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Peptidoglycan recognition proteins in insect immunity

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ABSTRACT

Insects lack an acquired immune system and rely solely on the innate immune system to combat microbial infection. The innate immunity of insects mainly depends on the interaction between the host's pattern recognition receptor (PRR) and pathogen-associated molecular pattern (PAMP). The peptidoglycan recognition proteins (PGRPs) family is the most important pattern recognition receptor (PRR) for insects. It can recognize the main component of the cell wall of the pathogenic microorganism, peptidoglycan (PGN), and plays an important role in the innate immunity of insects. In this paper, the structure, classification, and function of PGRPs is summarized, and the role of PGRPs in the innate immunity of insects is also discussed.

1. Introduction

In long-term evolution, insects have developed several lines of defense system against microbial infection. The first line of defense is composed of insect body structures, such as the exoskeleton and peritrophic matrix. When a microbe breaks the first line of defense, the innate immune response of the insect is activated. The innate immune response of the insect is mainly composed of humoral immunity and cellular immunity (Ferrandon et al., 2007; Lavine and Strand, 2002; Lemaitre and Hoffmann, 2007). Humoral immunity produces antimicrobial peptides (AMPs) through the Toll and IMD pathways (Hetru and Hoffmann, 2009) or lead to produce the melanin and cause melanization of the invading microbe at the site of injury through the prophenoloxidase (PPO) activation pathway (Cerenius et al., 2008; Kurata, 2014). Cellular immunity occurs through the phagocytosis of microorganisms and the formation of nodules (Strand, 2008). The activation of the humoral immune response occurs mainly through the pattern recognition receptor (PRR), which recognizes pathogen-associated molecular patterns (PAMP) that exist only in microorganisms but not in the host, such as lipopolysaccharide (LPS), peptidoglycan (PGN), and lipophosphoric acid (Akira et al., 2006; Dzik, 2002; Leulier et al., 2003a; Medzhitov and Janeway, 2002; Royet et al., 2011). Peptidoglycan recognition protein (PGRP), an important PRR, can recognize PGN, which is one of the main components of the pathogenic microorganism cell wall.

The first reported PGRP was purified from the hemolymph of the silkworm, *Bombyx mori*, with a molecular weight of approximately 19 KDa. It can bind to PGN and activate the phenoloxidase pathway (Yoshida et al., 1996). To date, numerous PGRPs have been reported, and these PGRPs can be divided into long and short types. In *Drosophila melanogaster*, there are 13 PGRP genes that encode 19 proteins (Royet et al., 2011). PGRP-SA, PGRP-SB1, PGRP-SB2, PGRP-SC1A, PGRP-SC1B, PGRP-SC2 and PGRP-SD in *Drosophila* are short PGRPs, while PGRP-LA, PGRP-LB, PGRP-LC, PGRP-LD, PGRP-LE and PGRP-LF are long PGRPs (Werner et al., 2000). There are 12 PGRP genes in silkworm. PGRP-L1, PGRP-L2, PGRP-L3, PGRP-L4, PGRP-L5 and PGRP-L6 are long types, while PGRP-S1, PGRP-S2, PGRP-S3, PGRP-S4, PGRP-S5 and PGRP-S6 are short types (Tanaka et al., 2008). It was also reported that there are 7 PGRP genes in the yellow fever mosquito, *Aedes aegypti* (Christophides et al., 2002). PGRP-S1 and PGRP-SC2 are short types, while PGRP-LA, PGRP-LB, PGRP-LC, PGRP-LD and PGRP-LE are long types (Wang and Beerntsen, 2015). Table 1 summarizes the reported PGRPs from other insects.

2. Structural analysis of PGRP

PGN is the main component of the bacterial cell wall. It is a polymer consisting of sugars and amino acids with long glycan chains of alternating residues of β-(1,4)-linked N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). It can be classified into DAP- and Lys-types according to the difference in amino acid residues and cross-linking methods (Kurata et al., 2006; Schleifer and Kandler, 1972). Most gram-negative PGNs are DAP-type, which activate the IMD pathway to produce AMPs, while most gram-positive PGNs are Lys-type, which are

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Table 1
PGRPs from insects.

Protein name	Accession number	Number of amino acids	Transmembrane domain	Signal peptide	Amidase activity	Binding peptidoglycan	Participation pathway	Literature
AgPGRP-S1	XM-310547	200	–	–	No	–	–	(Mendes et al., 2010)
AgPGRP-S2	XM-557000	188	–	–	Yes	–	–	(Mendes et al., 2010)
AgPGRP-S3	XM-316359	188	–	–	Yes	–	–	(Mendes et al., 2010)
AgPGRP-LA	XM_001688476	275	–	–	–	–	–	–
AgPGRP-LB	XM-321943	278	–	–	–	–	–	–
AgPGRP-LC1	XM-314103	397	Yes	–	–	DAP,Lys	Imd	(Meister et al., 2009)
AgPGRP-LC2	XM-558599	414	Yes	–	–	DAP,Lys	Imd	(Meister et al., 2009)
AgPGRP-LC3	XM-558600	407	Yes	–	–	DAP,Lys	Imd	(Meister et al., 2009)
AmPGRP-SA	KC766482	124	–	Yes	–	DAP,Lys	Toll	(Liu et al., 2018)
AmPGRP-S1	XM_001121036	217	No	Yes	Yes	DAP	Imd	(Li et al., 2017)
AmPGRP-S2	NM_001163716	194	No	Yes	Yes	DAP	Imd	(Li et al., 2017)
AmPGRP-S3	NM_001163715	189	No	Yes	No	Lys	Toll	(Li et al., 2017)
AmPGRP-LC	XM_392452	474	Yes	No	No	DAP	Imd	(Schwarz and Evans, 2013)
AsPGRP-LC1a	GU214232	454	–	–	–	–	Imd	(Chen and Ling, 2010)
AsPGRP-LC1b	GU214233	429	–	–	–	–	Imd	(Chen and Ling, 2010)
AsPGRP-LD	XM_556195	287	Yes	No	No	Not binding	–	(Song et al., 2018)
BmPGRP-S1	NM_001043371	196	No	Yes	No	Lys	PO	(Yoshida et al., 1996)
BmPGRP-S2	NM_001044095	195	No	Yes	No	DAP	Imd	(Yang et al., 2015; Zhao et al., 2018)
BmPGRP-S3	NM_001257020	200	No	Yes	Yes	DAP	Imd	(Kun et al., 2014)
BmPGRP-S4	XM_004928822	199	No	Yes	Yes	DAP、Lys	PO	(Yang et al., 2017a)
BmPGRP-S5	NM_001043393	208	No	Yes	Yes	DAP、Lys	PO	(Chen et al., 2016; Kangkang et al., 2014)
BmPGRP-L1	KT907183	304	Yes	No	No	DAP	Imd	(Zhan et al., 2017)
BmPGRP-L6	LC064805	374	Yes	No	No	DAP	Imd	(Tanaka and Sagisaka, 2016)
DmPGRP-SA	CG11709	203	No	Yes	No	Lys	Toll	(Reiser et al., 2004a; Wang et al., 2006)
DmPGRP-SB1	CG9681	190	No	Yes	Yes	DAP	Toll	(Mellroth and Steiner, 2006; Zaidmanrémy et al., 2011)
DmPGRP-SC1a	AJ556594	185	No	Yes	Yes	Lys	Toll,,Imd	(Bischoff et al., 2006; Zaidmanrémy et al., 2011)
DmPGRP-SC1b	XM_002080607	185	No	Yes	Yes	Lys	Toll,,Imd	(Mellroth et al., 2003)
DmPGRP-SC2	CG14745	184	No	Yes	Yes	DAP、Lys	Toll,,Imd	(Bischoff et al., 2006; Costechareyre et al., 2015)
DmPGRP-SD	CG7496	186	No	Yes	No	DAP	Toll,,Imd	(Bischoff et al., 2004; Iatsenko et al., 2016)
DmPGRP-LA	CG32042	138	Yes	No	No	Not binding	Imd	(Gendrin et al., 2013)
DmPGRP-LB	CG14704	215	No	Yes	Yes	DAP	Imd	(Dziarski and Gupta, 2018; Girardin and Philpott, 2006; Zaidmanrémy et al., 2006)
DmPGRP-LC	CG4432	501	Yes	No	No	DAP	Imd,,PO	(Choe et al., 2002; Kurata, 2010; Neyen et al., 2012; Rämet et al., 2002; Schmidt et al., 2008)
DmPGRP-LE	CG8995	345	No	No	No	DAP	Imd,,PO	(Boscodrayon et al., 2013; Kurata, 2010; Neyen et al., 2012; Takehana et al., 2002)
DmPGRP-LF	CG4437	369	Yes	No	No	Not binding	Imd	(Basbous et al., 2011; Maillet et al., 2008; Persson et al., 2007)
GfPGRP-LB	FJ195347	81	–	–	Yes	–	Imd	(Wang et al., 2009).
GlmPGRP-LB	DQ307160	211	No	Yes	Yes	–	Imd	(Wang and Aksoy, 2012)
GlmPGRP-LC	DQ307161	413	–	–	–	–	–	–
GmPGRP-S	JQ687224	211	–	Yes	–	–	–	–
GmPGRP-A	AF394583	93	–	–	–	–	–	–
GmPGRP-B	AF394587	143	–	–	–	–	–	–
HdPGRP-1	AB115774	197	No	Yes	No	Binding	PO	(Lee et al., 2004)
HdPGRP-2	AB115775	187	No	Yes	No	Binding	PO	(Lee et al., 2004)
HdPGRP-3	AB115776	187	–	–	–	–	–	–
RfPGRP-LB	MG457266	228	No	Yes	Yes	DAP,Lys	—	(Dawadi et al., 2018)
SzPGRP-1	EU282122	262	–	–	–	–		(Anselme et al., 2008)
SzPGRP-2	EU282121	187	–	–	–	–		(Anselme et al., 2008)
MsPGRP-1A	AF413068	192	No	Yes	No	DAP,Lys	PO	(Sumathipala, 2009; Sumathipala and Jiang, 2010)
MsPGRP-1B	AF413061	191	–	–	–	–	–	–
MsPGRP-2	GQ293365	196	–	–	–	–	–	–
TmPGRP-SA	AB219970	193	No	Yes	Yes	DAP,Lys	Toll,,PO	(Kan et al., 2008; Kurokawa et al., 2011; Park et al., 2007)
TmPGRP-SC2	AB560751	188	No	Yes	Yes	DAP,Lys	Toll	(Yu et al., 2010)
TmPGRP-LE	HF935084	329	No	No	No	DAP	Imd,,PO	(Hamisi et al., 2013)
TnPGRP-S	AF076481	182	No	Yes	Predicted activation	Lys	–	(Kang et al., 1998)

produced by activating the Toll pathway to produce AMPs (Valanne et al., 2011a). Interestingly, PPO activation pathway and Toll pathway can be connected through the common serine proteinase, which involved in the AMPs production (Kan et al., 2008; Kim et al., 2008).

By constructing the PGRP phylogenetic tree, it was found that PGRPs are highly conserved during evolution (Fig. 1). All PGRPs contain a conserved PGRP domain that consists of approximately 160 amino acid residues. This domain is similar to 30% of T7 lysozyme and has amidase activity (Fig. 2a). In the presence of Zn^{2+}, it can combine and cleave PGN (Fig. 2b). However, some PGRPs have no amidase activity due to the lack of key amino acid residues. PGRPs can be divided into two types, catalytic PGRPs and non-catalytic PGRPs, depending on

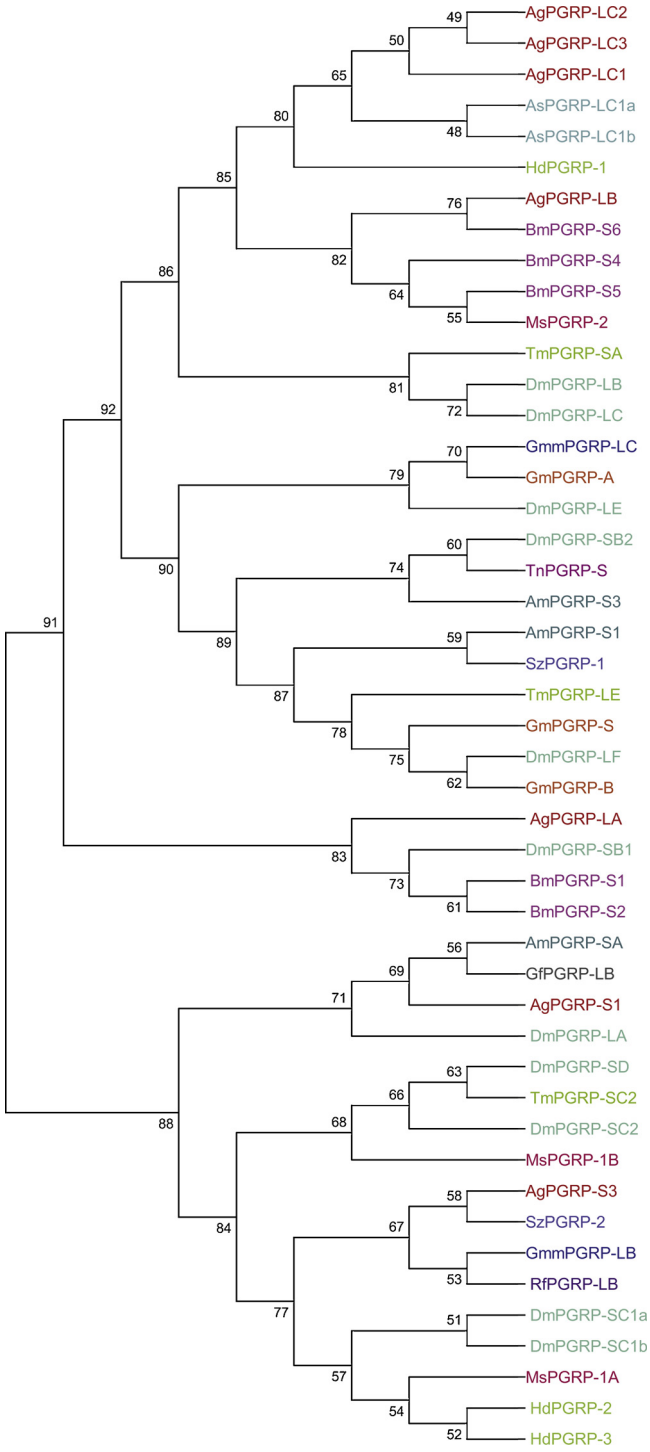

Fig. 1. Phylogenetic analysis of PGRP. A scale in the upper left of the tree represents the distance. Ag, *Anopheles gambiae*; Am, *Apis mellifera*; As, *Anopheles stephensi*; Bm, *Bombyx mori*; Dm, *Drosophila melanogaster*; Gf, *Glossina fuscipes*; Glm, *Glossina morsitans*; Gmm, *Galleria mellonella*; Hd, *Holotrichia diomphalia*; Ms, *Manduca sexta*; Rf, *Rhynchophorus ferrugineus*; Sz, *Sitophilus zeamais*; Tm, *Tenebrio molitor*; Tn, *Trichoplusia ni*.

whether there is amidase activity (Reiser et al., 2004b; Royet et al., 2011) (Fig. 2c). Catalytic PGRPs are mainly located extracellularly and usually act as a bactericide or as a regulatory immune pathway to prevent excessive activation of the immune pathway. Non-catalytic PGRPs are located intracellularly, in the transmembrane, or extracellularly. These PGRPs activate hydrolase, play an important role in signal transduction or can enhance the activation of the immune pathway.

All PGRPs have a conservative L-shaped PGN binding groove that contains 30 to 50 residues of N-terminal fragments. By analyzing the structure of PGRP-LB from *Drosophila*, Zn^{2+} was found in the PGN binding slot, and three amino acid residues (His42, His152, Cys160) were involved. This structure is strictly conserved in all the catalytic PGRPs, which reveals the mechanism for catalytic PGRP hydrolysis of PGN. Zn^{2+} acts as an electrophilic catalyst to promote amide bond cleavage between MurNAc and L-Ala (Guan et al., 2004). Although most of the non-catalytic PGRPs retains His42 and His152 residues corresponding to PGRP-LB, they always lack the zinc ion ligand Cys160, which is shown to be necessary for the hydrolysis of PGN. Non-catalytic PGRPs do not contain Zn^{2+}-coordinating residues and cannot hydrolyze PGN.

3. The role of PGRP in insect immunity

Toll, IMD and PPO are the main signaling pathways in insects to eliminate invading pathogens. PGRP plays an important role in all these pathways. Toll pathways are involved in gram-positive bacterial and fungal infection (Lemaitre et al., 1996; Valanne et al., 2011a), while the IMD pathway is primarily responsible for gram-negative bacterial infection (Alexandre et al., 2009; Myllymäki et al., 2014; Lemaitre et al., 1995). There is also some overlap between Toll and IMD pathway in response to gram-positive or gram-negative bacteria. In some conditions, *Drosophila* PGRP-SD can recognize gram-negative bacteria and activate Toll pathway (Leone et al., 2008). However, some gram-positive bacteria such as *Bacillus* with DAP type peptidoglycan can activate the IMD pathway rather than Toll pathway (Henna et al., 2014; Kaneko et al., 2004; Leulier et al., 2003b) (Fig. 3).

3.1. Participation in the toll pathway

When insects (such as *Drosophila*) are infected by fungi or Lys-PGN bacteria, the Toll pathway is activated to produce AMPs (Lu and Leger, 2016; Yang et al., 2017b). Unlike mammalian TLRs, insect TLRs do not directly bind PAMPs of bacteria, fungi, and viruses. There is only one Toll pathways in insect (Lindsay and Wasserman, 2014; Valanne et al., 2011b). PGRP-SA, PGRP-SD and GNBP1 act upstream of the Toll pathway and function as a PRR for activation of the Toll pathway (Lemaitre and Hoffmann, 2007). PGRP-SA is a secreted protein located in the hemolymph of *Drosophila* that recognizes and binds Lys-PGN (Michel et al., 2001). When PGRP-SA was mutated, it was found that Lys-PGN bacteria could not activate the Toll pathway, while DAP-PGN could activate the IMD pathway (Michel et al., 2001). Similar results were also observed when GNBP1 was mutated. These results indicate that both PGRP-SA and GNBP1 are involved in the Toll pathway, and PGRP-SD serves as a cofactor to participate in PGRP-SA and GNBP1 complexes (Gobert et al., 2003; Pili-Floury et al., 2004). When the PGRP-SA, PGRP-SD, and GNBP1 complexes recognize Lys-PGN, they activate serine protease activity and cleave the Spatzle precursor into a mature Spatzle. The mature Spatzle can bind to the Toll protein to initiate the downstream signal transduction pathway, which leads to activation of the transcription factors Dif and Dorsal to initiate transcription of AMPs (Duneau et al., 2017; Issa et al., 2018; Rahimi et al., 2016; Yamamoto-Hino and Goto, 2016) (Fig. 3).

3.2. Participation in the IMD pathway

When *Drosophila* is infected with DAP-PGN bacteria, it activates the IMD pathway to produce AMPs (Capo et al., 2016). PGRP-LC is a transmembrane receptor protein in the IMD pathway that recognizes DAP-PGN. PGRP-LC has three isoforms in *Drosophila*, namely, PGRP-LCa, PGRP-LCx, and PGRP-LCy, in which PGRP-LCa and PGRP-LCx form a dimer to recognize the DAP-PGN monomer. PGRP-LCx itself forms a dimer to recognize DAP-PGN multimers, with weak recognition

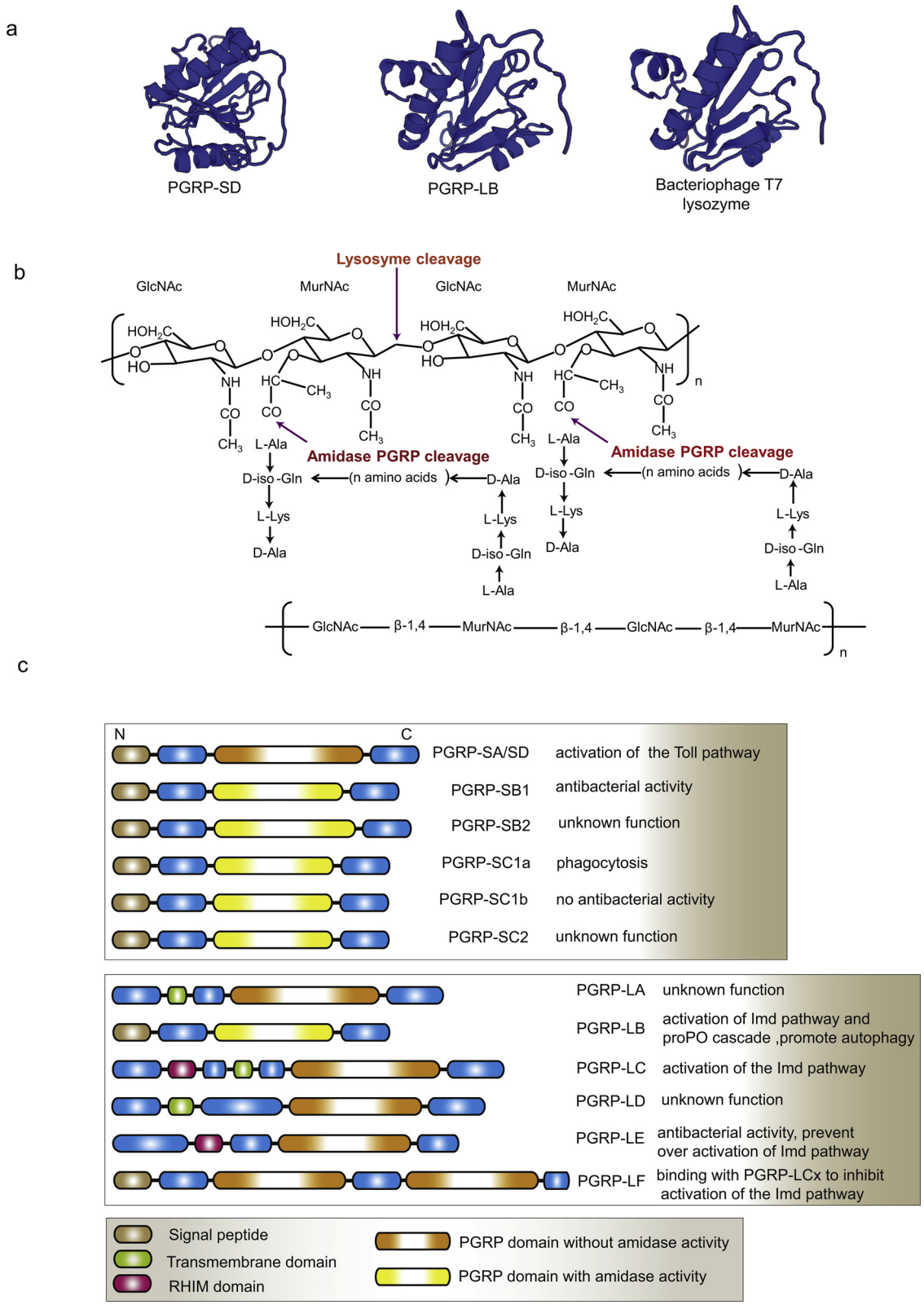

Fig. 2. Structure of PGRP proteins. (a) Prediction of the tertiary structure of *Drosophila* PGRP-SD, LB and T7 lysozyme. (b) DAP-type peptidoglycan structure. (c) The difference between long and short types of *Drosophila* PGRP.

of Lys-PGN (Choe et al., 2002; Gottar et al., 2002; Kaneko et al., 2004; Rämet et al., 2002). Studies have found that PGRP-LE can also bind to PGN, which can activate the IMD pathway when overexpressing PGRP-LE in cells (Kaneko et al., 2006). PGRP-SD and PGRP-LB act as antagonists in the IMD pathway. PGRP-LB can bind and cleave PGN to prevent excessive activation of the immune response (Paredes et al., 2011; Zaidmanrémy et al., 2006), while PGRP-SD binds PGN and re-localizes it to the cell surface to promote PGRP-LC binding to PGN to enhance the activation of the IMD pathway (Iatsenko et al., 2016). This pathway ultimately leads to activation of the transcription factor Relish

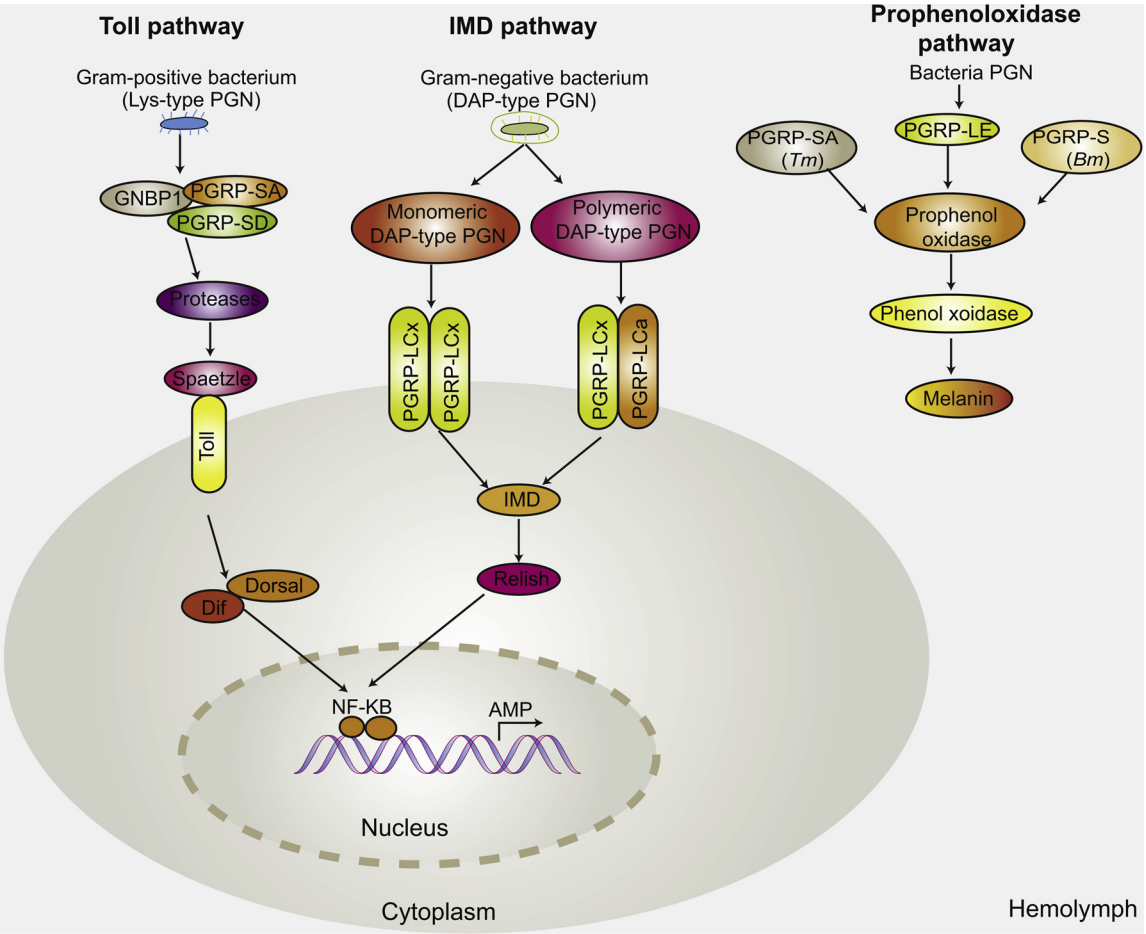

Fig. 3. Functions of PGRP proteins. Gram-positive peptidoglycan binds to PGRP-SA, PGRP-SD, and GNBP1 of *Drosophila*, and acts on the Spatzle precursor activating enzyme. The cleaved Spatzle activates the Toll pathway to produce antimicrobial peptides to kill bacteria. When the gram-negative peptidoglycan binds to *Drosophila*'s transmembrane receptor PGRP-LC, its intracellular binding domain directly binds to and activates IMD, and the activated IMD activates the IMD pathway to produce antibacterial peptides to kill bacteria. Prophenoloxidase (PPO) is activated by the action of serine proteases to produce PO, which is then enzymatically cascaded to produce melanin or other active substances to protect against invading pathogenic microorganisms.

to initiate transcription of AMPs (Capo et al., 2016; Hedengren et al., 1999; Hori et al., 2017; Zhai et al., 2018) (Fig. 3). In addition, a recent study found that knocking out PGRP-S2 in silkworms resulted in a significant decrease in transcription factor Relish and some AMP genes, suggesting that PGRP-S2 is involved in the IMD pathway (Yang et al., 2015).

3.3. Participation in the PPO activation pathway

Some PGRPs bind to bacterial PGN to activate the PPO pathway, which promotes wound healing and melanization (Fig. 3). The first reported PGRP-S1 was purified from the hemolymph of the silkworm, which binds to PGN and triggers activation of the phenoloxidase pathway. In *Drosophila*, PGRP-LE recognizes and binds DAP-type PNG, which leads to the conversion of zymogenic PPO into catalytically active phenoloxidase. Then PGRP-LE activates the prophenoloxidase cascade to produce the melanin and encapsulation of the pathogen (Kurata, 2010; Neyen et al., 2012; Takehana et al., 2002; Yoshida et al., 1996). In *Helicoverpa armigera* (Ha), PGRP-A acts as a PRR and binds to Lys- and DAP-type PGN, respectively. After binding to the PGN, PGRP-A trigger the prophenoloxidase activation pathway of *H. armigera* and participate in the melanization process of nodulation and encapsulation responses. Knockdown of HaPGRP-A decreased PPO activity in bacteria-challenged larval hemolymph. While recombinant PGRP-A enhances phenoloxidase activation in vitro and enhances nodule formation and melanization in vivo (Li et al., 2015). In addition, in *Bombyx*, PGRP-S5 also functions as a PRR to bind the Lys- and DAP-type PGN from certain bacterial strains and then activates phenoloxidase pathway in the same way (Chen et al., 2016; Kangkang et al., 2014; Kurata, 2010; Mellroth and Steiner, 2006; Neyen et al., 2012; Yang et al., 2017a; Zaidmanrémy et al., 2011).

3.4. Antibacterial activity

Some PGRPs not only participate in the immune signal transduction pathway, but also act directly as a bactericide to kill the microorganism. These PGRPs usually have amidase activity or have the ability to cause bacterial agglutination. For example, PGRP-S5 in silkworm can not only activate the PPO pathway when combined with PGN but also cleave PGN to exhibit antibacterial activity, which Zn^{2+} promotes (Chen et al., 2016; Kangkang et al., 2014). PGRP-SB1 kills *Bacillus megaterium* in the presence of Zn^{2+} in *Drosophila* but has no bactericidal effect on other gram-positive or negative bacteria (Mellroth and Steiner, 2006; Zaidmanrémy et al., 2011). PGRP-A in *Helicoverpa* can agglutinate *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). Zn^{2+} was not required for *E. coli* agglutination; however, Zn^{2+} was needed for *S. aureus* agglutination (Li et al., 2015).

4. Conclusion

To date, a tremendous number of studies on PGRPs and PGRPs in Toll and IMD pathways have been carried out on *Drosophila*. These

studies provide insight into the role of PGRPs in other insects in innate immunity. Analysis PGRPs in insects innate immunity revealed that PGRPs detect PGN as the basis for their recognition of infectious bacteria, activation and regulation of immune responses. The diversity of PGRPs can recognize structural diversity of PGN and activate different innate immunity pathway, such as the Toll pathway, the IMD pathway and the PPO activation pathway.

Despite tremendous progress have been made since the discovery of PGRPs, there are still much remains to be solved. Firstly, The structures of PGRPs in insects still need to be determined. Secondly, the exact function of PGRPs in various insects also need to be clarified. Thirdly, Although studies have shown that some PGRPs are involved in the PPO pathway, their specific role in the activation of the PPO pathway is still unknown. Therefore, further studies are needed to explore the specific role of PGRPs in innate immunity.

Through a genome-wide analysis of silkworm, it was found that the silkworm has complete Toll and IMD pathways. However, due to different living environments, such as the silkworm diet of mulberry leaves and fruit fly diet of the fermented material, there are some differences in immune signal transduction and regulation mechanisms for AMPs gene expression. Detailed differences are still unknown. For other insects, there are also some differences in their innate immunity due to different living environments. Although some PGRPs have been identified and characterized, their detailed functions in the innate immune process have been studied less.

PGRP is a highly conserved molecule involved in the innate immune response from insects to mammals (Dziarski and Gupta, 2010). Four PGRPs have been found in mammals. However, mammals PGRPs do not act as activating molecules for innate immune responses, but directly inhibit or kill bacteria (Lu et al., 2006; Sun et al., 2006). These four PGRPs, as a new type of antimicrobial peptide, are significantly different from other antimicrobial peptides. However, their specific mechanisms are still elusive and further research is needed to clarified. Furthermore, the function of mammalian PGRPs in vivo and clinical application also need to be examined (Bobrovsky et al., 2016; Saha et al., 2010). The study of insect PGRPs can help us understand the function of mammalian PGRPs.

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