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REVIEW

Application of Proteins Binding Components of Bacterial Cell Wall for Extraction, Concentration, and Analysis of Biological Samples

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Abstract—Proteins that bind components of bacterial cell wall play a key role in innate immunity and interactions between bacteria and host organisms. They participate in the control of peptidoglycan synthesis and degradation, determine the pathogenic specificity of bacteria, affect their ability to adhere and invade, and serve as important elements of molecular recognition. The review discusses proteins of diverse origins and their recombinant analogues, their structure and binding mechanisms, and prospects for application in the diagnostics of bacterial infections and functionalization of nanomaterials.

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INTRODUCTION

According to the World Health Organization, infectious diseases are among the top ten causes of death worldwide [1]. Hundreds of bacterial species can cause severe infections in humans [2]. The growing antibiotic resistance has re-established pathogenic bacteria as a major global health threat. Antibiotic resistance is closely associated with nosocomial infections, which frequently lead to disease exacerbation. Early diagnostics are therefore essential for effective management of bacterial infections and prevention of complications, as it enables timely administration of targeted antimicrobial therapy and helps limit the spread of drug-resistant pathogens [3, 4].

Currently, the gold standard for diagnosing bacterial infections relies on colony counting methods and biochemical tests for antibiotic resistance [5]. However, conventional microbiological methods are time-consuming, as they typically require 18-24 h or longer to yield results, which makes them unsuitable for clinical scenarios that need immediate intervention [6].

The reproducibility of genomic methods used as alternatives to conventional culture-based techniques, such as quantitative PCR, fluorescence *in situ* hybridization (FISH), and 16S rRNA gene sequencing, is often insufficient to meet the requirements of clinical diagnostics [7]. Moreover, these approaches generally fail to provide information on the antibiotic susceptibility, as direct identification of resistance determinants is not feasible in most cases [8].

A variety of methods have been developed for the rapid phenotypic characterization of bacterial pathogens, including enzyme-linked immunosorbent assay (ELISA), impedance measurement, mass spectrometry (MS), Raman spectroscopy, image analysis, and others [4]. However, their performance can be inconsistent when applied to complex biological systems [9]. Samples, such as whole blood, stool, saliva, and sputum, are particularly challenging due to their multicomponent composition and high viscosity [9-11].

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In addition, pathogenic bacteria in these samples are often present at concentrations too low for reliable analysis [7]. Consequently, successful phenotyping typically requires preliminary sample preparation, including selective capture, extraction, and concentration of bacterial cells. For this purpose, functionalized substrates or particles coated with molecular recognition agents can be used as sorbents [12-14], enabling rapid isolation and concentration of intact bacterial cells without sample centrifugation or chromatographic separation and greatly simplifying sample processing [15]. The choice of molecules for functionalization is critical for ensuring the specificity and reliability of the method. Various recognition systems have been reported in the literature that employ aptamers, bacteriophages, enzymes, lectins, antibodies, and affinity molecules [16].

This review examines innate immune receptors, members of the immunoglobulin superfamily (IgSF) and scavenger receptors (SRs), as well as their application as molecular recognition elements in the diagnostics of bacterial infections. These receptors show considerable promise due to their ability to specifically bind molecular structures exposed on the surfaces of various groups of bacteria, including pathogenic species, thereby reducing the risk of false-negative diagnostic outcomes [16]. Such receptor–bacterium interactions typically do not have the bactericidal effects, which is critically important for accurate phenotyping of antibiotic resistance. Moreover, many of these receptors exhibit a modular architecture with defined ligand-binding domains, which facilitates the rational design of chimeric proteins.

BACTERIAL CELL WALL COMPONENTS CRITICAL FOR RECOGNITION

To understand the mechanisms of pattern recognition receptors (PRRs), it is essential to consider the nature of their primary ligands. The most important of these ligands are in the bacterial cell wall, a structure that plays a fundamental role in maintaining cell morphology and protecting bacteria from external stresses. The cell wall is an essential component of most bacteria, providing the maintenance of cell shape and protection against mechanical and osmotic stresses [17, 18]. Pathogen-associated molecular patterns (PAMPs), which are absent from eukaryotic cells, serve as universal targets recognized by the innate immune system. Peptidoglycan (PGN, also known as murein), teichoic acids, lipopolysaccharides (LPSs), and bacterial lipoproteins are of particular importance among PAMPs. These components vary in their chemical composition and organization between Gram-positive and Gram-negative bacteria.

Peptidoglycans. PGN is a three-dimensional polymeric matrix composed of alternating residues of *N*-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) linked by β-1,4 glycosidic bonds. Short peptide fragments (peptide stems) are covalently attached to MurNAc residues, and cross-linking between these peptides creates a rigid scaffold of the bacterial cell wall. The interpeptide linkers may include various L- and D-amino acids (L- and D-alanine, L-serine, D-glutamate, L-ornithine, and others), contributing to the structural diversity of PGNs [19, 20].

Two major types of PGN are distinguished: the lysine-type and the meso-diaminopimelic acid (meso-DAP)-type. The lysine-type PGN is characteristic of Gram-positive cocci, such as *Staphylococcus aureus*, where cross-linking occurs via the bridging peptide connecting L-lysine residues in the peptide stems. In contrast, the meso-DAP type is typical of Gram-negative bacteria and many bacilli (e.g., *Escherichia coli* and *Bacillus subtilis*), in which cross-links are formed directly through meso-DAP residues in peptide stems (Fig. 1a) [21].

The degree of PGN cross-linking varies among bacterial species: in *E. coli*, most murein chains remain uncross-linked, whereas in *S. aureus*, more than 90% of murein is covalently cross-linked [22]. Studies in *E. coli* have demonstrated that the composition of muropeptides depends on the metabolic state of the cell [23]. Thus, during the transition of a bacterial culture from the exponential growth to the stationary phase, the length of PGN chains decreases, the degree of cross-linking increases [24], and the amount of PGN per cell surface area unit changes [25]. In addition, PGN undergoes continuous remodeling during cell growth: hydrolases cleave their fragments, while newly synthesized units are incorporated into the matrix. The resulting muropeptides exhibit pronounced immunomodulatory properties [26].

Cell wall of Gram-positive bacteria. In Gram-positive bacteria, the thick PGN layer is covalently linked to teichoic and lipoteichoic acids. These polymers, composed of glycerol, mannitol, or ribitol residues, provide structural rigidity, mediate cation binding, and contribute to ion homeostasis (Fig. 1b) [27-29].

The cell wall of Gram-positive bacteria also functions as a scaffold for surface-exposed proteins that mediate interactions with the environment. These include covalently anchored M proteins of *Streptococcus pyogenes*, protein A of *S. aureus*, and non-covalently bound autolysins, lysostaphins, bacteriophage lytic enzymes, and S-layer proteins [30]. Collectively, these proteins serve both structural and virulence-related roles, facilitating immune evasion.

Cell wall of Gram-negative bacteria. In Gram-negative bacteria, the thin PGN layer resides in the

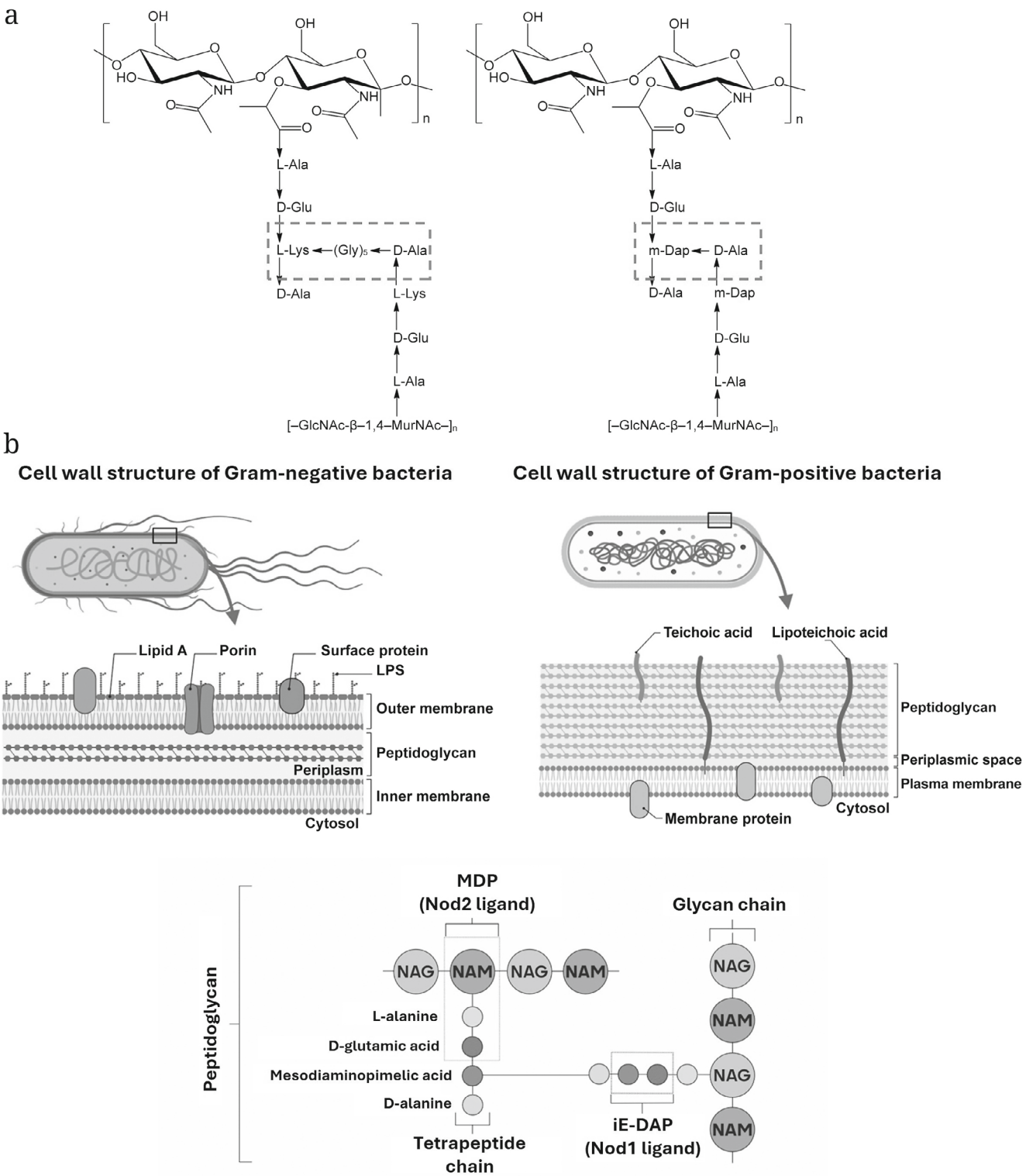

Fig. 1. a) Structures of lysine-type (left) and meso-DAP-type (right) PGNs [21]. b) Cell wall architecture of Gram-positive and Gram-negative bacteria (top) and PGN organization (bottom).

periplasmic space, which also contains enzymes, transport proteins, and chaperones. Externally, the cell is enclosed by the outer membrane, whose major structural components are LPSs. LPS consist of three parts: lipid A, core oligosaccharide, and O-specific polysaccharide (O-antigen). Lipid A is the most conserved fragment, whereas the core oligosaccharide and O-antigen exhibit structural variability that determines the serological specificity [29, 31]. The outer membrane is anchored to the PGN layer via lipoproteins,

whose N-termini are modified with fatty acids [32] and inserted into the outer membrane, while the C-termini associate with PGN [33]. Most bacterial lipoproteins feature conserved triacylated cysteine residues at the N-termini [34, 35], whereas mycoplasmal lipopeptides contain diacylated cysteines [36]. All these structures serve as canonical PAMPs recognized by PRRs. The outer membrane also contains porins and proteins involved in transport, secretion, and assembly of surface structures (Fig. 1b).

Overall, bacterial cell wall components are key PAMPs that activate the innate immune system. PGNs, teichoic acids, LPSs, and lipoproteins are recognized by PRRs and trigger signaling cascades that lead to phagocyte activation, production of inflammatory mediators, and initiation of adaptive immune responses.

INNATE IMMUNITY AND PATTERN RECOGNITION RECEPTORS

Innate immunity plays an essential role in the host's defense against infection. Since pathogenic microorganisms pose a constant threat, their proliferation must be tightly and rapidly regulated by the host's immune mechanisms. However, an excessively strong response aimed at complete pathogen elimination can cause significant collateral damage to host tissues. Innate immunity represents an evolutionarily conserved system that provides the first line of defense against pathogens, maintains homeostasis by activating effector mechanisms, and induces the expression of endogenous signals regulating processes such as inflammation and cell death [37].

In invertebrates, the primary immune cells responsible for pathogen recognition are hemocytes circulating in the hemolymph [38]. In vertebrates, the main components of the innate immune system are leukocytes; they not only detect pathogenic microorganisms but also initiate adaptive immunity responses [39]. While innate immunity lacks the antigen specificity and immune memory toward individual antigens, it is characterized by rapid recognition and activation in response to external stimuli [40].

Pathogens have evolved diverse adaptive strategies to evade or suppress innate immune mechanisms. These strategies include the disruption of innate signaling pathways via secretion of effector proteins, modulation of host's anti-inflammatory responses, and structural alterations of microbial antigens. For example, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Mycobacterium smegmatis*, *S. aureus*, and *Neisseria meningitidis* have evolved mechanisms to modify their PGN, preventing its recognition by the host immune system and facilitating efficient infection [41].

The concept of pathogen recognition by the innate immunity system has driven the discovery of numerous PRRs [42, 43]. The competition between the hosts and pathogens is thought to direct the evolution of innate immunity toward the recognition of conserved molecular structures shared across broad groups of pathogens [37]. Indeed, PRRs exhibit broad specificity and can potentially bind diverse molecules sharing common structural motifs [44, 45]. As a result, PRRs can interact not only with pathogenic microorganisms but also with other microbial components [37]. The structures recognized by the immune system are distinct from host's antigens, thereby preventing damage to the host's own cells and tissues. These pathogen-associated structures include LPSs of Gram-negative bacteria and teichoic acids of Gram-positive bacteria, viral double-stranded RNAs, mannans from yeast cell wall, and others [37].

In animals, PRRs include membrane-bound, intracellular, and secreted receptors with diverse specificities that enable the detection of a broad range of molecular signatures from viral, bacterial, fungal, and multicellular pathogens [41]. Depending on the receptor type, PRR activation can trigger multiple responses, including hemolymph coagulation, cell agglutination, release of antimicrobial factors, generation of reactive oxygen species, cytokine production, activation of phenoloxidase, phagocytosis, recruitment of immune cells, and induction of adaptive immune responses [46, 47]. PRRs are essential components of the innate immune system. Unlike adaptive immune system receptors expressed by lymphocytes (T-cell receptors, TCRs), PRRs are encoded by genes present in the inherited genome. They are constitutively expressed, recognize a wide variety of pathogens, and provide rapid systemic response to the pathogen invasion. PRRs are predominantly expressed by innate immune effector cells, including dendritic cells, natural killer (NK) cells, monocytes/macrophages, and granulocytes, as well as by endothelial and epithelial cells that among the first cells to encounter invading pathogens [37, 48]. This distribution 0f PRRs enables both immediate activation of innate effector mechanisms within cells and induction of a systemic host's response to infectious agents. With the emergence of adaptive immunity in vertebrates, signals initiated by innate (nonclonal) receptors have acquired a central role in regulating the activation and differentiation of lymphocytes bearing clonally specific antigen receptors [49, 50]. Thus, in *Drosophila*, activation of the Toll receptor stimulates the synthesis of antifungal and antibacterial peptides [51, 52], whereas in mammals, Toll-like receptors (TLRs) induce the synthesis of cytokines and costimulatory molecules required for the initiation of adaptive immune response [53].

PRRs can bind a wide range of molecules that share common structural motifs [44, 45]. Recognition of ligands by PRRs activates signaling cascades, such as nuclear factor κB (NF-κB) and type I interferon pathways, and inflammasome assembly. These events culminate in the production of proinflammatory or antiviral cytokines and chemokines, enabling the innate immune system to ensure the host survival during the early hours of infection [49].

PRRs recognize molecules exposed on the surface of microorganisms through the catalytically inactive ligand-binding domain. Ligand binding induces conformational changes in this domain and "switches on" the effector domain, which initiates the downstream signaling cascades. A defining feature of PRRs is the functional separation between ligand recognition and signal transduction that are mediated by different domains. This modular organization allows a relatively limited number of receptors to respond to a broad spectrum of ligands and to activate diverse signaling pathways. As a result, a single microbial component can be recognized by multiple types of PRRs, ensuring an appropriate and multifaceted immune response. Conserved microbial structures recognized by PRRs are referred to as PAMPs. These include bacterial cell wall components, such as LPSs of Gram-negative bacteria, PGNs, lipoteichoic acids, and lipoproteins [40, 54].

Thus, PRRs recognize conserved microbial molecular structures and trigger essential innate immune signaling pathways. Their modular organization allows a limited number of receptors to recognize a broad spectrum of pathogens and to elicit a coordinated host response. These features make PRRs not only central components of immune defense but also attractive tools for the development of diagnostic and biotechnological platforms, as they enable PAMP binding without compromising bacterial integrity.

Multiple classes of PRRs are involved in the recognition of bacterial PAMPs. In vertebrates, these include TLRs, NOD (nucleotide-binding and oligomerization domain)-like receptors (NLRs), PGN recognition proteins (PGRPs), and C-type lectin receptors (CLRs) [40, 55]. Invertebrates possess a more extensive PRR repertoire, reflecting the absence of adaptive immunity and the inability of invertebrate Toll receptors to directly bind PAMPs. In addition to the classes shared with vertebrates, invertebrate PRRs include lectins, members of the IgSF, β-1,3-glucan recognition proteins (βGRPs), and lysin motif-containing (LysM) proteins [40].

LECTINS

Lectins are a diverse group of proteins capable of specific reversible binding of carbohydrate residues through the carbohydrate recognition domain (CRD) without chemically modifying their ligands [56]. They can be classified according to several criteria, including primary structure, properties of CRD and associated domains, carbohydrate binding specificity, and subcellular localization [56-58].

C-type lectin receptors. In animals, PAMP recognition is mediated by Ca^{2+}-dependent lectins of the CLR family [59, 60]. Compared to other PRRs, CLRs are more numerous and exhibit greater morphological and functional diversity [61]. All Ca^{2+}-dependent lectins contain CRD, which is absent from other types of animal lectins. The CRD of C-type lectins is a compact globular structure of 110-130 amino acid residues, characterized by a double loop and two antiparallel β-sheets, a unique protein fold distinct from any other known structure [58, 61]. However, neither the amino acid sequence nor the three-dimensional structure of CRD reliably predicts its carbohydrate-binding specificity, as different lectins may recognize similar carbohydrate structures [62].

Structural analysis of a typical CRD from the human mannose-binding C-type lectin revealed conserved cysteine residues, a characteristic set of hydrophobic residues, and invariant glycine and proline residues. These conserved residues contribute to the formation of disulfide bonds and hydrophobic core essential for the establishment of the canonical CRD fold [63, 64]. Additional residues within the C-terminal domain are involved in the binding of Ca^{2+} ion, which constitutes the central component of the carbohydrate-binding site. Some C-terminal domains bind multiple Ca^{2+} ions; however, in all cases, the carbohydrate-binding activity is invariably associated with the conserved primary Ca^{2+}-binding site [65].

Within the CRD, one of two conserved amino acid motifs coordinates Ca^{2+} and forms hydrogen bonds with the sugar hydroxyl groups, thereby determining the primary binding specificity: the Glu-Pro-Asn (EPN) motif confers specificity for mannose, glucose, fucose, and GlcNAc, whereas Glu-Pro-Asp (QPD) ensures recognition of galactose and N-acetylgalactosamine [63, 64, 66].

Animals express two forms of CLRs: soluble and transmembrane. CLRs lacking the transmembrane domains are found in body fluids, such as mucosal secretions and blood plasma, where they participate in microbial recognition and activation of host's defense mechanisms. Soluble CLRs tend to form extended multimeric structures that enhance their capacity for microbial capture [40]. Recognition by soluble CLRs promotes opsonization, complement activation, initiation of phagocytosis, and inhibition of microbial growth. Soluble CLRs also modulate adaptive immune responses by mediating interactions between antigen-presenting cells and microbial surface carbohydrates [65, 67].

Soluble CLRs include ficolins and collectins, such as mannose-binding lectin (MBL), lung surfactant proteins A and D, and kidney collectin CL-K1 [40, 68].

Collectins. Collectin molecules consists of four regions: N-terminal leucine-rich repeat (LRR) domain, collagen-like domain, α-helical domain, and C-terminal CRD. Collectins can assemble into oligomeric structures. By binding to oligosaccharides and/or lipid moieties on the surface of microorganisms, collectins induce microbial aggregation and trigger immune responses, including modulation of inflammatory and allergic reactions [69, 70].

A typical representative of the collectin family is MBL [71]. In rodents, rabbits, and humans, MBL is synthesized in the liver and then released into the circulation [72]. Mature MBL consists of three identical glycosylated subunits of 24 kDa, linked via their collagen-like domains. These trimers further assemble into oligomers containing two to six units, forming a quaternary structure resembling a tulip bouquet [72-74]. Oligomerization markedly increases the ligand-binding affinity of MBL [72]. Within each trimer, the ligand-binding sites are spaced approximately 54 Å apart, a distance which readily permits interaction with mannose residues of bacterial cell wall LPSs, but is suboptimal for binding to mannose-containing structures of mammalian origin [71].

MBL recognizes glycans from a wide range of pathogens, including *S. aureus* and group A hemolytic streptococci [75, 76]. In the case of the meningococcal pathogen *N. meningitidis*, the binding to MBL depends on the degree of sialylation and is inhibited for encapsulated isolates [77, 78].

The binding of microorganisms to MBL activates the lectin pathway of the complement system [71, 72]. In addition, the N-terminal LRR domain of the MBL bound to a ligand on the microbial cell surface can interact with collectin receptors on macrophages, leading to phagocytosis [79].

Notably, human MBL has been used to generate functionalized magnetic particles capable of concentrating bacterial cells from biological samples [80, 81]. For this purpose, MBL lacking the collagen-like domain was expressed as a hybrid protein fused to the Fc fragment of human IgG1 (FcMBL) in CHO-DG44 cells, biotinylated, and immobilized on streptavidin-coated magnetic particles [80]. FcMBL-coated magnetic particles bound *S. aureus*, *Candida albicans*, and *E. coli* cells, enabling the capture and concentration of more than 90% bacterial cells from saliva, blood, and tears.

Ficolins. Ficolins are structurally and functionally similar to collectins. At the N-terminus, ficolins contain the LRR domain, followed by the collagen-like domain characterized by typical Gly-Xaa-Yaa repeats of variable length, and the C-terminal fibrinogen (FBG)-like domain [82-84]. The FBG domain consists of 220-250 amino acid residues and is found in a number of proteins other than fibrinogen and ficolins [85]. Individual ficolin polypeptide chains of approximately 35 kDa assemble into trimers, which further oligomerize into functional dodecamers [86].

Ficolins bind GlcNAc-containing bacterial glycans and activate the complement system [87]. L-ficolin recognizes various encapsulated *S. aureus* serotypes, group B streptococci, and *Streptococcus pneumoniae*, but does not bind nonencapsulated strains [88, 89].

In humans, three types of ficolins have been identified: M-ficolin, L-ficolin, and H-ficolin. L-ficolin and H-ficolin circulate in the bloodstream, whereas M-ficolin is expressed in tissues by activated macrophages [82, 90].

Transmembrane CLRs. Transmembrane CLRs of vertebrates are expressed on the surface of antigen-presenting cells, where they form a high-density receptor pattern. This organization facilitates strong interactions with microorganisms over limited contact areas [40]. The binding of microorganisms by transmembrane CLRs triggers endocytosis, phagocytosis, and antigen presentation to effector cells [91]. Transmembrane CLRs activate diverse intracellular signaling pathways that directly modulate cellular, homeostatic, and immune responses [67]. In particular, CLR activation can induce the release of inflammatory mediators [67]. This functional diversity is enabled by the presence of distinct effector domains within CLRs.

The cytoplasmic domains of transmembrane CLRs may contain the immunoreceptor tyrosine-based activation motif (ITAM), composed of tandem YXXL repeats, or they may signal through association with ITAM-bearing adaptor proteins such as the Fc receptor γ-chain (Fig. 2). Other CLRs include the hemi-ITAM sequence consisting of a single tyrosine-containing YXXL motif. Some CLRs contain the immunoreceptor tyrosine-based inhibitory motif (ITIM). Finally, several CRLs lack both ITAM and ITIM and utilize alternative signaling pathways [67].

The extracellular domains of many transmembrane CLRs, such as the macrophage mannose receptor (MMR), attractin, CD93, or thrombomodulin, can be shed to perform extracellular functions [92].

Based on their molecular structure, transmembrane CLRs are generally classified as either type I or type II receptors [40]. Type I CLRs feature multiple CRDs and the N-terminal region exposed on the cell surface, whereas type II CLRs have only one extracellular CRD and a cytoplasmic N-terminus. The binding of type I CLRs to PAMPs induces endocytosis followed by antigen presentation [91, 93]. Type I CLRs include CD205 and MMR. MMR is expressed on the surface of tissue macrophages and immature dendritic cells

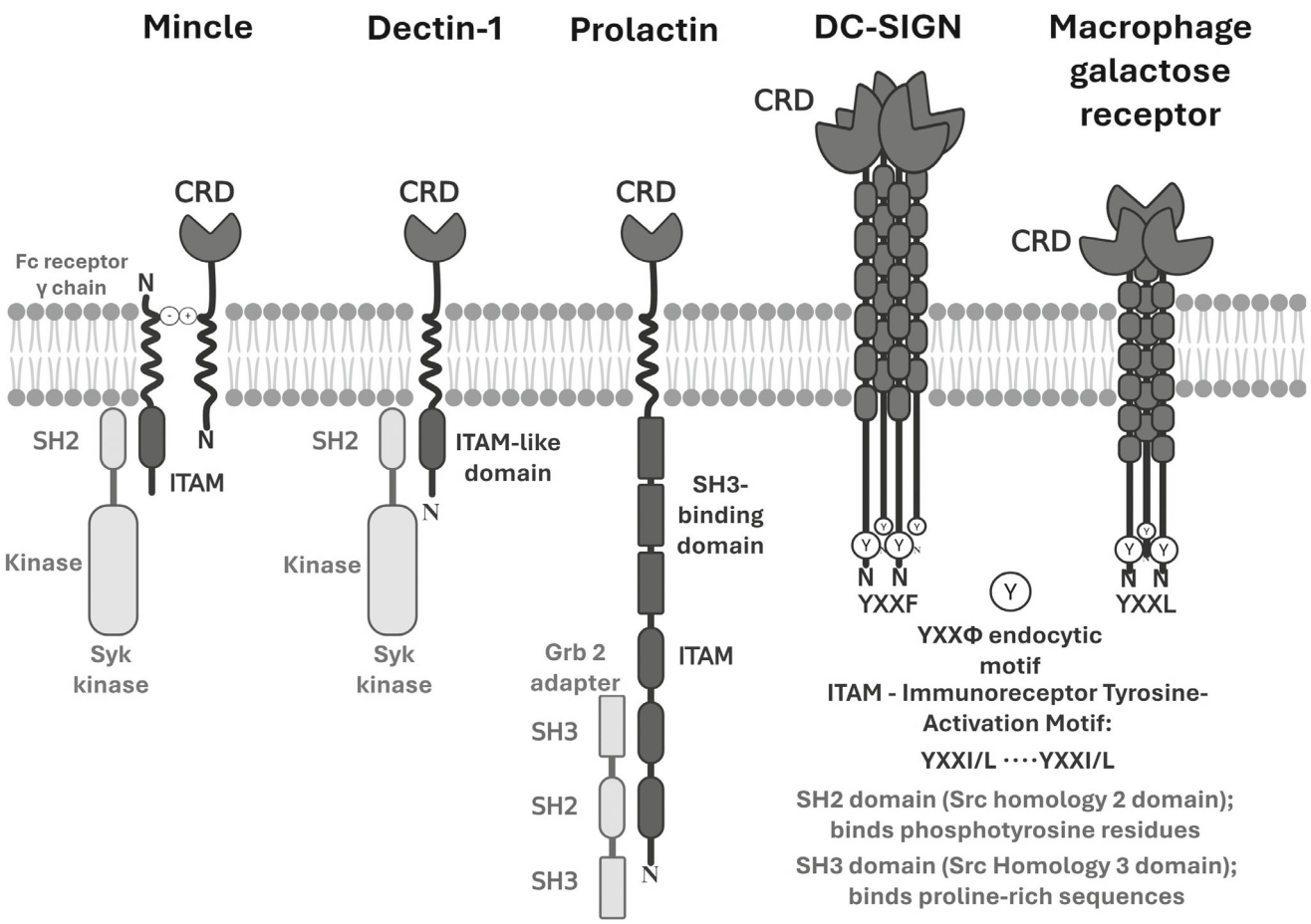

Fig. 2. Organization of proteins containing extracellular C-type CRDs and cytoplasmic domains involved in signal transduction. Phosphorylation of tyrosine residues in the ITAMs in the cytoplasmic domain generates binding sites for SH2 domain-containing signaling proteins [65].

and can bind *M. tuberculosis*, *Mycobacterium kansasii*, *Klebsiella pneumoniae*, *S. pneumoniae*, and *Francisella tularensis* cells [93]. It primarily interacts with mannose and fructose, and to a lesser extent with glucose and GlcNAc. Ligand binding by MMR is mediated by several lectin domains [94, 95].

Type II CLRs include Dectin-1, Dectin-2, Mincle, DC-SIGN (dendritic cell-specific ICAM-3 grabbing non-integrin), and DNGR-1 (dendritic cell natural killer group receptor-1) [40]. DC-SIGN interacts with a wide range of bacterial pathogens, including *M. tuberculosis*, *Mycobacterium leprae*, *Helicobacter pylori*, *Lactobacillus reuteri*, and *Lactobacillus casei* [93].

In invertebrates, PRRs of the CLR family are even more widely distributed than in vertebrates. Because invertebrates lack adaptive immunity, protection against pathogens relies entirely on the innate immune system [61]. For example, 34 CLR genes have been identified in the genome of the tobacco hornworm (*Manduca sexta*), encoding proteins with one, two, or three CRDs [96]; 23 CLR genes in the silkworm (*Bombyx mori*) [97]; and 52 CLR genes in the yellow fever mosquito (*Aedes aegypti*) [98]. Single-CRD CLRs include lectins from the flesh fly *Sarcophaga peregrina* [99] and from the hemolymph of the American cockroach *Periplaneta americana* [100]. Immulectins IML-1 and IML-2 from the hemolymph of *M. sexta* larvae, BmLBP from *B. mori*, and Hdd15 from the fall webworm (*Hyphantria cunea*) belong to a group of humoral PRRs that bind LPSs, contain two CRDs, are upregulated in response to infection, and activate the phenoloxidase cascade (a humoral innate immune pathway in invertebrates) [61].

Galectins. Galectins are S-type lectins that specifically recognize β-galactosides. They are anchored to cells via interactions between CRDs and cellular glycoconjugates. Galectins contain one or several conserved CRDs and bind ligands irrespectively of the presence of Ca^{2+} ions [101].

Galectins are expressed not only in mammals but also in birds, fish, nematodes, sponges, and fungi. They play an essential role in immune responses, inflammation, tumor progression, and metastasis [102-104]. In mammals, galectins are ubiquitously

expressed in tissues and are found in most cells of the innate immune system (dendritic cells, macrophages, mast cells, NK cells, γδ T cells, and B1 cells) and adaptive immune system (activated B and T cells) [105]. Several galectins, in pa1rticular, galectins-1 and -3, have been identified in exosomes derived from tumor cells and biological samples [106-109]. Galectin-3 has also been detected in human sperm-derived exosomes and other sources [110, 111]. Notably, galectin-3 exhibits antimicrobial activity against bacteria and fungi [112-114]. The presence of galectin-5 on extracellular vesicles released by rat reticulocytes is essential for vesicle uptake by macrophages [115]. Galectin-9 has been identified on extracellular vesicles derived from nasopharyngeal carcinoma cells infected with the Epstein–Barr virus [116].

Overall, vertebrate galectins are characterized by diverse ligand specificity. For example, rLhGal-1 from the redlip mullet (*Liza haematocheila*) binds both Gram-positive (*Lactococcus garvieae*, *Streptococcus iniae*, *Streptococcus parauberis*) and Gram-negative (*E. coli*, *Edwardsiella tarda*, *Vibrio anguillarum*, *Vibrio harveyi*) bacteria [117]. Human galectin-3 binds LPSs from *K. pneumoniae*, *Salmonella enterica*, mycolic acids of *M. tuberculosis*, the O-antigen of *H. pylori*; it also induces neutrophil recruitment to the sites of *S. pneumoniae* invasion. Moreover, *H. pylori* infection promotes expression of galectin-8 and, to a lesser extent, galectins-3 and -4 [105]. Mammalian galectins-4 and -8 contain two CRDs located at the at the N- and C-termini, from which only the N-terminal CRD exhibits bactericidal activity. These CRDs also differ in ligand specificity, enabling galectins to recognize both microbial oligosaccharides and endogenous lactosamine-containing glycans. By forming cross-links between endogenous and exogenous glycans, galectins facilitate opsonization.

Galectins also play important roles in invertebrate immunity. For instance, MjGal from the Kuruma shrimp *Marsupenaeus japonicus* acts as a typical PRR: its expression is induced upon infection, and it recognizes both Gram-positive and Gram-negative bacteria. MjGal also binds carbohydrates on the surface of shrimp hemocytes and potentially mediates their interactions with pathogens, facilitating phagocytosis and clearance of pathogens from the circulatory system. Notably, some viruses, bacteria, and protozoan parasites exploit galectins to promote invasion and evade the host's immune response [101]. In the oyster *Crassostrea virginica*, galectins CvGal1 and CvGal2 recognize multiple bacterial species, as well as the protozoan parasite *Perkinsus marinus*. These galectins function as opsonins, enhancing pathogen adhesion and phagocytosis. However, *P. marinus* can survive phagocytosis and replicates within host cells, leading to systemic infection and high mortality, thus exemplifying parasite–host coevolution [118].

Interestingly, CvGal contains four non-identical CRDs, yet minor sequence variations among these conserved domains do not result in significant differences in their binding properties. CvGal can form cross-links between self and foreign glycans. Remarkably, even galectins with a single CRD can mediate interactions with both pathogen- and host-derived oligosaccharides. The binding specificity of CRDs is thought to be regulated by multiple factors, including local lectin concentration and extent of oligomerization, spatial arrangement of multivalent carbohydrate ligands on the cell surface, CRD solvation, and properties of the microenvironment in which interactions occur [119]. Other examples of pathogens exploiting host galectins for invasion have also been reported [101, 115, 116].

In addition to the lectin classes discussed above, other lectins have been identified, including intelectins, which recognize galactose determinants, and sialic acid-binding lectins (type I lectins). These proteins largely share the structural and functional features of lectins described above.

Therefore, lectins constitute a functionally diverse group of innate immune molecules, encompassing transmembrane CLRs, soluble collectins and ficolins, and calcium-independent galectins. Their capacity to recognize a broad spectrum of carbohydrates, modular organization, and diversity of signaling pathways make lectins key biorecognition molecules and promising tools in the development of diagnostic and therapeutic applications.

TOLL-LIKE RECEPTORS

TLRs of vertebrates are homologs of Toll receptors first discovered in *Drosophila* [120]. The Toll signaling pathway is conserved in many multicellular organisms [121-123]. In *Drosophila*, Toll signaling mediates defense against Gram-positive bacteria and fungi; its activation induces expression of antimicrobial peptides and cellular immune responses [124].

Components of the Toll pathway have been identified in a broad range of invertebrate species, including planarians, mussels, tardigrades, mollusks, crustaceans, and others [125]. In vertebrates, TLRs directly recognize and bind PAMPs [126, 127]. In contrast, in insects, PAMP recognition by TLRs is mediated by the Spätzle protein [128]. Despite these differences, the cytoplasmic signaling cascades downstream of both Toll receptors and TLRs are highly conserved. Activation of either TLRs or Toll receptors leads to the nuclear translocation of NF-κB transcription factors (Dorsal and Dif in *Drosophila* and NF-κB p65 in vertebrates),

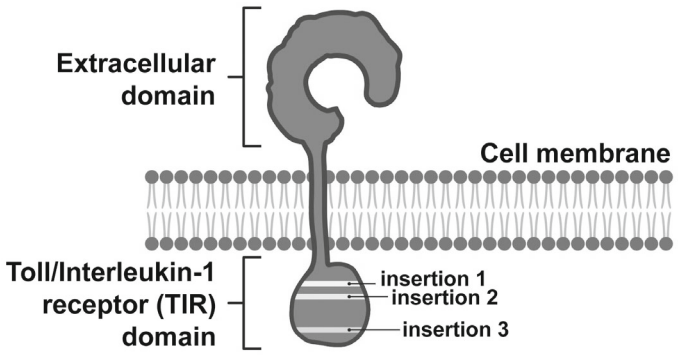

Fig. 3. TRL structure.

which in turn activates the expression of antimicrobial peptides in insects and cytokines stimulating the adaptive immune system in vertebrates [122].

TLRs are critical for linking innate and adaptive immunity, as they regulate the activation of antigen-presenting cells and expression of key cytokines. TLR signaling directly influences activation, growth, differentiation, development, and function of T cells across multiple physiological contexts [53].

To date, 13 TLRs have been identified in mammals. Each recognizes specific ligands and is expressed in various cell types [129]. TLRs are integrated into the plasma membrane (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) or can be located in the membranes of intracellular endosomal compartments, such as endoplasmic reticulum, endosomes, lysosomes, and endolysosomes (TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13) [130]. All TLRs undergo N-glycosylation as a post-translational modification, which is essential for their normal function, biosynthesis, and secretion [131].

Structurally, TLRs are type I transmembrane proteins composed of the extracellular, transmembrane, and cytosolic domains. The ectodomains of TLRs contain 19-25 tandem LRRs, each consisting of 24-29 amino acids and including the XLXXLXLXX motif, along with other conserved residues. LRRs are composed of β-strands and α-helices connected by unstructured regions, forming a horseshoe-shaped structure (Fig. 3) [132]. The LRR domains are thought to provide rapid evolutionary adaptation of the ligand-binding specificity toward recognition of a wide variety of ligands [131]. More broadly, LRRs are components of domains involved in specific protein interactions. Approximately 500 LRR-containing proteins with diverse, often unknown, functions have been identified in the human genome [129].

In their inactive state, TLRs exist as monomers in the membrane. Ligand binding induces receptor dimerization, resulting in the formation of either homo- or heterodimers. For example, TLR2 forms heterodimers with TLR1 or TLR6 depending on the ligand: the TLR2–TLR1 complex recognizes triacylated lipopeptides, whereas TLR2–TLR6 recognizes diacylated lipopeptides [35, 129]. The activity of certain TLRs relies on co-receptors. Thus, effective recognition of bacterial LPS by TLR4 requires MD-2, CD14, and LPS-binding protein [133]. Ligand-induced multimerization is considered a critical step in the activation of multiple TLRs [35]. Conformational changes induced by ligand binding and/or receptor dimerization initiate signal transduction to the intracellular Toll/interleukin-1 receptor (TIR) domain, which in turn recruits specific adaptor molecules (MyD88, TIRAP, TRIF, and others), ultimately leading to the activation of the transcription factor NF-κB and transcription of proinflammatory cytokine genes [32].

TLRs recognize a broad array of PAMPs from virtually all known microbial groups. Plasma membrane-associated TLRs primarily detect microbial surface structures. Several TLR subfamilies can be distinguished based on recognized PAMPs: the TLR1/TLR6 subfamily recognizes PGN, TLR2 detects lipoproteins and lipopeptides, TLR4 recognizes bacterial LPS, and TLR5 binds flagellin. In contrast, intracellular TLR3, TLR7, TLR8, and TLR9 recognize nucleic acids [134-138].

Therefore, TLRs represent a highly conserved pathogen-recognition system. In invertebrates, Toll signaling mediates antimicrobial peptide production via the Toll–Spätzle pathway, whereas mammalian TLRs directly recognize PAMPs and initiate cascades leading to the activation of NF-κB and interferon regulatory factors (IRFs) and production of proinflammatory cytokines. By integrating innate and adaptive immune responses, TLRs play a central role in host defense and are among the most extensively studied PRR families.

NOD-LIKE RECEPTORS

NLRs are a family of cytoplasmic PRRs responsible for the recognition of bacterial cell wall components,

viral nucleic acids, and endogenous stress signals [139, 140]. A defining structural feature of these proteins is the presence of the oligomerization-mediating NACHT domain, C-terminal LRRs involved in ligand recognition, and N-terminal effector domain (CARD, PYD, or BIR) providing interactions with adaptor molecules [141].

Among the best-characterized members of this family are NOD1 and NOD2. They recognize distinct PGN fragments: NOD1 binds γ-D-glutamyl-meso-DAP (iE-DAP) characteristic of Gram-negative bacteria, while NOD2 binds muramyl dipeptide (MDP), present in the cell walls of most bacteria. Ligand binding to NOD1/2 leads to the recruitment of the adaptor RIPK2 protein, activation of NF-κB and MAPK (mitogen-activated protein kinase), and subsequent induction of proinflammatory cytokines and antimicrobial peptides [142].

A distinct subset of NLRs participates in the assembly of inflammasomes, which are multiprotein complexes responsible for the activation of caspase-1 and processing of IL-1β and IL-18 [143]. The most extensively studied inflammasome-forming NLR is NLRP3 activated by a wide range of stimuli, including bacterial toxins, uric acid crystals, ATP, and reactive oxygen species. Other inflammasome-forming NRLs are NLRP1 and NLRC4, which is activated by bacterial flagellin.

Collectively, NLRs represent a critical arm of intracellular immune surveillance enabling detection of bacterial and viral invasion of cytoplasm and endogenous stress signals. Their activation provides rapid production of proinflammatory mediators and initiation of programmed inflammatory responses through the inflammasome formation.

PEPTIDOGLYCAN RECOGNITION PROTEINS

PGN recognition proteins (PRPs) are referred to as PGRPs in invertebrates and PGLYRPs in vertebrates [144]. Both the PGRP and PGLYRP families play important roles in pathogen recognition, with different proteins recognizing specific classes of microorganisms (Fig. 4). In insects, PGRPs constitute the major class of PRRs. They activate Toll signaling and immune deficiency (Imd) pathways, induce proteolytic cascades leading to local melanization at infection sites, stimulate the expression of antimicrobial peptides, hydrolyze PGN, and trigger phagocytosis [54, 144, 145]. The Imd/Relish pathway specifically contributes to defense against Gram-negative bacteria, promoting NF-κB-dependent expression of antimicrobial peptides.

More than a dozen genes encoding PGRPs have been identified in insects. Alternative splicing of their transcripts produces short (S) and long (L) splice isoforms. For example, in *D. melanogaster*, 13 loci generate 19 splice isoforms, whereas in *Anopheles gambiae*, seven PGRP loci give rise to nine splice isoforms [149, 150]. Long insect PGRPs are expressed in hemocytes and lack catalytic activity, except for PGRP-LB, which is expressed in enterocytes and functions as an N-acetylmuramoyl-L-alanine amidase [144]. PGRP-LC mediates elimination of primarily of Gram-negative bacteria and triggers the Imd signaling pathway [151]. PGRP-LC is the main type II transmembrane receptor of the Imd pathway; its activation results in the processing of Relish, a member of the Rel/NF-κB family. Activated Relish translocates to the nucleus where it induces the expression of genes encoding antibacterial peptides, such as drosomycin, mechnikovin, attacin, diptericin (Dpt), and cecropin A1 (CecA1) [152-155]. The three PGRP-LC splice isoforms share identical cytoplasmic and transmembrane domains, whereas their extracellular domains are only 39% identical and are activated by different PGNs [155]. PGRP-LCx homodimers recognize polymeric DAP-type PGN, while PGRP-LCx/PGRP-LCa heterodimers bind Lys-type PGN [150].

Another form, PGRP-LE, exists as a secreted receptor, whereas the non-cleaved form functions as an intracellular receptor [156] that binds DAP-type PGN [151].

In *Drosophila*, PGRP-LB binds DAP-type PGN and is encoded by the gene producing three isoforms: cytosolic PGRP-LBPA and PGRP-LBPD expressed in enterocytes and secreted PGRP-LBPC present in the intestinal lumen [157]. PGRP-LBPC and PGRP-LBPA represent the same mature protein (PGRP-LBPA/PC), whereas PGRP-LBPD features an extended N-terminus. PGRP-LB is thought to degrade PGN into non-immunogenic fragments, thereby preventing constitutive systemic immune activation in response to gut microbiota [158].

Soluble PGRP-SD binds DAP-type PGN and facilitates its representation to PGRP-LC on the cell surface, thus promoting activation of the Imd pathway [159].

X-ray crystallographic analysis of the PGRP domains of PGRP-LC and PGRP-LE has elucidated the mechanism of recognition of DAP- and Lys-type PGNs. In DAP-type PGN recognition, an electrostatic interaction occurs between the two negatively charged carboxyl groups of DAP and an arginine residue in the PGRPs. In contrast, PGRPs that bind Lys-type PGN lack this arginine residue [146, 148, 151]. Moreover, two distinct binding sites were identified in the PGRP domain: the first binds PGN in an L-shaped groove, while the second binds a PGN fragment already associated with the L-shaped groove of another PGRP domain. This results in the formation of a PGRP homodimer that tightly binds the ligand [146].

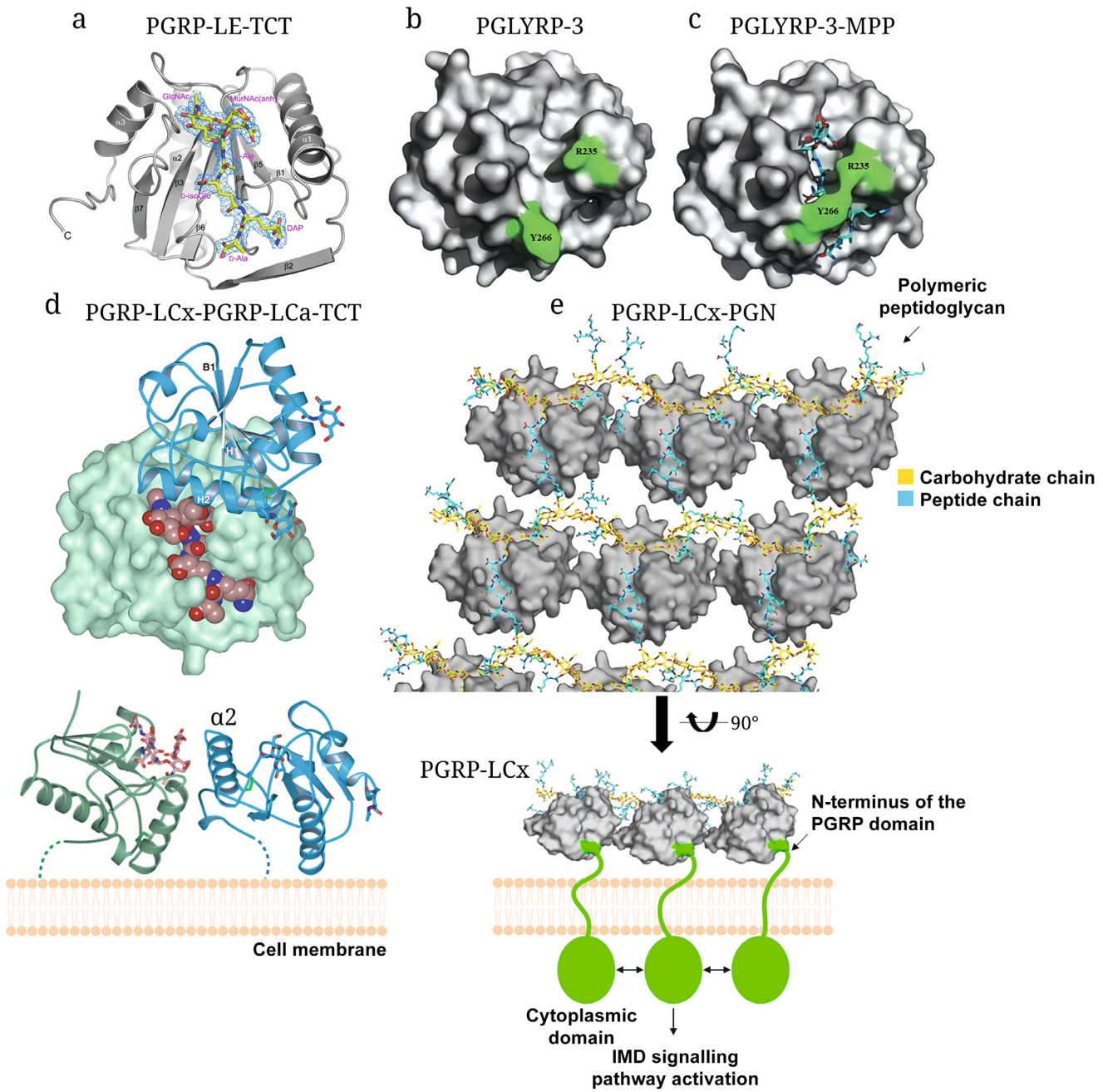

Fig. 4. PGRP complexes with PGN fragments: structure, ligand-induced conformational changes, dimerization, and oligomerization. a) Ribbon diagram of *D. melanogaster* PGRP-LE with the C-terminus in complex with a monomeric PGN fragment of the tracheal cytotoxin (TCT; GlcNAc-1,6-anhydro-MurNAc-L-Ala-D-isoGlu-DAP-D-Ala) [146]. b and c) The surface of the C-terminal domain of human PGLYRP-3 [147] (b) and its complex with N-acetylmuramic acid pentapeptide (MPP) [147], which induces conformational changes in the PGRP domain (green), locking the ligand within the PGN-binding groove (c). d) TCT induces dimerization of the extracellular domains of PGRP-LCx (green, space-filling model) and PGRP-LCa (blue ribbon) through interactions with the PGN-binding groove of PGRP-LCx and second α-helix (α2) of PGRP-LCa [148]. e) Binding of polymeric PGN to *D. melanogaster* PGRP-LCx at the cell surface induces PGRP-LCx oligomerization. Dimerization or oligomerization of PGRP-LC leads to the activation of the Imd signaling pathway [146].

Short PGRPs of insects recognize Lys-type PGN and initiate a proteolytic cascade that results in Spätzle cleavage and release of Toll receptors [160]. An exception is the soluble PGRP-SC1b of *Drosophila*, which recognizes DAP-type PGNs. PGRP-SC1b exhibits the N-acetylmuramoyl-L-alanine amidase activity, enabling PGN cleavage and manifestation of bactericidal properties of PGRP-SC1b [161]. Short PGRPs are present in the hemolymph, cuticle, and fat bodies, and are sometimes found in intestinal epithelial

cells and hemocytes [144]. Soluble PGRP-SA, present in the hemolymph, is required for normal immune responses to Gram-positive bacteria [162]. PGRP-SA predominantly recognizes Lys-type PGN [151]. The binding of Gram-positive PGN by PGRP-SA and GNBP1 (Gram-negative bacteria-binding protein 1) activates a proteolytic cascade that produces the mature Toll ligand [150, 163-165]. Activation of Toll receptors promotes the nuclear translocation of Dif and Dorsal (members of the Rel/NF-κB family), which induce expression of the antimicrobial peptide drosomycin [166].

Four PGLYRP genes have been identified in mammals. *PGLYRP-1* encodes the short form PGRP-S (19-25 kDa); *PGLYRP-2* encodes the long form PGRP-L (up to 90 kDa), while *PGLYRP-3* and *PGLYRP-4* encode the intermediate forms PGRP-Iα and PGRP-Iβ (40-45 kDa) [167]. All four human PGLYRPs bind PGN, as well as Gram-positive and Gram-negative bacteria [168, 169].

PGLYRP-2 is constitutively expressed in the liver and secreted into the bloodstream. It is also found in intestinal epithelial cells and is induced in keratinocytes and other epithelial cells in response to bacteria and cytokines [169]. PGLYRP-2 is the only N-acetylmuramoyl-L-alanine amidase that hydrolyzes PGN and reduces its pro-inflammatory activity [144, 170]. It preferentially binds soluble PGNs [171] and induces inflammatory responses, with its immunomodulatory effects occurring independently on the amidase activity [167].

PGLYRP-1, PGLYRP-3, and PGLYRP-4 are soluble proteins that exist as homo- and heterodimers linked by disulfide bonds [144]. All three proteins exhibit direct bactericidal activity against a wide range of Gram-positive and Gram-negative bacteria [172]. In addition, PGLYRP-3 stimulates phagocytosis and modulates immune responses in a context-dependent manner [167]. PGLYRP-1 primarily localizes to the granules of polymorphonuclear leukocytes, whereas PGLYRP-3 and PGLYRP-4 are expressed in the skin, eyes, salivary glands, tongue, throat, esophagus, stomach, and intestine [172]. In mammals, PGLYRP-3 and PGLYRP-4 contain two non-identical PGRP domains [160]. The bactericidal activity of these proteins is mediated through their interaction with PGN. During bacterial cell division, the PGRP domain binds an exposed region of PGN and activates the CssR–CssS two-component system, which detects misfolded secreted proteins. The bound PGRP domain is recognized by bacterial cells as a defect in protein secretion, triggering a cascade that results in membrane depolarization, production of hydroxyl radicals in the cytoplasm, and, ultimately, bacterial death [170, 172].

Thus, PGRPs/PGLYRPs constitute a family of PRRs that provide defense in both invertebrates and mammals. In insects, PGRPs participate in humoral and cellular defense through the Toll, Imd, and phenoloxidase pathways. In mammals, PGLYRPs combine direct bactericidal activity with enzymatic inactivation of PGN and immunomodulatory functions. Such functional versatility makes this family one of the most unique components of innate immunity crucial for maintaining the balance between inflammation and tolerance to the microbiota. In addition to PGRP/PGLYRP, invertebrates possess abundant βGRPs and GNBPs, which interact with PGRPs and jointly activate the Toll pathway and the phenoloxidase system.

β-1,3-GLUCAN RECOGNITION PROTEINS AND GRAM-NEGATIVE BACTERIA-BINDING PROTEINS

βGRPs are found in most invertebrates, including insects, crustaceans, and mollusks [173]. βGRPs/GNBPs are structurally and functionally related to PGRPs: they act as invertebrate PRRs in the hemolymph and initiate similar signaling cascades. However, βGRPs/GNBPs primarily recognize β-1,3-glucans and LPSs, hereby expanding the spectrum of detectable pathogens [173]. GNBPs and βGRPs belong to the same PRR family that recognizes β-1,3-glucans [174, 175].

The first βGRP was described in the silkworm *B. mori* as a protein capable of binding to the cell wall of Gram-negative bacteria. The *B. mori* GNBP (BmGNBP) shares sequence similarity with CD14, a co-receptor of vertebrate TLRs, and specifically binds anti-CD14 antibodies [176]. *Drosophila* GNBP1 exhibits structural resemblance to CD14 due to its glycosylphosphatidylinositol (GPI)-mediated membrane anchoring [126].

In insects, βGRPs are expressed in the fat body and are constitutively present in the hemolymph. Upon binding to microbial cells, βGRPs activate the Toll pathway and initiate prophenoloxidase cascades, leading to melanization at the site of tissue damage [175, 177, 178].

Full-length recombinant βGRPs bind whole bacterial cells [175, 177, 179, 180] through the cysteine-rich (CR) domain recognizing β-1,3-glucan, LPSs, or lipoteichoic acid [178, 181]. Most βGRPs contain the glucanase-like domain that is susceptible to proteolytic cleavage and generally exhibits lower affinity for polysaccharides than the CR domain [178]. Ligand binding promotes interaction of βGRPs with an initiating serine protease which undergoes autoactivation and triggers a series of reactions resulting in the proteolytic activation of phenoloxidases, Spätzle, and other cytokines [182]. However, in βGRP from the Indianmeal moth *Plodia interpunctella*, both CR and glucanase-like domains bind laminarin (soluble β-1,3-glucan). This protein is used for diagnosing

fungal infections [179, 183]. The glucanase-like domain of *B. mori* GNBP3 lacks the glucanase activity and affinity for β-1,3-glucan [173]. Similarly, this domain is enzymatically inactive in *Drosophila* and *P. interpunctella* βGRPs, whereas genomes of *A. gambiae* and *Daphnia pulex* encode proteins with and without predicted catalytic sites [178]. Although the glucanase-like domain had been initially proposed to have evolved for glucan binding [179], subsequent evidence indicates that its primary function in catalytically inactive βGRPs is to recruit adaptor proteins required for the initiation of the serine protease cascade [175].

Some βGRPs interact with PGRP-family receptors that recognize Lys-type PGN [165]. For example, *Drosophila* GNBP1 and GNBP2 participate in the Toll pathway activation in response to Gram-positive bacterial infection [173]. GNBP1 is thought to hydrolyze Gram-positive PGN with the generation of muropeptides that are subsequently recognized by PGRP-SA; GNBP1 and PGRP-SA physically interact [160, 184]. Target recognition initiates a proteolytic cascade leading to the activation of Spätzle, the ligand of the Toll receptor on the surface of immune cells [185].

Three distinct GNBPs have been identified in *D. melanogaster* (DmGNBP1–3). DmGNBP1 exhibits high affinity for both β-1,3-glucan and LPS and exists in both soluble and membrane-anchored forms, the latter being covalently linked to the membrane via a GPI anchor. DmGNBP3 plays a key role in the defense against fungal infections and represents an ortholog of βGRP family proteins from *B. mori* and *A. gambiae* [173, 180].

In mosquitoes of the *Anopheles* genus, GNBPB4 is of particular importance due to its broad specificity. In addition to the antibacterial defense, it contributes to protection against *Plasmodium* parasites by interacting with *Plasmodium berghei* ookinetes in the midgut epithelium [185].

Related proteins with similar sequences and functions have been described in insects from other orders. For instance, in *M. sexta*, recombinant GNBP induced prophenoloxidase activation in the hemolymph, enhanced antimicrobial peptide expression, and acted synergistically with PGRP, indicating close cooperation among different PRRs [186].

Comparative analysis of amino acid sequences reveals a high degree of conservation among GNBPs across diverse insect species. Notably, most GNBPs lack the catalytic residues required for the glucanase hydrolytic activity, indicating that the primary function of βGRPs/GNBPs is ligand binding and signal transmission rather than ligand degradation [47, 174, 176, 186-190].

Together with PGRPs, βGRPs/GNBPs form a major PRR family in invertebrates. While PGRPs primarily recognize PGN, βGRPs/GNBPs expand the immune recognition repertoire to include fungal β-1,3-glucans and LPSs from Gram-negative bacteria. Through their interactions with protease cascades and PGRPs, βGRPs/GNBPs provide integrate multiple signals and coordinate activation of the Toll and phenoloxidase pathways, emphasizing the highly cooperative nature of invertebrate innate immune system.

IMMUNOGLOBULIN SUPERFAMILY RECEPTORS

PRRs of the IgSF are characterized by the presence of one or more Ig-like domains, each forming a sandwich-like structure composed of two β-sheets. The IgSF represents one of the largest and diverse protein families, unified by the presence of these conserved structural domains. Members of this superfamily play essential roles in cell–cell interactions, adhesion, and recognition of foreign molecules. Many IgSF receptors participate in both innate and adaptive immune responses, thereby forming a functional “bridge” between different branches of the immune system [191].

In invertebrates, IgSF members play a significant role in immune defense and, similar to mammalian immunoglobulins, exhibit substantial diversity, which is critical for their functional activity [192, 193]. A particularly well-studied example is DSCAM (down syndrome cell adhesion molecule) found in insects and crustaceans. Through extensive alternative splicing, DSCAM forms tens of thousands of isoforms, each with unique ligand specificity. This hypervariability functionally parallels DSCAM with components of the vertebrate adaptive immune system, enabling recognition of a broad spectrum of pathogens and providing phenotype-level immune memory in invertebrates [192, 194].

Another important class is fibrinogen-related proteins (FREPs), which have been most extensively studied in the gastropod *Biomphalaria glabrata*. FREPs contain variable Ig domains at the N-terminus and a conserved fibrinogen-like domain of approximately 200 amino acids at the C-terminus, which is homologous to the β- and γ-chains of vertebrate fibrinogen [195, 196]. Through somatic mutations and exon loss, FREPs exhibit pronounced polymorphism, enabling selective binding of a broad range of pathogens [192]. For example, FREP3 interacts with bacteria and fungi, whereas FREP2 predominantly binds sporocysts of pathogenic trematodes [196]. FREP3 has been shown to bind monosaccharides, with the highest affinity toward α-D-galactose [197, 198]. Some FREPs form multimers, which presumably enhances their antigen-binding efficiency [199-201].

FREP analogues have also been described in other invertebrates, including the Mediterranean mussel *Mytilus galloprovincialis*, the mud crab *Scylla paramamosain*, the bay scallop *Argopecten irradians*, the signal crayfish *Pacifastacus leniusculus*, the Chinese razor clam *Sinonovacula constricta*, and the Pacific oyster *Crassostrea gigas* [198, 202, 203]. The latter contains the IgSF family member CgIgIT2 composed of four Ig domains, one fibronectin type III domain, a transmembrane region, and a cytoplasmic effector domain. Recombinant CgIgIT2 binds LPSs, PGN, and mannose, with the highest affinity for LPSs, and efficiently interacts with Gram-negative bacteria (*Vibrio splendidus*, *V. anguillarum*, *E. coli*), Gram-positive bacteria (*S. aureus*, *B. subtilis*), and the yeast *Pichia pastoris* [204].

Hemolin is a characteristic IgSF receptor in insects, which was first isolated from pupae of Cecropia moth (*Hyalophora cecropia*) infected with bacteria (Fig. 5) [205]. Hemolin contains four Ig domains [206, 207]; it is secreted into the hemolymph and also exists in a membrane-bound form associated with hemocytes [208].

Hemolin binds LPSs of Gram-negative bacteria and lipoteichoic acids of Gram-positive bacteria, resulting in microbial agglutination. It does not exhibit direct bactericidal activity but functions as an agglutinin that restricts pathogen dissemination [206, 210, 211].

Recombinant hemolin expressed in *E. coli* cells induced agglutination of *E. coli* cells in the presence of calcium, thereby confirming its role as a biorecognition molecule (Fig. 5) [209]. Interestingly, hemolin-like proteins, which had previously been thought to be specific to *Lepidoptera*, have also been identified in the whiteleg shrimp *Litopenaeus vannamei* [212].

Thus, IgSF receptors in invertebrates are represented by a number of specialized molecules (DSCAM, FREPs, hemolin, CgIgIT2, and others). Their distinguishing features are hypervariability and capacity for multimerization, which substantially broaden the spectrum of foreign structures they can recognize. In contrast to PGRPs or βGRPs/GNBPs, IgSF receptors do not exhibit direct bactericidal activity; instead, they play a key role in pathogen agglutination, activation of signaling cascades, and integration of innate immune responses with more complex adaptive mechanisms.

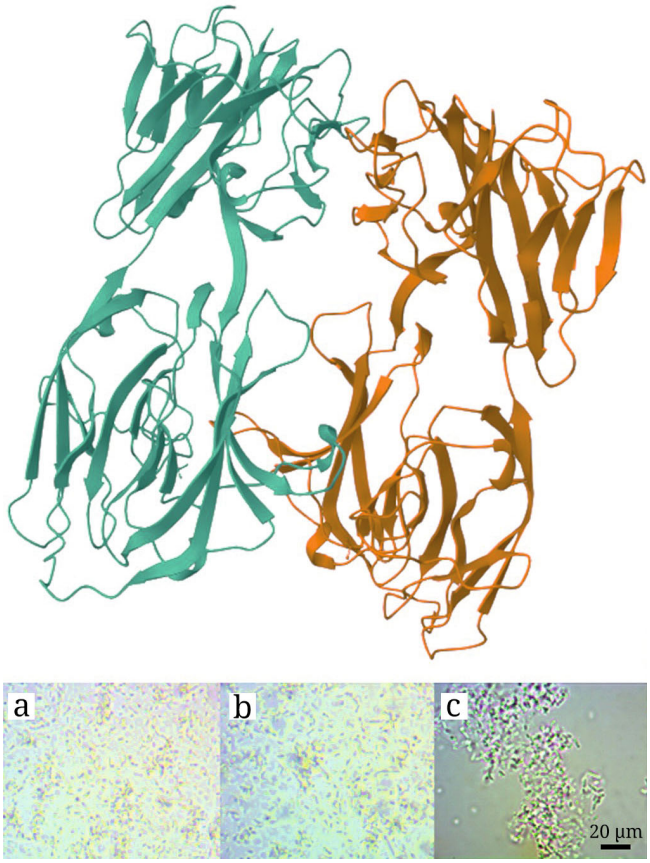

Fig. 5. Structure of hemolin (UniProt P25033) (top panel). Agglutination of *E. coli* cells by recombinant hemolin (bottom panel): *E. coli* cell in PBS (a), in PBS with BSA (b), and in PBS containing recombinant hemolin (c) [209].

PROTEINS CONTAINING THE LysM DOMAIN

LysM is a highly conserved carbohydrate-binding module of approximately 40 amino acids, that is widely distributed among proteins in most living organisms except archaea [213]. LysM binds a variety of ligands containing GlcNAc [214]. Despite the variability of their amino acid sequences, LysM domains adopt a highly conserved fold consisting of two α-helices adjacent to two antiparallel β-strands [215]. Conserved residues include Ile/Leu at positions 23 and 30 and Asn at position 27. Most LysM-containing proteins contain multiple LysM repeats, which enhances their ligand-binding affinity [213].

The name *LysM* originates from the first identification of these motifs in lysins of *Bacillus* phage *θ29*, which degrade bacterial cell wall [216]. Since then, LysM domains have been found in numerous proteins involved in diverse biological processes:

1. In bacteria, LysM sequences are present in PGN hydrolases, adhesins, and virulence factors [217];
2. In fungi, LysM-containing effector proteins, such as Ecp6 in *Cladosporium fulvum* and Slp1 in *Magnaporthe oryzae*, block chitin recognition by plant PRRs [218];
3. In plants, LysM receptor-like proteins (LysM-RLPs) and receptor-like kinases (LysM-RLKs) recognize chitin and PGN and initiate immune responses [79, 215];

4. In vertebrates, LysM proteins are represented by the highly conserved subfamilies LysMD and OXR [219-221]. Interestingly, expression of these proteins was not induced by bacterial pathogens in either zebrafish (*Danio rerio*) or mice (*Mus musculus*) [220, 222, 223]. The physiological functions of LysM proteins in vertebrates remain largely unknown [221].

In contrast to vertebrates, LysM-containing proteins play a more prominent role in the immune defense in invertebrates. They are expressed in hemocytes, gills, and the intestine. These proteins bind components of bacterial cell wall and can induce the expression of antimicrobial peptides [222, 224, 225]:

1. In the red swamp crayfish *Procambarus clarkii*, PcLysM is strongly upregulated following infection with *V. anguillarum* and *S. aureus* and participates in antibacterial defense [222];
2. In the mud crab *S. paramamosain*, SpLysMD3 expression increases upon bacterial invasion. The knockout of this protein reduces antimicrobial peptide levels. SpLysMD3 binds Gram-negative (*Vibrio* spp., *E. coli*) and Gram-positive (*S. aureus*, *Bacillus* spp.) bacteria and the yeast *C. albicans*, confirming its role as a PRR [224];
3. In the Kuruma shrimp *M. japonicus*, a LysM protein regulates the transcription of immune genes and promotes elimination of *V. anguillarum in vivo* [226];
4. In the Hong Kong oyster *Crassostrea hongkongensis*, ChLysM is expressed mainly in hemocytes and gills. It binds PGN and LPSs and exhibits direct bactericidal activity against *S. aureus*, *B. subtilis*, *E. coli*, and *Vibrio alginolyticus* [227];
5. In the whiteleg shrimp *L. vannamei*, LvLysM2 regulates antimicrobial peptide expression and binds various bacterial polysaccharides [228].

LysM domains are found across virtually all kingdoms of living organisms. In plants and fungi, LysM proteins play a key role in the immune recognition of PAMPs. In vertebrates, their functions remain poorly characterized. In invertebrates, LysM proteins function as bona fide PRRs: they bind PGN and LPS, stimulate the expression of antimicrobial peptides, and exhibit intrinsic bactericidal activity.

SCAVENGER RECEPTORS

Scavenger receptors (SRs) constitute a functionally defined, rather than structurally homologous, family of innate immune receptors. They are united by their ability to bind a wide range of endogenous and exogenous ligands, from modified lipoproteins and apoptotic cells to bacterial cell wall components. The SR family includes more than 30 members grouped into several classes (A-J), which differ in the architecture of extracellular domains but share overlapping functional properties [37, 178].

SRs can interact with LPS, PGN, lipoteichoic acids, fungal surface polysaccharides, as well as oxidized lipids and nucleic acids. Thus, by combining the properties of PRRs and scavengers, they remove both pathogenic microbial components and products of cellular degradation from the organism [229].

In *D. melanogaster*, SR-CI has been identified as a PRR that binds bacteria and mediates their phagocytosis. Mutations in its gene reduce the phagocytic activity of hemocytes [229]. Other *Drosophila* SRs, such as Croquemort (SCRBQ2), are involved in the clearance of apoptotic cells and can also bind bacterial components [151]. These findings indicate that insect SRs perform a dual function, contributing to both the antibacterial immunity and the maintenance of tissue homeostasis.

In vertebrates, SRs are represented by multiple subfamilies [230]:

1. Class A (SR-A, MARCO). Macrophage receptors that bind LPS, lipoteichoic acid, and PGN. MARCO is expressed on macrophages and dendritic cells and plays a key role in bacterial uptake.
2. Class B (CD36, SR-BI) participates in lipid metabolism and bind bacterial cell components.
3. Class E (LOX-1) binds oxidized lipoproteins and bacterial antigens, contributing to endothelial inflammatory responses.
4. Class F (SREC-I) is involved in bacterial phagocytosis and antigen presentation.

Overall, SRs contribute to immunity through multiple mechanisms including phagocytosis of bacteria and apoptotic cells, recognition of bacterial cell wall components (LPS, PGN, lipoteichoic acids), innate immune signal transduction (NF-κB activation, cytokine production), regulation of inflammation (both pro- and anti-inflammatory processes), and participation in autophagy.

Thus, SRs represent a broad and functionally heterogeneous family of PRRs united by their ability to bind a wide range of foreign and modified self molecules. In insects, SRs mediate bacterial phagocytosis and clearance of apoptotic cells, whereas in vertebrates, they play a crucial role in the clearance of pathogens and endogenous ligands, integrating immune recognition with the maintenance of tissue homeostasis.

APPLICATION OF PRRS AS BIOSENSING MOLECULES

Natural PRRs are molecules with a high selectivity for conserved PAMPs, which makes them highly

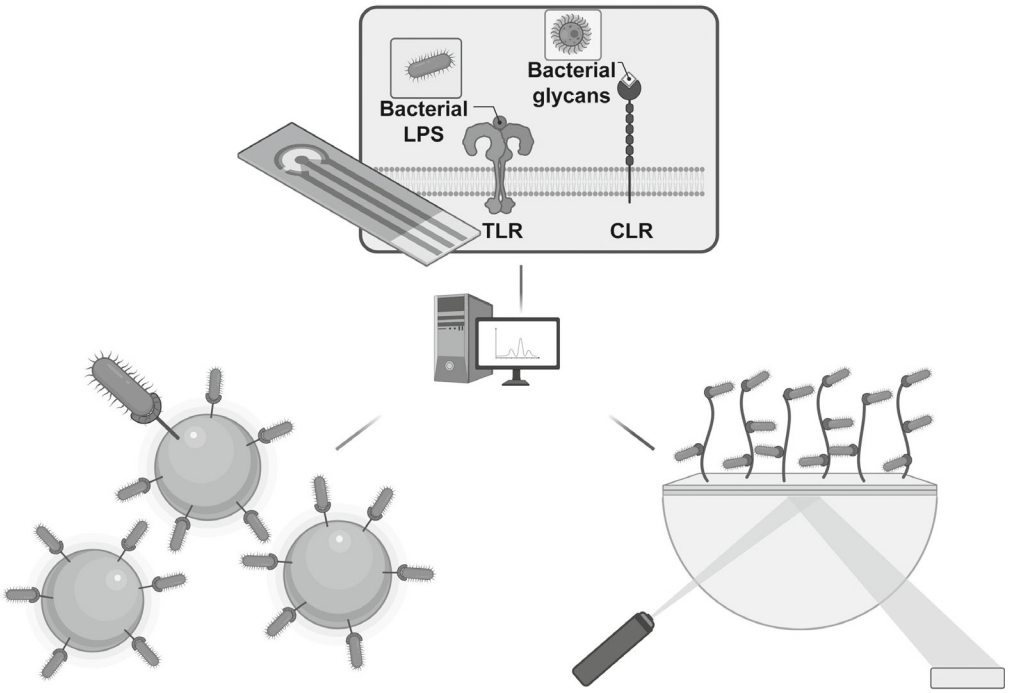

Fig. 6. Applications of PRRs: microfluidic devices for binding microbial cell wall components (top); adsorption of microorganisms on particles for concentrating microbial cells from clinical samples prior to analysis (left); investigation of interactions between microorganisms or their cell wall fragments and surfaces, for example, using surface plasmon resonance (SPR) analysis (right).

attractive as biorecognition modules in diagnostic and biosensor systems. Unlike antibodies or aptamers, PRRs are directed toward fundamentally conserved structures of microbial cells, such as PGNs, LPSs, β-glucans, and mannose-containing oligosaccharides, ensuring broad applicability and versatility.

Among the most extensively studied PRR-based sensing platforms are those utilizing TLRs, primarily TLR4, which recognizes LPSs from Gram-negative bacteria. Immobilized TLR4/MD-2/CD14 complexes have been employed on SPR and electrochemical chips for LPS detection and for investigating phagocytosis in cell-based models (Fig. 6). These platforms have demonstrated high sensitivity and compatibility with clinical matrices [231-233].

PRRs are also used for pathogen concentration from complex samples. Magnetic carriers functionalized with PRRs have proven effective for pre-analytical enrichment from both purified and clinical samples. For example, the FcMBL construct consisting of the IgG Fc fragment fused to MBL can be immobilized on magnetic particles and used for capturing a broad spectrum of bacteria, fungi, and viruses, including antibiotic-lysed cells and free PAMPs (Fig. 6). After immobilization, such particles can be readily concentrated, and the bound components can be identified using ELISA, sequencing, or mass spectrometry. Such a platform was developed for rapid diagnostics of sepsis and has demonstrated effective performance with clinically relevant blood samples [234].

Proteins of the PGRP family and their recombinant analogues are also recognized as universal elements of biosensors for detecting PGN. Based on these platforms, magnetic nanoparticles and nanostructured substrates have been developed that can selectively catch bacteria for subsequent identification using surface-enhanced Raman spectroscopy (SERS) or impedancemetry (Fig. 6). These systems enable rapid and highly sensitive analysis of both Gram-positive and Gram-negative microorganisms [235, 236]. For example, magnetic nanoparticles functionalized with a PGN-recognizing protein provided selective binding of *S. aureus* from blood for subsequent identification and analysis of antibiotic resistance, which reduced the overall assay time and increased the number of target cells at the detection stage. The enriched cellular fraction (or a fraction of cell wall fragments) can then be assessed by SERS on substrates or using metallic particles, impedancemetry, or electrochemical methods, effectively combining the high specificity of PRRs with the sensitivity of physicochemical analytical methods [237].

CLRs, particularly Dectin-1, have been employed for the detection of fungal β-(1→3)-glucans. For example, sensors incorporating immobilized Dectin-1

CRD domain have demonstrated high specificity in amperometric analysis [238]. Other lectin-type PRRs, e.g., MBL and DC-SIGN, have been used for recognizing mannose- and fucose-containing bacterial glycans. Such biosensors enable detection of both bacterial pathogens and fungal infections [239, 240].

LysM domains, which exhibit high affinity for GlcNAc, serve as universal modules for designing sensors that bind PGN and chitin. Due to their compact size and modular architecture, LysM domains are particularly suitable for integration into nanomaterials and construction of multivalent platforms [217, 241, 242].

SRs, including SR-A, MARCO, CD36, LOX-1, and SREC-I, have also been explored as biorecognition elements. They bind a broad range of microbial patterns, such as LPS, lipoteichoic acid, and PGN, and have been employed in studies investigating pathogen-binding kinetics using SPR and quartz crystal microbalance (QCM) methods [243-246].

Thus, PRRs represent promising candidates for the development of biorecognition platforms. Their high selectivity toward PAMPs and structural diversity across families (TLRs, PGRPs, lectin receptors, LysM domains, SRs) enable the adaptation of sensors to different types of pathogens. Recent studies indicate that PRR-modified systems may become effective tools for both the therapy and diagnostics of infectious diseases.

CONCLUSION

PRRs are evolutionary conserved molecules that serve as the first line of the host's defense by selectively recognizing bacterial cell wall components. In this review, we examined the major PRR classes, including TLRs, NLRs, PGRPs, βGRPs/GNBPs, lectin receptors, IgSF members, LysM-containing proteins, and SRs. Each family possesses unique structural features and functional specialization, enabling recognition of a broad range of PAMPs.

PRRs not only initiate innate signaling cascades but also form the basis for the activation of adaptive immune response, acting as a link between different immune system levels. Another key area of research is understanding how PRRs regulate tolerance toward commensal microorganisms.

Recent studies highlight a significant potential of PRRs in biotechnology and medicine, as biorecognition molecules in diagnostic platforms and biosensors. The use of PRRs enables the development of highly specific detection systems for PGN, LPS, β-glucans, and other microbial PAMPs, opening prospects for creating advanced diagnostic systems.

Overall, PRRs are both fundamental components of the innate immunity and promising tools for applied biotechnology and design of next-generation diagnostic platforms.

Abbreviations

βGRP	β-1,3-glucan recognition protein
CLRs	C-type lectin receptor
IgSF	immunoglobulin superfamily
LPS	lipopolysaccharide
LysM	lysine-binding domain, lysin motif
MBL	mannan-binding lectin
NLR	NOD (nucleotide-binding oligomerization domain)-like receptor
NOD	nucleotide binding and oligomerization domain
PAMP	pathogen-associated molecular pattern
PGN	peptidoglycan
PGRP/ PGLYRP	peptidoglycan recognition protein
PRR	pattern recognition receptor
SR	scavenger receptor
TLR	Toll-like receptor

Contributions

E.D.N. and I.N.K. supervised the study; E.Yu.E., E.V.T., N.G.Ya., E.D.N., and I.N.K. developed the study concept; E.Yu.E., E.V.T., N.G.Ya., and M.B.S. wrote the text of the article; M.A.K., M.B.Ch., and M.R.M. prepared the figures; N.G.Ya. and E.D.N. edited the manuscript.

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Ethics approval and consent to participate

This work does not contain any studies involving human or animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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