Protein family review

The peptidoglycan recognition proteins (PGRPs)

Roman Dziarski and Dipika Gupta

Address: Indiana University School of Medicine-Northwest, Gary, IN 46408, USA.

Correspondence: Roman Dziarski. Email: rdziar@iun.edu

Published: 23 August 2006

Genome Biology 2006, 7:232 (doi:10.1186/gb-2006-7-8-232)

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2006/7/8/232
© 2006 BioMed Central Ltd

Summary

Peptidoglycan recognition proteins (PGRPs) are innate immunity molecules present in insects, mollusks, echinoderms, and vertebrates, but not in nematodes or plants. PGRPs have at least one carboxy-terminal PGRP domain (approximately 165 amino acids long), which is homologous to bacteriophage and bacterial type 2 amidases. Insects have up to 19 PGRPs, classified into short (S) and long (L) forms. The short forms are present in the hemolymph, cuticle, and fat-body cells, and sometimes in epidermal cells in the gut and hemocytes, whereas the long forms are mainly expressed in hemocytes. The expression of insect PGRPs is often upregulated by exposure to bacteria. Insect PGRPs activate the Toll or immune deficiency (Imd) signal transduction pathways or induce proteolytic cascades that generate antimicrobial products, induce phagocytosis, hydrolyze peptidoglycan, and protect insects against infections. Mammals have four PGRPs, which are secreted; it is not clear whether any are directly orthologous to the insect PGRPs. One mammalian PGRP, PGLYRP-2, is an \( N \)-acetylmuramoyl-L-alanine amidase that hydrolyzes bacterial peptidoglycan and reduces its proinflammatory activity; PGLYRP-2 is secreted from the liver into the blood and is also induced by bacteria in epithelial cells. The three remaining mammalian PGRPs are bactericidal proteins that are secreted as disulfide-linked homo- and hetero-dimers. PGLYRP-1 is expressed primarily in polymorphonuclear leukocyte granules and PGLYRP-3 and PGLYRP-4 are expressed in the skin, eyes, salivary glands, throat, tongue, esophagus, stomach, and intestine. These three proteins kill bacteria by interacting with cell wall peptidoglycan, rather than permeabilizing bacterial membranes as other antibacterial peptides do. Direct bactericidal activity of these PGRPs either evolved in the vertebrate (or mammalian) lineage or is yet to be discovered in insects.

Gene organization and evolutionary history

Peptidoglycan recognition proteins (PGRPs) are innate immunity molecules that contain a conserved peptidoglycan-binding type 2 amidase domain that is homologous to bacteriophage and bacterial type 2 amidases [1-6]. PGRPs are ubiquitous in most animals. Insects have multiple PGRP genes that are classified into short (S) and long (L) transcripts and are often alternatively spliced into up to 19 different proteins (Table 1) [1-5]. PGRPs have also been identified in mollusks, echinoderms, and vertebrates (Table 1), but plants and lower metazoa, including nematodes such as Caenorhabditis elegans, do not have PGRPs. PGRP genes usually form clusters that suggest their origin by gene duplication.

Mammals have a family of four PGRPs, which were initially named PGRP-S, PGRP-L, and PGRP-Ia and PGRP-Iβ (for ‘short’, ‘long’, or ‘intermediate’ transcripts, respectively), by analogy to insect PGRPs [3]. Subsequently, the Human Genome Organization Gene Nomenclature Committee changed their symbols to PGLYRP-1, PGLYRP-2, PGLYRP-3, and PGLYRP-4, respectively. This terminology is also used for mouse PGRPs, and is beginning to be adopted for all
Table 1

Accession numbers, chromosomal locations, and functions of PGRPs

| Organism (abbreviation) | Protein name* | Accession number † | Gene ID | Chromosome | PDB ID ‡ | Function§ |
|-------------------------|---------------|-------------------|--------|-----------|----------|-----------|
| **Insects**             |               |                   |        |           |          |           |
| Anopheles gambiae,      | PGRP-LA       | XM_314105         | 1274911| 2L        | -        | -         |
| mosquito (Ag)           | PGRP-LB       | XM_321943         | 1281956| 2R        | -        | Predicted amidase |
|                         | PGRP-LC1      | XM_314103         | 1274909| 2L        | -        | -         |
|                         | PGRP-LC2      | XM_558599         | 1274909| 2L        | -        | -         |
|                         | PGRP-LC3      | XM_558600         | 1274909| 2L        | -        | -         |
|                         | PGRP-S1       | XM_310547         | 1271702| X         | -        | -         |
|                         | PGRP-S2       | XM_557000         | 3290146| 2L        | -        | -         |
|                         | PGRP-S3       | XM_316359         | 1276947| 2L        | -        | Predicted amidase |
|                         | PGRP-SC2      | XM_316360         | 1276948| 2L        | -        | Predicted amidase |
| Apis mellifera, honey   | PGRP-L        | XM_392452         | 408924 | LG7       | -        | -         |
| bee (Am)                | PGRP-S        | XM_395941         | 412484 | LG13      | -        | Predicted amidase |
| Bombyx mori, domestic   | BTL-LP1       | AB017519          | -      | -         | -        | Predicted amidase |
| silkworm (Bm)           | BTL-LP2       | AB017520          | -      | -         | -        | -         |
|                         | PGRP          | AF441723          | -      | -         | -        | -         |
|                         | PGRP-S        | AB016249          | -      | -         | -        | PPO activation [36] |
| Calpodes ethlius,       | PGRP-L-C      | NM_206306         | 39062  | 3L 67A7   | -        | -         |
| Brazilian skipper       | PGRP-L-D(a)   | NM_206305         | 39062  | 3L 67A7   | -        | -         |
| butterfly (Ce)          | PGRP-L-E      | NM_206304         | 39062  | 3L 67A7   | -        | -         |
| Drosophila melanogaster,| PGRP-L-A-C    | NM_206307         | 39062  | 3L 67A7   | -        | -         |
| fruit fly (Dm)          | PGRP-L-A-D(a)| NM_001031942      | 3771920| 3L 67A7   | -        | -         |
|                         | PGRP-L-B-A    | NM_141822         | 41379  | 3R 86E8   | 1OHT     | Amidase [7,40] |
|                         | PGRP-L-B-B    | NM_169393         | 41379  | 3R 86E8   | -        | Predicted amidase |
|                         | PGRP-L-B-C    | NM_169392         | 41379  | 3R 86E8   | -        | Predicted amidase |
|                         | PGRP-L-C-A(x)| NM_168324         | 39063  | 3L 67AB   | 2F2L     | Imd activation [19,25,29-34], phagocytosis [31] |
|                         | PGRP-L-C-B(a)| NM_140041         | 39063  | 3L 67AB   | 1Z6l, 2F2L | Imd activation [19,29-34] |
|                         | PGRP-L-C-C(y)| NM_206308         | 39063  | 3L 67A7   | -        | Imd activation [33] |
|                         | PGRP-L-D-A    | NM_0132850        | 32534  | X 13F1    | 2CB3     | Imd and PPO activation [35] |
|                         | PGRP-L-E      | NM_140042         | 39064  | 3L 67AB-67A9 | -     | -         |
|                         | PGRP-L-F      | NM_132499         | 32099  | X 10C6    | 1SXR, 1S2J | Toll activation [8], carboxypeptidase [12], phagocytosis [24] |
|                         | PGRP-S1       | NM_140660         | 39870  | 3L 73C1   | -        | Predicted amidase |
|                         | PGRP-S2       | NM_140659         | 39869  | 3L 73C1   | -        | Predicted amidase |
|                         | PGRP-SC1a¶    | NM_136563         | 35859  | 2R 44E2   | -        | Amidas [14]. Toll activation [24], phagocytosis [24] |
|                         | PGRP-SC1b¶    | NM_136565         | 35861  | 2R 44E2   | -        | Amidas [14] |
|                         | PGRP-SC2      | AJ56662           | -      | 2R 44E2   | -        | Predicted amidase |
|                         | PGRP-SD       | AJ56628           | -      | 3L 66A8   | -        | Toll activation [23] |
| Glossina morsitans,     | PGRP-LB       | DQ307160          | -      | -        | -        | Predicted amidase |
| tsetse fly (Gm)         | PGRP-LC       | DQ307161          | -      | -        | -        | -         |
| Galleria mellonella,    | PGRP-A        | AF394583          | -      | -        | -        | -         |
| greater wax moth (Gm)   | PGRP-B        | AF394587          | -      | -        | -        | -         |
| Holotrichia diomphalia, | PGRP-I        | AB115774          | -      | -        | -        | PPO activation [38] |
| beetle (Hd)             | PGRP-2        | AB115775          | -      | -        | -        | -         |
|                         | PGRP-3        | AB115776          | -      | -        | -        | -         |
| Manduca sexta,          | PGRP-1A       | AF413068          | -      | -        | -        | -         |
| tobacco hornworm (Ms)   | PGRP-1B       | AF413061          | -      | -        | -        | -         |
| Tenebrio molitor, yellow| PGRP-5A       | AB219970          | -      | -        | -        | PPO activation [37] |
| mealworm (Tm)           | Trichoplusia ni, | PGRP-S             | AF076481| -        | -        | -         |
| cabbage looper (Tn)    | Mollusks       |                   |        |           |          |           |
| Argopecten irradians,   | PGRP          | AY437875          | -      | -        | -        | Predicted amidase |
| bay scallop (Ai)        | Euprymna scolopes, | PGRP-I            | AY956811| -        | -        | Predicted amidase |
|                         | PGRP-2        | AY956812          | -      | -        | -        | Predicted amidase |
Table I (continued)

| Organism (abbreviation) | Protein name* | Accession number† | Gene ID | Chromosome | PDB ID‡ | Function§ |
|-------------------------|---------------|------------------|--------|------------|---------|-----------|
|                         | PGRP-3        | AY956813         | -      | -          | -       | Predicted amidase |
|                         | PGRP-4        | AY956814         | -      | -          | -       | -          |
| **Echinoderms**         |               |                  |        |            |         |            |
| *Asterias rubens,*      | PGRP-S1a      | DQ222477         | -      | -          | -       | Predicted amidase |
| European starfish (Ar)  | PGRP-S2a      | DQ222478         | -      | -          | -       | Predicted amidase |
| Strongylocentrotus      | PGRP-S        | XM_781925        | 581948 | -          | -       | Predicted amidase |
| purpuratus, purple sea  |               |                  |        |            |         |            |
| urchin (Sp)             |               |                  |        |            |         |            |
| **Fish**                |               |                  |        |            |         |            |
| *Danio rerio,* zebrafish(Dr) | PGLYRP-2      | DQ447202         | 568634 | 8          | -       | Predicted amidase |
|                         | PGLYRP-5      | DQ447203         | 553387 | 18         | -       | Predicted amidase |
|                         | PGLYRP-6      | DQ447204         | 571817 | -          | -       | Predicted amidase |
| Tetraodon nigroviridis,| PGLYRP-2      | CAG06114         | -      | -          | -       | Predicted amidase |
| spotted green pufferfish|               |                  |        |            |         |            |
| (Ten)                   |               |                  |        |            |         |            |
| **Amphibians**          |               |                  |        |            |         |            |
| *Xenopus laevis,*       | PGLYRP-5      | BC087429         | 496035 | -          | -       | Predicted amidase |
| African clawed frog (Xf)|               |                  |        |            |         |            |
|                         | PGLYRP-1      | NM_001030455     | 595014 | -          | -       | Predicted amidase |
|                         | PGLYRP-5      | NM_001015775     | 548492 | -          | -       | Predicted amidase |
| **Birds**               |               |                  |        |            |         |            |
| *Gallus gallus,* chicken| PGLYRP-2      | AY740510         | -      | -          | -       | Predicted amidase |
| (Gg)                    |               |                  |        |            |         |            |
| **Mammals**             |               |                  |        |            |         |            |
| *Bos taurus,* cow (Bt)  | PGLYRP-1      | NM_174573        | 282305 | 18         | -       | Bactericidal [46,47] |
|                         | PGLYRP-2      | XM_588006        | 510803 | 7          | -       | Predicted amidase |
|                         | PGLYRP-3      | XM_611696        | 532575 | 3          | -       | Predicted bactericidal* |
| Camelus dromedaries,    | PGLYRP-1      | AJ409286         | -      | -          | -       | Predicted bactericidal |
| camel (Cd)              |               |                  |        |            |         |            |
| *Canis familiaris,* dog | PGLYRP-1      | XM_849945        | 612209 | 1          | -       | Predicted bactericidal |
| (Cf)                    | PGLYRP-2      | XM_847906        | 610405 | 20         | -       | Predicted amidase |
| *Homo sapiens,* human   | PGLYRP-1      | NM_005091        | 8993   | 19q13.2-q13.3 | 1YCK | Bactericidal [17] |
| (Hs)                    | PGLYRP-2      | NM_052890        | 114770 | 19p13.12   | -       | Amidase [9,16] |
|                         | PGLYRP-3      | NM_052891        | 114771 | 1q21       | ISK3, ISK4, | Bactericidal [17] |
|                         | PGLYRP-4      | NM_020393        | 57115  | 1q21       | -       | Bactericidal [17] |
| *Mus musculus,* mouse   | PGLYRP-1      | NM_009402        | 21946  | 7 A3       | -       | Antibacterial [45,48] |
| (Mm)                    | PGLYRP-2      | AY282722         | 57757  | 17         | -       | Amidase [15] |
|                         | PGLYRP-3      | NM_207247        | 242100 | 3 F1       | -       | Predicted bactericidal |
|                         | PGLYRP-4      | NM_207263        | 384997 | 3 F1       | -       | Predicted bactericidal |
| *Pan troglodytes,*      | PGLYRP-2      | XM_512455        | 455797 | 19         | -       | Predicted amidase |
| chimpanzee (Pt)         |               |                  |        |            |         |            |
| *Rattus norvegicus,*    | PGLYRP-1      | NM_053373        | 84387  | 1q21       | -       | Predicted bactericidal |
| rat (Rn)                | PGLYRP-2      | BC088306         | 299567 | 7q11       | -       | Predicted amidase |
|                         | PGLYRP-3      | XM_57498         | 499658 | 2q34       | -       | Predicted bactericidal |
|                         | PGLYRP-4      | XM_227383        | 310611 | 2q34       | -       | Predicted bactericidal |
| *Sus scrofa,* pig (Ss)  | PGLYRP-1      | NM_001001260     | 397213 | -          | -       | Predicted bactericidal |
|                         | PGLYRP-2A     | AF541955         | -      | -          | -       | Amidase [44] |
|                         | PGLYRP-2B     | AF541956         | -      | -          | -       | Amidase [44] |

*Vertebrate PGRPs were initially named PGRP-S, PGRP-L, and PGRP-I (for short, long, and intermediate transcripts). The human and mouse PGRPs have been renamed PGLYRP-1, PGLYRP-2, PGLYRP-3, and PGLYRP-4, respectively, and this new nomenclature is followed here for all vertebrate PGRP orthologs. Current nomenclature of *D. melanogaster* PGRP-LA, -LB, and -LC isoforms (-A, -B, and so on) is indicated. Previous names are also included, indicated by lower case letters in parentheses. For *D. melanogaster* PGRP-LD, isoforms -A, -B, and -C have the same amino-acid sequence, and only isoform A is shown. †Accession numbers starting with XM are predicted proteins. ‡A dash in the PBD ID column indicates that a structure or function has not been determined. §Amidase activities were predicted on the basis of the presence of all four Zn2+-binding amino acids and other amino acids required for the amidase activity, as described [9,14,15]. PPO, prophenol-oxidase. ¶*D. melanogaster* PGRP-SC1a and PGRP-SC1b are encoded by two adjacent genes translated into proteins with identical amino acid sequences. ¥Bactericidal activities were predicted on the basis of homology to human PGLYRPs.
vertebrate PGRPs. In this article, the abbreviation PGRP will be used for all invertebrate members and PGLYRP for all vertebrate members of the PGRP family.

Phylogenetic analysis of insect PGRPs reveals an early separation of PGRPs into enzyme-active amidases and the remaining PGRPs, which activate signal transduction pathways and proteolytic cascades (Figure 1). PGRPs from other animals cannot easily be grouped with any individual insect PGRPs, so they are considered separately here. The non-insect PGRPs also evolved into two groups. The first group are all amidases, which in echinoderms, mollusks, fish, and amphibians are evolutionarily older and which more recently evolved into the mammalian amidases (PGLYRP-2; Figure 2). The second group are mammalian bactericidal proteins, which separated into two well defined branches: PGLYRP-1 (present in phagocytic granules) and PGLYRP-3 and PGLYRP-4 (present on skin and mucous membranes; Figure 2). The only probable orthologs between non-insect and insect PGRPs are the amidase-active PGRPs (Figures 1, 2 and Table 1).

### Characteristic structural features

Most PGRPs have one carboxy-terminal type 2 amidase domain (approximately 165 amino acids-long; Figure 3), which is homologous to bacteriophage and bacterial type 2 amidases [1-4]. It is also called a PGRP domain, because it is longer at its amino terminus than a type 2 amidase domain and contains a PGRP-specific segment not present in type 2 amidases [7]. Across all animals, the PGRP domains are approximately 42% identical and about 55% similar. The short PGRPs (invertebrate PGRP-S and vertebrate PGLYRP-1) are about 200 amino acids long, have a signal peptide and one PGRP domain, and have a molecular weight

![Figure 1](image-url)

**Figure 1**

A phylogenetic tree of insect PGRPs, indicating their known and deduced functions. For branches supported by bootstrap analysis with the proportion of 1,000 replications higher than 70%, the percentage is indicated. The bar indicates the p-distance. Abbreviations: Ag, Anopheles gambiae; Am, Apis mellifera; Bm, Bombyx mori; Ce, Calpodes ethlius; Dm, Drosophila melanogaster; Gm, Glossina morsitans; Gm, Galleria mellonella; Hd, Holotrichia dioniaphila; Ms, Manduca sexta; Tm, Tenebrio molitor; Tn, Trichoplusia ni. Accession numbers and references are listed in Table 1. PPO, prophenol-oxidase.
of about 18-20 kDa. Most long or intermediate-sized PGRPs (invertebrate PGRP-L and vertebrate PGLYRP-2) are at least twice as large and have one carboxy-terminal PGRP domain and an amino-terminal sequence of variable length that is not conserved and is unique for a given PGRP. These amino-terminal sequences have no homology to other PGRPs or any other proteins, and they lack easily identifiable functional motifs. Some PGRPs, such as Drosophila PGRP-LC, are transmembrane molecules, whereas most other PGRPs have a signal peptide and are secreted, or do not have a signal peptide and therefore are intracellular or are secreted by another mechanism. Some PGRPs, most notably all mammalian PGLYRP-3 and PGLYRP-4 and some insect PGRPs (such as Drosophila PGRP-LF), have two PGRP domains, but these are not identical (for example, in human PGLYRP-3 and PGLYRP-4 they have only 37-43% identity).

Almost all PGRPs have two closely spaced conserved cysteines in the middle of the PGRP domain that form a disulfide bond, which is needed for the activity of PGRPs. A mutation in one of these cysteines in Drosophila PGRP-SA (Cys80Tyr) abolishes the ability of PGRP-SA to activate the Toll pathway and to induce a protective response against Gram-positive bacteria [8], whereas a mutation in one of these cysteines in human PGLYRP-2 (Cys419Ala) abolishes its amidase activity [9]. Most vertebrate PGLYRPs and some invertebrate PGRPs have two additional conserved cysteines that form a second disulfide bond, and many mammalian PGLYRPs (PGLYRP-1 and the carboxy-terminal PGRP domain of PGLYRP-3 and PGLYRP-4) have another conserved pair of cysteines that form a third disulfide (Figure 3).

The crystal structures of PGRPs reveal a general design similar to type 2 bacteriophage amidases: they all have three peripheral α helices and several central β-sheet strands (Figure 3) [7,10-13]. The front face of the molecule has a cleft that forms a peptidoglycan-binding groove (Figure 3), and the back of the molecule has a PGRP-specific segment (not present in bacteriophage amidases), which is often hydrophobic and is also
more diverse among various PGRPs. All amidase-active PGRPs (invertebrate and vertebrate) have a conserved Zn$^{2+}$-binding site in the peptidoglycan-binding groove, which is also present in bacteriophage type 2 amidases and consists of two histidines, one tyrosine, and one cysteine (Cys168 in Drosophila PGRP-SC1 and Cys530 in human PGLYRP-2). In non-amidase PGRPs, this cysteine is substituted with serine; the presence of this cysteine can therefore be used to predict the amidase activity of PGRPs (Figures 1, 2 and Table 1) [9,14,15].

All mammalian PGLYRPs are secreted, and PGLYRP-1, PGLYRP-3, and PGLYRP-4 form disulfide-linked homodimers [16,17]. Moreover, if PGLYRP-3 and PGLYRP-4 are expressed in the same cells, they almost exclusively form disulfide-linked heterodimers [17]. Insect PGRPs have not been shown to form disulfide-linked dimers, but binding to their ligands may induce dimerization [18,19].

**Localization and function**

**Insect PGRPs**

Both invertebrate and vertebrate PGRPs function as pattern-recognition and effector molecules in innate immunity. Consistent with their role in insect immunity, most insect PGRPs are expressed in immune-competent organs [1,2,20-22]. Insect PGRP-S and other short PGRPs are present in the hemolymph and cuticle and are constitutively synthesized or induced, mainly in the fat-body cells, and some also in the epidermal cells, in the gut, and to a lesser extent in hemocytes. Long insect PGRPs are expressed mainly in hemocytes, although some are also present in the hemolymph (for example Drosophila PGRP-LE). The expression of several short and long insect PGRPs is upregulated by exposure to bacteria or purified bacterial peptidoglycan, which is an essential cell wall component of virtually all bacteria. Differential induction of expression of different PGRPs by different stimuli suggests specificity of induction and effector function of different PGRPs [21,22].

Insect PGRPs have recognition, signaling, and effector functions, all of which are important for antimicrobial innate immunity (Figure 4). Three Drosophila PGRPs - PGRP-SA, PGRP-SD, and PGRP-SC1 - recognize bacterial peptidoglycan and activate proteases that cleave Spaetzle, an extracellular cytokine-like protein present in insect hemolymph, which in turn serves as an endogenous activator of Toll [8,23,24] (Figure 4a). Activation of Toll initiates a signal...
transduction pathway that results in the activation of the Dorsal and Dif transcription factors (which are similar to mammalian nuclear factor NF-κB), which translocate into the nucleus, bind to the NFκB sites in the genome, and initiate transcription of drosomycin and other antimicrobial peptides, which are mainly active against Gram-positive bacteria and fungi (Figure 4a). This pathway is essential for Drosophila immunity to Gram-positive bacteria: mutations in recognition or signal-transduction molecules for this pathway make the flies highly susceptible to infections with Gram-positive, but not Gram-negative, bacteria [8,23,24].

Peptidoglycan is a polymer of β(1→4)-linked N-acetylmuramoyl-L-Ala amidases and N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc), crosslinked by short peptides containing alternating L- and D-amino acids (Figures 3a, 4d and 5c). In position 3, the peptide has either diaminopimelic acid (DAP-type peptidoglycan, found in all Gram-negative bacteria and in Gram-positive bacilli; Figure 4d) or L-lysine (Lys-type peptidoglycan, found in most other Gram-positive bacteria, Figures 3a and 5c). The Toll pathway is preferentially triggered by the Lys-type peptidoglycan and only weakly by the DAP-type peptidoglycan.
Figure 5 (see legend on following page)
[25], although both types of peptidoglycan bind to PGRP-SA [12]. The probable reason for the weak Toll-activating capacity of DAP-type peptidoglycan is that this peptidoglycan, but not Lys-type peptidoglycan, is the substrate for the carboxypeptidase activity of PGRP-SA [12] (Figure 4d). Efficient triggering of the Toll pathway by PGRP-SA requires cooperation (and probably formation of a complex) with another pattern-recognition molecule, Gram-negative binding protein (GNBP)-1 [26,27] (Figure 4a). GNBP-1 digests peptidoglycan and generates free reducing ends of MurNAc, which are then recognized by PGRP-SA [28]. Drosophila PGRP-SC1 and PGRP-SD [23,24], as well as other pattern-recognition molecules such as GNBP-3, also activate the Toll pathway (Figure 4a). Both PGRP-SA and PGRP-SC1 are required for the activation of Toll pathway, whereas PGRP-SD is not essential but enhances Toll activation. Recognition of bacteria by PGRP-SC1 and PGRP-SA may also trigger phagocytosis by an as yet unidentified mechanism [24].

Activation of Drosophila PGRP-LC by Gram-negative bacteria and Gram-positive bacilli (also called rods) triggers another signal transduction pathway, the Imd pathway [19,25,29-34] (Figure 4b). Binding of peptidoglycan to Drosophila PGRP-LC induces its oligomerization and recruitment and activation of the death-domain-containing Imd protein [19]. The Imd pathway is Toll-independent and results in the activation of Relish transcription factor (which is also similar to mammalian NF-κB) and induction of transcription of dipterin and other antimicrobial peptides that are active primarily against Gram-negative bacteria [29-31]. PGRP-LC responds primarily to DAP-type peptidoglycan. It is a transmembrane protein and has three alternative splice forms (LC-A, LC-B, and LC-C), which differ in the extracellular PGRP domains; they probably cooperate with each other and have somewhat different recognition specificities [25,29,32-34]. PGRP-LC activates the Imd pathway in cooperation with PGRP-LE [35] and also probably with another, as yet unidentified co-receptor (Figure 4b). Drosophila PGRP-LC may also have a role in phagocytosis of Gram-negative bacteria, because inhibition of PGRP-LC expression in Drosophila S-2 cells diminishes phagocytosis of Escherichia coli, but not of Staphylococcus aureus [31]; the mechanism of this phenomenon is still unclear, however.

Silkworm (Bombyx mori) and mealworm (Tenebrio molitor) PGRP-S are present in the hemolymph and cuticle, bind bacteria and Lys- and DAP-peptidoglycan, and activate the prophenol-oxidase cascade (Figure 4e) [36,37]. This generates antimicrobial products, such as melanin and reactive oxygen species, surrounds the infection site with melanin, and contains the infection. Drosophila PGRP-LE [35] and beetle (Holotrichia diomphalia) PGRP-1 [38] (and probably other PGRPs) also activate the prophenol-oxidase cascade, but H. diomphalia PGRP-1 responds to 1,3-β-D-glucan, a common constituent of fungal cell walls.

Drosophila PGRP-SC1 and PGRP-LB are N-acetylmuramoyl-L-alanine amidases [7,14], which hydrolyze the amide bond between MurNAc and L-alanine and thus remove stem peptides from peptidoglycan (Figure 4d). Stem peptides are the four to five amino acids directly bound to MurNAc. Digestion of peptidoglycan with amidase reduces or eliminates the ability of polymeric peptidoglycan to stimulate insect cells [14], and thus the function of amidase PGRPs in vivo may be to prevent excessive activation of the immune system by bacteria [39,40]. On the basis of the conserved structure of the active site of the amidase, several other insect PGRPs are predicted to have amidase activity, whereas several others are not [9,14,15] (Figure 1 and Table 1). One PGRP that is not an amidase, Drosophila PGRP-SA, has an L,D-carboxypeptidase activity with specificity for the bond between DAP and β-Ala of the stem peptide present in peptidoglycan of Gram-negative bacteria and Gram-positive rod bacteria [12] (Figure 4). The biological significance of this carboxypeptidase activity is not certain.

**Mammalian PGLYRPs**

Mammalian PGLYRPs are differentially expressed in various organs and tissues and have two major functions: amidase...
activity and antibacterial activity. Mammalian PGLYRP-2 (and probably other vertebrate PGLYRP-2s) is an N-acetyl-
muramoyl-L-alanine amidase that hydrolyzes the lactyl bond
between the MurNAc and L-alanine in bacterial peptidogly-
can (Figure 5c) [9,15]. PGLYRP-2 is constitutively produced
in the liver and is secreted from the liver into the blood [16].
This liver PGLYRP-2 and serum N-acetylmuramoyl-L-alanine
amidase (which was identified earlier but not cloned) are the
same protein, encoded by the PGLYRP2 gene [16]. The func-
tion of this amidase is probably to eliminate the proinflam-
atory peptidoglycan and thus to prevent overactivation of
the immune system and excessive inflammation.

Mammalian PGLYRP-2 is also expressed in the intestinal
follicle-associated epithelial cells [41]. PGLYRP-2 is not
expressed in healthy human skin, but its expression is
induced in keratinocytes and other epithelial cells by ex-
posure to bacteria and cytokines [42,43]. Some mammals
express multiple splice forms of PGLYRP-2 that may have
different expression and possibly multiple functions. For
example, pigs have two PGLYRP-2 splice forms, short and
long. They both have N-acetylmuramoyl-L-alanine amidase
activity, and the long form has similar expression to human
PGLYRP-2, whereas the short form is constitutively
expressed in several tissues, including bone marrow, intesti-
tine, liver, spleen, kidney, and skin [44].

Mammalian PGLYRP-1 is highly expressed in the bone
marrow [1,3], and the protein is almost exclusively present in
the granules of polymorphonuclear leukocytes [45-49]
(Figure 5d). Mammalian PGLYRP-3 and PGLYRP-4 proteins
are selectively expressed in the skin epidermis, hair follicles,
sebaceous glands and sweat glands; in the eye’s ciliary body
(which produces aqueous humor that fills the anterior and
posterior chambers of the eye); in the eye’s corneal epitel-
ium; in the mucus-secreting cells of the main salivary (sub-
mundibular) gland and in mucus-secreting glands in the
throat (both mucus-secreting glands selectively express
PGLYRP-4, but not PGLYRP-3); in the tongue and esophagus
in squamous epithelial cells; in the stomach in acid-secreting
parietal cells (PGLYRP-3) and glycoprotein-secreting neck
mucous cells (PGLYRP-4); and in the small and large intesti-
tine in the columnar absorptive cells, but not in mucus-
secreting goblet cells and not in Paneth cells in the crypts,
which produce antimicrobial peptides [17,50] (Figure 5a,b).
Bacteria and their products increase the expression of
PGLYRP-3 and PGLYRP-4 in keratinocytes [17] and oral
epithelial cells [51], probably through activation of the Toll-
like receptors TLR2, TLR4, Nod1, and Nod2.

Human PGLYRP-1, PGLYRP-3, PGLYRP-4, the heterodimer
formed by PGLYRP-3 and PGLYRP-4, (PGLYRP-3:4), and
bovine PGLYRP-1 are bactericidal for many pathogenic and
nonpathogenic Gram-positive and Gram-negative bacteria
[17,46,47] (Figure 5a,d). PGLYRP-1, PGLYRP-3, and
PGLYRP-4 from other mammalian species are also likely to
have similar bactericidal activity. Bovine PGLYRP-1 also has
some microbicidal activity against a fungus, Cryptococcus
neoforms [46,47]. This broader spectrum of microbicidal
activity of bovine PGLYRP-1 could reflect a true difference
between the human and bovine orthologs, or it might simply
reflect a difference in the protein purification methods and
assay conditions.

Mechanism
Crystallographic analysis of human PGLYRP-1 and the
carboxy-terminal PGRP domain of PGLYRP-3, as well as
insect PGRP-LB, -SA, -LC and -LE, show that all these PGRPs
have a ligand-binding groove that binds peptidoglycan and is
specific for MurNAc bound to three peptide-bonded amino
acids (muramyl-tripeptide), which is the minimum peptido-
glycan fragment hydrolyzed by PGLYRP-2 [7,9,10,13,52-55].
It can accommodate a larger structure, such as GlcNAc-
MurNAc-tetrapeptide or MurNAc-pentapeptide (Figure 3),
but it does not bind muramyl-dipeptide or a peptide
without MurNAc [56-58]. These results are consistent with
the specificity of human PGLYRP-2 for muramyl-tripeptide
and with the specificity and high affinity (Kd = 13 nM)
of murine PGLYRP-1 for uncrosslinked polymeric peptidogly-
can but not muramyl-dipeptide or pentapeptide [45]. The
high-affinity binding of peptidoglycan to PGLYRP is
achieved by burying both the peptide and MurNAc portions
of peptidoglycan in a deep cleft that completely excludes
solvent [52].

Human PGLYRP-1 and a carboxy-terminal fragment of
PGLYRP-3 bind muramyl-tetrapeptide and muramyl-pen-
tapeptide with higher affinity than muramyl-tripeptide
[56,58]. Moreover, binding of muramyl-pentapeptide (but
not muramyl-tripeptide) to the carboxy-terminal fragment
of PGLYRP-3 induces a conformational change in the
PGLYRP-3 molecule that locks the ligand in the binding
groove (Figure 3) [58]. Some PGRPs (such as a carboxy-
terminal fragment of human PGLYRP-3) have a preference
for binding the Lys-type over the DAP-type peptidoglycan,
whereas others (such as human PGLYRP-1 or
Drosophila PGRP-LCx and PGRP-LE) bind DAP-type peptidoglycan
with higher affinity than Lys-type peptidoglycan [54-57].
The only difference between Lys and DAP is the presence
of an additional carboxylate at carbon 1 of DAP. Discrimination
between Lys- and DAP-type peptidoglycan is based on three
amino acids in the peptidoglycan-binding groove, corre-
sponding to Asn236, Phe237, and Val256 in human
PGLYRP-3 for binding Lys, or Gly68, Trp69, and Arg88 in
human PGLYRP-1 in the same position for binding DAP, or
Gly234, Trp235 and Arg254 in Drosophila PGRP-LE for
binding DAP [54-57]. The importance of these Asn and Phe
or Gly and Trp for binding Lys and DAP is verified by muta-
tions in these positions that can change the specificity of the
binding from Lys to DAP or Lys to DAP [57]. This allows pre-
diction of binding specificity of various PGRP domains for
Lys- or DAP-type peptidoglycan. Moreover, both human and
insect PGRPs have a dual strategy for discrimination among different types of peptidoglycan, using detection of Lys or DAP in the stem peptide together with the type of peptide crossbridge [57]. Detection of peptide-crosslinked peptido-
glycan would require engagement of two peptidoglycan-
binding sites in two PGRP domains, which could be
accomplished by PGRPs with two PGRP domains and/or by
dimeric PGRPs, which is consistent with recent demonstra-
tion of dimeric PGRPs in mammals [17] and insects [18,19].

There is likely, however, to be considerable variation in the
fine specificity of different PGRPs, because the residues in
and around the peptidoglycan-binding groove are relatively
variable; they are less than 50% conserved among PGRPs
[7,11,52]. This structural variation may correspond to differ-
tent ligand specificities of different PGRPs. Mammalian
PGLYRPs bind to both Gram-positive and Gram-negative
bacteria and also some fungi [17,47], and some insect PGRPs
(such as H. diomphalia PGRP-1) bind fungal β-glucan [38].
Therefore, binding to peptidoglycan is not always respon-
sible for PGRP binding, and even with bacteria there are indica-
tions that some PGRPs may also bind to other polymers,
such as lipoteichoic acid and lipopolysaccharide [17,45,47].
Human and mouse PGLYRPs have the highest affinity for
peptidoglycan, however, and much lower affinities for lip-
oteichoic acid and lipopolysaccharide [17,45], whereas bovine
PGLYRP-1 seems to have high affinity for lipoteichoic acid
and lipopolysaccharide [47]. It is not clear, however,
whether these other ligands bind to the peptidoglycan-
binding groove or to another portion of the PGLYRP mole-
cule, such as the hydrophobic region on the opposite side of
the molecule. Binding of peptidoglycan outside the peptido-
glycan-binding groove was recently shown, which con-
tributes to the formation of PGRP-LE oligomers [54] or
PGRP-LCx:PGRP-LCa dimers [55].

The diversity of PGRP specificities is also increased by dupli-
cation of PGRP domains and dimerization. PGLYRP-3 and
PGLYRP-4 both have two PGRP domains, and each PGRP
domain has one ligand-binding site [52]. Thus, whereas
PGLYRP-1 monomers and dimers have one and two identi-
cal ligand-binding sites, respectively, PGLYRP-3 and
PGLYRP-4 monomers and dimers have two and four ligand-
binding sites, respectively (Figure 5). Because these PGRP
domains in PGLYRP-3 and PGLYRP-4 are not identical (they
have 37-43% identity), however, the fine binding specificity
or affinity of each PGRP domain in these PGLYRP molecules
is probably different. For example, the carboxy-terminal and
amino-terminal PGRP domains in human PGLYRP-3 are
specific for DAP-type and Lys-type peptidoglycan, respec-
tively [57]. The diversification of PGLYRP specificities
is then further increased by formation of PGLYRP-3:4 het-
erodimers, which have four different binding sites. In
this way, the host can fine-tune the specificities of PGLYRPs by
expressing PGLYRP-3 and PGLYRP-4 either in the same or in
separate cells, to form hetero- or homodimers, respectively. In
addition, PGRPs have hydrophobic domains on the opposite
side of the molecule from the ligand-binding groove, which
were previously hypothesized to interact with signal transduc-
tion molecules [7]. In mammalian PGLYRPs, however, these
hydrophobic domains may either have a role in the interaction
of PGLYRPs with bacteria, or in the formation of dimers.

Mammalian PGLYRP-1, PGLYRP-3, and PGLYRP-4 form a
new class of bactericidal proteins that have a different
structure, mechanism of action, and expression from those
of currently known mammalian antimicrobial peptides
[6,17]. PGLYRPs are much larger than all currently known
vertebrate antibacterial peptides: PGLYRP-1, PGLYRP-3,
PGLYRP-3:4, and PGLYRP-4 proteins are disulfide-linked
glycosylated 44 kDa, 89 kDa, 98 kDa, and 115 kDa dimers
[17], and vertebrate antimicrobial peptides are typically
3 kDa to 15 kDa. PGLYRPs require divalent cations and
N-glycosylation for bactericidal activity, which are not
usually required by membrane-permeabilizing antibacterial
peptides, such as defensins or magainin [17]. Mammalian
PGLYRPs also differ from antimicrobial peptides in their
mechanism of bactericidal activity: they kill bacteria by
interacting with cell-wall peptidoglycan, whereas antimicro-
bial peptides do so by permeabilizing bacterial membranes
[17]. Furthermore, the expression patterns of mammalian
PGLYRPs and antimicrobial peptides are different, and
some cells that produce large amounts of these peptides,
such as Paneth cells (which produce defensins, phospholi-
pase A₂, and lysozyme), do not express PGLYRPs [17].

Frontiers

Despite enormous progress since the discovery of PGRPs in
1996 [36], much remains to be done. The structures and speci-
cificities of many insect and mammalian PGRPs still need to
determined. For example, the PGRP/amidase domain of
mammalian PGLYRP-2 or many insect long PGRPs is located
in the carboxy-terminal one third of the molecule, but the role
and the structure of the remaining amino-terminal two thirds
of PGLYRP-2 or several insect long PGRPs is unknown, as this
portion has no homology to any other PGRPs or to any other
known proteins [3,9]. These amino-terminal portions of
PGLYRP-2 and several insect long PGRPs may therefore have
unique and so far unidentified functions.

The functions of many insect PGRPs and their mechanisms of
action also still need to be determined (Figure 1 and Table 1).
It should be especially interesting to look for direct antimi-
crobial activity of insect PGRPs, which will establish whether
this function developed in mammalian or vertebrate
PGLYRPs or whether it was already present in their common
ancestor with insects. PGRPs in other invertebrates and in
nonmammalian vertebrates (fish, amphibians, reptiles, and
birds) are beginning to be discovered and nothing is known
about their functions, although most of them are predicted
to have amidase activity (Figure 2 and Table 1).
The exact mechanism of antibacterial activity of mammalian PGLYRP s needs to be determined. Moreover, although the main functions of mammalian PGLYRPs have been identified, it remains possible that they have other unidentified functions, because many mammalian proteins have evolved to have multiple functions. Indeed, even some insect PGRPs, such as Drosophila PGRP-SA, have multiple functions (Figure 4), and pig PGLYRP-2 has two splice forms, both of which have amide synthase activity but also seem to have a role in the induction of β-defensin synthesis [44].

The role and significance of mammalian PGLYRPs in vivo also need to be established, as well as their clinical significance, including any possible associations with diseases. For example, human PGLYRP3 and PGLYRP4 genes are located in the epidermal differentiation gene cluster in the psoriasis susceptibility PSORS1 locus, and, thus mutations in PGLYRP3 and PGLYRP4 genes may contribute to the pathogenesis of psoriasis [59]. It is likely that associations of other PGLYRPs with disease will be found in the future.

Acknowledgements
This work was supported by USPHS Grants AI28797 and AI56395 from the NIH.

References
1. Kang D, Liu G, Lundstrom A, Gellus E, Steiner H: A peptidoglycan recognition protein in innate immunity conserved from insects to mammals. Proc Natl Acad Sci USA 1998, 95:10078-10082.
2. Werner T, Liu G, Kang D, Ekengren S, Steiner H, Hultmark D: A family of peptidoglycan recognition proteins in the fruit fly Drosophila melanogaster. Proc Natl Acad Sci USA 2000, 97:13772-13777.
3. Liu C, Xu Z, Gupta D, Dziarski R: Peptidoglycan recognition proteins: a novel family of four human innate immunity pattern recognition molecules. J Biol Chem 2001, 276:34686-34694.
4. Dziarski R: Peptidoglycan recognition proteins (PGRPs). Mol Immunol 2004, 40:877-886.
5. Steiner H: Peptidoglycan recognition proteins: on and off switches for innate immunity. Immunol Rev 2004, 198:83-96.
6. Dziarski R, Gupta D: Mammalian PGRPs: novel antibacterial proteins. Cell Microbiol 2006, 8:1059-1069.
7. Kim M-S, Byun M, Oh B-H: Crystal structure of peptidoglycan recognition protein LB from Drosophila melanogaster. Nat Immunol 2003, 4:787-793.
8. Michel T, Reichhart J-M, Hoffmann JA, Royet J: Drosophila Toll is activated by Gram-positive bacteria through a circulating peptidoglycan recognition protein. Nature 2001, 414:756-759.
9. Wang ZM, Li X, Cockett RR, Wang M, Wang M, Fukase K, Inamura S, Kusumoto S, Gupta D, Dziarski R: Human peptidoglycan recognition-L is an N-acetylmuramoyl-L-alanine amidase. J Biol Chem 2003, 278:49044-49052.
10. Reiser J-B, Teysen L, Wilson IA: Crystal structure of the Drosophila peptidoglycan recognition protein (PGRP)-SA at 1.56 Å resolution. J Mol Biol 2004, 340:909-917.
11. Guan R, Wang Q, Sundberg EJ, Mariusz RA: Crystal structure of the C-terminal peptidoglycan-binding domain of human peptidoglycan recognition protein IIa. J Biol Chem 2004, 279:31873-31882.
12. Chang CI, Pili-Floury S, Herve M, Parquet C, Chelliah Y, Lemaire B, Mengin-Lecreulx D, Deisenhofer J: A Drosophila pattern recognition receptor contains a peptidoglycan docking groove and unusual L,D-carboxypeptidase activity. Proc Natl Acad Sci USA 2004, 101:2277.
13. Guan R, Wang Q, Sundberg EJ, Mariusz RA: Crystal structure of human peptidoglycan recognition protein S (PGRP-S) at 1.70 Å resolution. J Mol Biol 2005, 347:683-691.
14. Mellroth P, Karlsson J, Steiner H: A scavenger function for a Drosophila peptidoglycan recognition protein. J Biol Chem 2003, 278:7059-7064.
15. Gellus E, Persson C, Karlsson J, Steiner H: A mammalian peptidoglycan recognition protein with N-acetylmuramoyl-L-alanine amidase activity. Biochem Biophys Res Commun 2003, 306:988-994.
16. Zhang Y, van der Fits L, Voerman JS, Melief MJF, Laman JD, Wang M, Wang H, Wang M, Li X, Walls CD, et al.: Identification of serum N-acetylmuramoyl-L-alanine amidase as liver peptidoglycan recognition protein 2. Biochem J 2005, 384:415-423.
17. Lu X, Wang M, Qi J, Wang H, Li X, Gupta D, Dziarski R: Peptidoglycan recognition proteins are a new class of human bactericidal proteins. J Biol Chem 2006, 281:5895-5907.
18. Mellroth P, Karlsson J, Hukansson J, Schultz N, Goldman WE, Steiner H: Ligand-induced dimerization of Drosophila peptidoglycan recognition proteins in vitro. Proc Natl Acad Sci USA 2005, 102:6455-6460.
19. Choe K-M, Lee H, Anderson KV: Drosophila peptidoglycan recognition protein LC (PGRP-LC) acts as a signa-transducing innate immune receptor. Proc Natl Acad Sci USA 2005, 102:1122-1126.
20. Ochiai M, Ashida M: A pattern recognition protein for peptidoglycan. Cloning of the cDNA and the gene of the silk worm, Bombyx mori. J Biol Chem 1999, 274:11854-11858.
21. Dimopoulos G, Christophides GK, Zdobnov E, Barillas-Mury C, Birney E, Blandin S, Blass C, Brey PT, Collins FH, Danielli A, Dimopoulos G, et al.: Immunity-related genes and gene families in Anopheles gambiae. Science 2002, 298:159-165.
22. Bischoff V, Vignal C, Boneca IG, Michel T, Hoffmann JA, Royet J: Function of the Drosophila pattern-recognition receptor PGRP-SD in the detection of Gram-positive bacteria. Nat Immunol 2004, 5:1175-1180.
23. Garver LS, Wu J, Wu LP: The peptidoglycan recognition protein PGRP-SC1 is essential for Toll signaling and phagocytosis of Staphylococcus aureus in Drosophila. Proc Natl Acad Sci USA 2006, 103:660-665.
24. Leulier F, Parquet C, Pili-Floury S, Ryu JH, Caroff M, Lee WJ, Mengin-Lecreulx D, Lemaire B: The Drosophila immune system detects bacteria through specific peptidoglycan recognition. Nat Immunol 2003, 4:45-51.
25. Gobert V, Gotter M, Matskevich AA, Rutschmann S, Royet J, Belvin M, Hoffmann JA, Ferrandon D: Dual activation of the Drosophila Toll pathway by two pattern recognition receptors. Science 2003, 302:212-2130.
26. Pili-Floury S, Leulier F, Takahashi K, Saigo K, Samain E, Ueda R, Lemaire B: In vivo RNA interference analysis reveals an unexpected role for GNB1 in the defense against Gram-positive bacterial infection in Drosophila adults. J Biol Chem 2004, 279:12848-12853.
27. Filipe SR, Tomasz A, Ligoxygakis P: Requirements of peptidoglycan structure that allow detection by the Drosophila Toll pathway. EMBO Rep 2005, 6:327-333.
28. Choe K-M, Werner T, Stoven S, Hultmark D, Anderson KV: Requirement for a peptidoglycan recognition protein (PGRP) in Relish activation and antibacterial immune responses in Drosophila. Science 2002, 296:359-362.
29. Gobert M, Gobert V, Michel T, Belvin M, Duyk G, Hoffmann JA: The Drosophila immune response against Gram-negative bacteria is mediated by peptidoglycan recognition protein. Nature 2002, 416:640-644.
30. Ramet M, Manfrelli P, Pearson A, Mathey-Prevot B, Ezechowitz RAB: Functional genomic analysis of phagocytosis and identification of a Drosophila receptor for E. coli. Nature 2002, 416:644-648.
31. Werner T, Borge-Renborg K, Mellroth P, Steiner H, Hultmark D: Functional diversity of the Drosophila PGRP-LC gene cluster in the response to lipopolysaccharide and peptidoglycan. J Biol Chem 2003, 278:26319-26322.
pathogen-associated molecular patterns increase the expression of peptidoglycan recognition proteins via toll-like receptors, NOD1 and NOD2 in human oral epithelial cells. Cell Microbiol 2005, 7:675-686.

52. Guan R, Roychowdhury A, Ember B, Kumar S, Boons G-J, Mariuzza RA: Structural basis for peptidoglycan binding by peptidoglycan recognition proteins. Proc Natl Acad Sci USA 2004, 101:17168-17173.

53. Chang CI, Ihara K, Chelliah Y, Mengin-Lecreulx D, Wakatsuki S, Deisenhofer J: Structure of the ectodomain of Drosophila peptidoglycan-recognition protein LCA suggests a molecular mechanism for pattern recognition. Proc Natl Acad Sci USA 2005, 102:10279-10284.

54. Lim J-H, Kim M-S, Kim H-E, Yano T, Oshima Y, Aggarwal K, Goldman WE, Silverman N, Kurata S, Oh B-H: Structural basis for preferential recognition of diaminopimelic acid-type peptidoglycan by a subset of peptidoglycan-recognition proteins. J Biol Chem 2006, 281:8286-8295.

55. Chang CI, Chelliah Y, Borek D, Mengin-Lecreulx D, Deisenhofer J: Structure of tracheal cytotoxin in complex with a heterodimeric pattern-recognition receptor. Science 2006, 311:1761-1764.

56. Kumar S, Roychowdhury A, Ember B, Wang Q, Guan R, Mariuzza RA, Boons G-J: Selective recognition of synthetic lysine and meso-diaminopimelic acid-type peptidoglycan fragments by human peptidoglycan recognition proteins Lq and S. J Biol Chem 2005, 280:37005-37012.

57. Swaminathan CP, Towns PH, Roychowdhury A, Wang Q, Guan R, Silverman N, Goldman WE, Boons GJ, Mariuzza RA: Dual strategies for peptidoglycan discrimination by peptidoglycan recognition proteins (PGRPs). Proc Natl Acad Sci USA 2006, 103:8646-8649.

58. Sun C, Mathur P, Dupuis J, Tizard R, Ticho B, Crowell T, Gardner H, Boons G-J, Carulli JP: Peptidoglycan recognition proteins Pglyrp3 and Pglyrp4 are encoded from the epidermal differentiation complex and are candidate genes for the Psors4 locus on chromosome 1q21. Hum Genet 2006, 119:113-125.