibacterial activity [85, 86]. A defensin-like antimicrobial peptide was purified and characterized from the venom of *N. vitripennis*, which exerted strong antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria, and fungi [87]. Several novel antimicrobial peptide genes were screened from the venom apparatus of *P. puparum* [88]. And some antimicrobial peptides were also purified from the venom of this parasitoid (unpublished data). These antimicrobial peptides may have unique functions with promising utilization.

4. Concluding Remarks

This paper summarizes the advances and insights in the venom of *P. puparum* available up to date. Although great progress has been made in characterizing its physiological functions and composition, our information is still meager. In the near future, exploring the molecular mechanisms of venom proteins to manipulate the hosts could be expected. More research is needed to determine the bioactivity of the identified venom peptides/proteins. Likewise, research

on discovering novel peptides/proteins present in this parasitoid venom would yield interesting new results with the development of bioinformatics and proteomics. Continued research can be expected for obtaining insecticidal genes or pharmaceutical agents used in biological control or medicine sector.

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