PGLYRP3,4 binds bacterial peptidoglycan

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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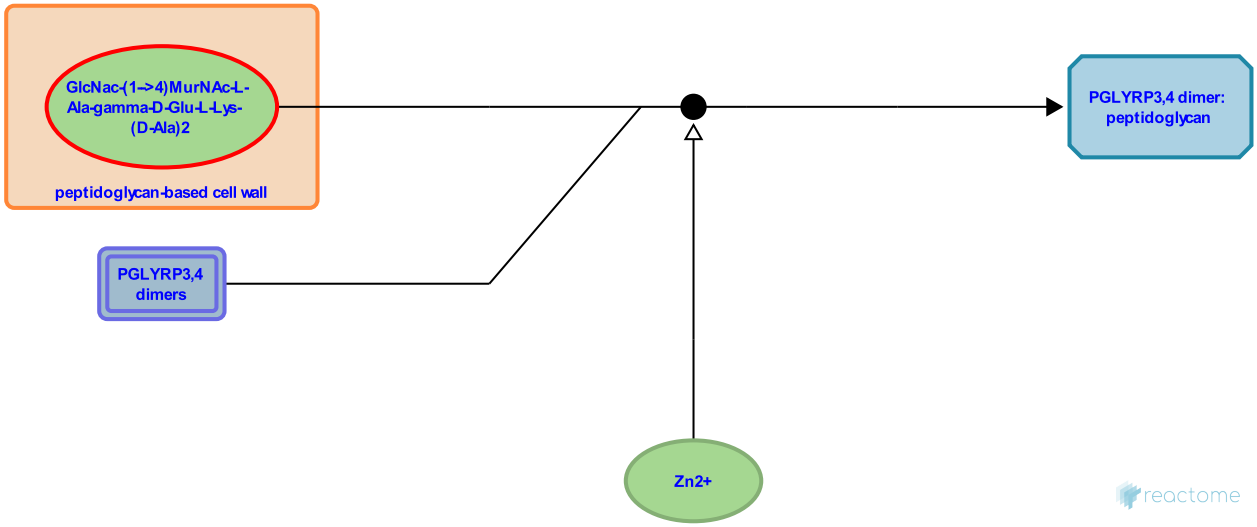
Stable identifier: R-HSA-6799959

Type: binding

Compartments: extracellular region



Peptidoglycan recognition proteins (PGRPs or PGLYRPs) are innate immunity molecules that contain a conserved peptidoglycan-binding type 2 amidase domain that is homologous to bacteriophage and bacterial type 2 amidases (Kang D et al. 1998; Liu C et al. 2001; Royet J and Dziarski R 2007; Royet J et al. 2011; Dziarski R et al. 2016). Mammals have a family of four PGRPs (PGLYRP1, 2, 3 & 4) that are differentially expressed in a cell-type or tissue-specific manner. Human PGLYRP3 and PGLYRP4 (also known as PGRP-Ialpha and PGRP-Ibeta) are expressed in keratinocytes and epithelial cells and are found in the skin, eyes, salivary glands, throat, tongue, esophagus, stomach, and intestine (Liu C et al. 2001; Lu X et al. 2006). Like PGLYRP1, PGLYRP3 and PGLYRP4 are secreted as disulfide-linked homodimers (Guan R et al. 2004, 2005; Lu X et al. 2006). However, PGLYRP3 and PGLYRP4 preferentially form heterodimers when coexpressed in the same cells (Lu X et al. 2006). PGLYRP3, PGLYRP4, and PGLYRP3:PGLYRP4 have Zn(2+)-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria at the physiological Zn(2+) concentrations found in serum, sweat, saliva, and other body fluids (Lu X et al. 2006; Wang M et al. 2007). PGLYRP3 and PGLYRP4 are also active against Chlamydia trachomatis (Bobrovsky P et al. 2016). Killing of both Gram-positive and Gram-negative bacteria by PGLYRP3 and PGLYRP4 is synergistically enhanced by antimicrobial peptides (phospholipase A2, alpha- and beta-defensins, and bactericidal permeability-increasing protein (BPI)) (Wang M et al. 2007). The bactericidal activity of PGRPs requires their N-glycosylation, as deglycosylation with N-glycosidase abolished their bactericidal activity against Bacillus subtilis, Staphylococcus aureus, and Escherichia coli (Lu X et al. 2006; Wang M et al. 2007).

PGRPs are thought to kill bacteria by interacting with cell wall peptidoglycan and by inducing lethal stress response in bacteria, as opposed to the hydrolysis of peptidoglycan or permeabilizing bacterial membranes seen with other antibacterial peptides (Lu X et al. 2006; Wang M et al. 2007; Cho S et al. 2007; Kashyap DR et al. 2011, 2014). In Gram-positive bacteria, including B. subtilis, PGLYRP1, 3 & 4 were found to enter the bacterial cell wall at the site of daughter cell separation during cell division and to bind to cell wall peptidoglycan in the vicinity of the cell membrane (Kashyap DR et al. 2011). Binding of PGLYRP3 to peptidoglycan induces a structural change in PGLYRP3 that locks peptidoglycan in the protein's bindings groove (Guan R et al. 2006). However, this binding did not inhibit the extracellular transglycosylation or transpeptidation steps in peptidoglycan synthesis (Kashyap DR et al. 2011), which are well-known targets for bactericidal antibiotics. Instead, this interaction of PGRP proteins with peptidoglycan activated the B. subtilis envelope stress response two-component system CssR-CssS that detects and disposes of misfolded proteins exported out of bacterial cells. This activation resulted in bacterial membrane depolarization, cessation of intracellular peptidoglycan, protein, RNA, and DNA

synthesis and production of toxic hydroxyl radicals, which were responsible for bacterial death (Kashyap DR et al. 2011). In Gram-negative bacteria (E. coli), PGRPs were found to bind the bacterial outer membrane activating the functionally homologous CpxA-CpxR two-component system (Kashyap DR et al. 2011). Genome expression arrays, qRT-PCR, and biochemical tests showed that PGLYRP3 & 4 kill both E. coli and B. subtilis by inducing oxidative, thiol, and metal stress (Kashyap DR et al. 2014).

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