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Drosophila immune response mediated by a receptor-type guanylate cyclase and a cyclic GMP-dependent protein kinase

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Abstract

Receptor-type guanylate cyclases (rGCs) are peptide receptors conserved in human and *Drosophila*, and produce cGMP in response to intrinsic ligands. By genome-wide gain-of-function screening, we found that an rGC is involved in innate immunity in *Drosophila*. Overexpression of rGC induces *Drosomycin*, an antimicrobial peptide, through cGMP and downstream components of the Toll receptor in a Toll receptor-independent manner. In order to elucidate signaling mechanisms of this novel cGMP-mediated immune response, we identified a cGMP-dependent protein kinase (cGK) in *Drosophila* and characterized its function in cultured cells. Knockdown of cGK expression by RNAi in *Drosophila* larvae completely abrogated rGC-induced *Drosomycin* expression. Similar to Toll-pathway mutant flies, cGK knockdown flies were susceptible to infection of Gram-positive bacteria but not Gram-negative bacteria. Overexpression of both cGK and rGC strongly augmented *Drosomycin* expression in *Drosophila* larvae or in cultured cells. Site-directed mutagenesis showed that kinase-dead mutants failed to activate *Drosomycin* expression. Furthermore, co-immunoprecipitation assay revealed that cGK and dMyD88 formed a protein complex. These results suggest that the cGMP-dependent immune response is required for host defense in *Drosophila*.