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Structural Basis for Peptidoglycan Binding by Peptidoglycan Recognition Proteins. Rongjin Guan¹, Abhijit Roychowdhury², Geert-Jan Boons², Roy A. Mariuzza¹, ¹Center for Advanced Research in Biotechnology, Univ. of Maryland Biotechnology Ins., Rockville, MD 20850 ²Complex Carbohydrate Research Center, Univ. of Georgia, Athens, GA 30602.

Peptidoglycan recognition proteins (PGRPs) are pattern recognition receptors of the innate immune system that bind and in some cases hydrolyze bacterial peptidoglycans (PGNs). We expressed and the crystallized C-terminal PGN-binding domain of human PGRP- α . We determined its structure both in unbound form and in complex with muramyl tripeptide (MTP) representing the core of Lys-type PGNs. This first PGRP-PGN complex structure reveals molecular basis for PGN recognition by PGRPs. The peptide stem of MTP is mostly buried at the deep end of the PGN-binding groove, with the MurNAc moiety situated in a pocket in the middle of the groove, whose unoccupied shallow end could accommodate the linked GlcNAc of natural PGNs. Most interactions are with the peptide, rather than glycan, portion of MTP. However, the glycan moiety is also important in PGN binding by PGRPs. The marked conservation of key PGN-contacting residues across insect and mammalian PGRPs indicates that all employ the same PGN-binding mode. By docking MTP into PGRP-LB, a Zn²⁺ dependent metallopeptidase, we proposed a mechanism for PGN hydrolysis by Zn²⁺-containing PGRPs.