BIOMEDICAL RESEARCH JOURNAL

Volume 35, 2020

Peptidoglycan recognition proteins: Players in inflammation, ageing and ageing-associated diseases: an insight from *Drosophila*

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Mini Review

Abstract: Peptidoglycan recognition proteins (PGRPs), belonging to the pattern recognition molecules, are important players in the innate immune system. The function of PGRPs in antimicrobial defense are conserved from insects to mammals. In this review, we discussed the basic function of PGRPs in Drosophila and mammals. Then the association of PGRPs with inflammation, ageing and age-related disease has been narrated. The review concludes with the role of PGRP-SC2's lifespan promoting effect in Drosophila and casts new insights of PGRPs in promoting health span in mammals.

Key words: Drosophila; PGRP; fly intestine; ageing; lifespan; inflammation.

PGRPs in Drosophila and mammals

PGRPs are innate immunity proteins that recognize bacterial peptidoglycan to activate antimicrobial host de-fense pathway in insects. They function as antibacterial molecules and were first discovered in the hemolymph of insects. The vertebrate homologues of PGRP-SCs, PGLYRP1-4, limit intestinal inflammation in rodents (-). Three of them were initially identified as bacterici-dal proteins. The rest one was identified as a peptidogly-can-hydrolytic enzyme, amidase with the similar function to PGRP-SC in fruit flies (,).

PGRP-SCs are catalytic PGRPs that can scavenge pep-tidoglycan and act as feedback inhibitors of the IMD/Rel innate immune signaling pathway, ensuring the mainte-nance of immune homeostasis (-). Drosophila depends on different forms of peptidoglycan (PGN) recognition to discriminate between gram positive and gram-negative bacteria. Most gram-positive bacteria peptides contain Lysine-containing PGNs, which are recognized by PGRP-SA and PGRP-SD. Gram-negative bacteria and gram-po-sitive bacilli contain meso-diaminopimelic acid (m-DAP) PGN which is sensed by PGRP-LC and PGRP-LE recep-tors, leading to the activation of the IMD/Rel pathway
(3). Once IMD/Relish pathway is activated, Relish can translocate into the nucleus and regulate downstream genes which include AMPs, Pirk and PGRPs. Notably, PGRP-SC and LB have amidase activity and cleave the PGN on the bacteria wall and reduce the immunostimu-latory characteristics of the bacterial antigen keeping the IMD/Relish pathway under control. So PGRP-SC proteins (PGRP-SC2 in particular) are negative modulators of the innate immune responses in the fruit flies ( ).

PGRPs in inflammation, ageing and age-related di-sease

Mammalian genomes encode four secreted PGRPs: PGLYRP1, PGLYRP2, PGLYRP3, PGLYRP4. PGLYRP-1, PGLYRP-3, and PGLYRP-4 have bacte-ricidal activity, while PGLYRP-2 has amidase activity. PGLYRP1 plays an important role in the host innate im-mune response of mice against a certain type of bacterial infection and can promote the development of a normal gut microflora to protect gut from inflammation (1, ,). Due to their role in modulating inflammation, PGRPs are involved in many complex inflammatory diseases such as arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, asthma, and atherosclerosis etc
(2). Furthermore, mutations in NOD2 (function similar to PGRPs) are associated with Crohn's disease (6, ,). Alto-gether, PGLYRPs or Nod proteins (PGRPs) are important in detection of peptidoglycan and coordinating defense to infection at cellular level or organism level (-). This in turn is crucial in initiating both innate and adaptive res-ponses to infection, which is related to acute inflamma-tion and chronic inflammation causing autoimmune di-seases and other inflammatory diseases (2).

PGRP-SC2, a negative regulator of innate immunity, promotes longevity in fruit flies

The function of PGRPs is conserved from insects to mammals (1). The beneficial effect of PGRPs is not only indicated by Guo & colleagues in fruit flies but also sup-ported by others in mammalian biology research as well
(5). As was briefly mentioned in last paragraph, in res-ponse to bacterial infection, mammalian genes PGLY-RPs are induced, limiting the innate immune response and preventing excessive inflammation (3, 4). For instance, during experimental colitis, PGRPs protect the colon of wild-type mice from inflammation and the loss of intes-tinal epithelium tissue homeostasis by promoting normal microflora and by preventing damage production from immune cells (5). In addition, PGRPs control the level of symbiotic microorganisms and protect hosts against bac-teria in different hosts including flies and mammals (5,

8). In Drosophila, Guo & colleagues have demonstrated that over-expression of PGRP-SC2 alone in the intestine is sufficient to limit intestinal dysbiosis and dysplasia in the ageing flies (8). The role of PGRPs in maintaining beneficial microorganisms in the gut has been displayed and bolstered based on that PGRP deficient mice is more susceptible to colitis and that mutations in some PGRP genes predispose patients to IBDs (5). In regards to the beneficial role of PGRPs in maintaining mammalian and fly healthy microbiome and tissue homeostasis, it is justi-fiable to seek the favorable effect of PGRP-SCs in health-span and eventually in promoting lifespan. In fruit flies, PGRP-SC2 over-expression in the intestinal enterocyte is sufficient to enhance lifespan (8). This casts new insights on analyzing the role of PGRPs in mammals for health-span and finding new strategies for targeting PGRPs in mammals for promoting lifespan.

Acknowledgements

I want to thank Dr Heinrich Jasper for the mentor-ship and suggestions for the related research.

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