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Human Peptidoglycan Recognition Protein 1 in Innate Immunity – A Review

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ABSTRACT

Peptidoglycan recognition proteins (PGRPs) are innate immunity proteins that are conserved from insects to mammals, recognize bacterial peptidoglycan, and function in antibacterial immunity and inflammation. Mammals have four PGRPs (PGLYRP1, PGLYRP2, PGLYRP3 and GLYRP4). They are secreted proteins expressed in different tissues. It is significant to make a study of human PGLYRP1 because neutrophils are a more dominant mechanism in human host defense. Related research results show the functions of human PGLYRP1 in the innate immunity of neutrophils is to conducive to the killing of intracellular and extracellular bacteria. Bactericidal activity of human PGLYRP-1, PGLYRP-3, PGLYRP-4, and PGLYRP-3:4 for both Gram-positive and Gram-negative bacteria require Zn^{2+}. In addition, for killing of Gram-negative bacteria, Zn^{2+} cannot be replaced by other cations, but for killing of Gram-positive bacteria, Zn^{2+} can be partially replaced by Ca^{2+}, which have been proved. Then, the effect of human PGLYRP1 on several human diseases (inflammatory bowel disease, ST-elevation myocardial infarction, atherosclerosis, rheumatoid arthritis, skin melanoma and renal carcinoma) have been reviewed. Taken together, these results indicate that human PGLYRP1 encodes an innate immunity protein that breaks down the structure of microbial cell wall, plays a role both in antibacterial defenses and several inflammatory diseases.

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INTRODUCTION

The innate immune system is a host defense mechanism, conserved from insects to mammalian evolutionarily, that mediates recognition and control of invading microorganisms (An *et al*., 2013; Hussain *et al*., 2017). PGRPs are a family of pattern recognition receptors (PRRs) that bind to, and in some cases hydrolyze the peptidoglycans (PGNs) of bacterial cell walls (Nylund *et al*., 2017). When first insect and mammalian PGRPs are cloned in 1998, it is noticed that they all contain an amidase homology domain (Brownell *et al*., 2016). In 2000, a family of thirteen PGRP genes in *Drosophila* and a year later a family of four PGRPs in humans are identified (Chen *et al*., 2016). They are initially named PGRP-S, PGRP-L, and PGRP-Iα and PGRP-Iβ (for 'short', 'long', or 'intermediate' transcripts, respectively) (Choe *et al*., 2005). Later, the names for human PGRPs are changed by the Human Genome Organization Gene Nomenclature Committee to PGLYRP1, PGLYRP2, PGLYRP3, and PGLYRP4, respectively, and this nomenclature has been adopted for all mammalian PGRPs (Cong *et al*., 2009).

One mammalian PGRP, PGLYRP-2 is secreted from liver into blood (Kashyap *et al*., 2017), and is also induced by bacteria in epithelial cells (Kashyap *et al*., 2011). The three remaining mammalian PGRPs are bactericidal or bacteriostatic proteins (Kibardin *et al*., 2006). PGLYRP-1 is expressed primarily in the granules of polymorphonuclear leukocytes (PMNs), and PGLYRP-3 and PGLYRP-4 are expressed in the skin, eyes, mouth, intestinal tract, saliva, and protect the host against infections.

PGLYRP1 is approximately 200 amino acids, has a signal peptide and one PGRP domain (Nylund *et al*., 2017), and a molecular mass of about 18-20 kDa. PGLYRP1 is highly expressed in the bone marrow in PMNs and their precursors (Persson *et al*., 2007), and the protein is almost exclusively present in the tertiary (secretory) granules, from which it could be released by exocytosis during phagocytosis.

FUNCTION OF HUMAN PGLYRP1

PGRPs influence host-pathogen interactions not only through their antibacterial or peptidoglycan hydrolytic properties (Yang *et al*., 2017), but also through their pro-inflammatory and anti-inflammatory properties that are independent of their hydrolytic and antibacterial activities (Wang *et al*., 2016a). They maybe play a key role both in antibacterial defenses and several inflammatory diseases (Wang *et al*., 2016b).

Bactericidal and bacteriostatic activity

Related research results show the functions of human PGLYRP1 in the innate immunity of neutrophils are

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conducive to the killing of intracellular and extracellular bacteria (Yoshida *et al*., 1996). Although in initial studies purified human PGLYRP-1 are only bacteriostatic, the latest results nave demonstrated that human PGLYRP-1 is bactericidal and that the bactericidal activity requires Ca^{2+}; the earlier preparations are not bactericidal because they did not contain Ca^{2+}.

Subsequently, some studies have demonstrated that human PGLYRP-1, PGLYRP-3, PGLYRP-4, and PGLYRP-3:4 have Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria at physiologic Zn^{2+} concentrations found in serum, sweat, saliva, and other body fluids (Choe *et al*., 2005). The requirement for Zn^{2+} can only be partially replaced by Ca^{2+} for killing of Gram-positive bacteria but not for killing of Gram-negative bacteria (Kim *et al*., 2003). This Zn^{2+} dependence explains why in their previous experiments PGLYRPs purified in the presence of Ca^{2+} (without Zn^{2+}) are not bactericidal for Gram-negative bacteria and were only bactericidal for some Gram-positive bacteria.

Role in diseases

Inflammatory bowel disease (IBD)

IBD is a chronic inflammatory condition of the gastrointestinal tract (Haas *et al*., 2017). Triggering receptor expressed on myeloid cells 1 (TREM-1) is expressed on neutrophils and most monocytes or macrophages constitutively and potently amplifies inflammation (Hakizimana *et al*., 2017). Recently, PGLYRP-1 is shown to be the ligand of TREM-1 (Zulfiqar *et al*., 2013). PGLYRP-1 is an antimicrobial peptide stored in neutrophil granules with PGN-binding activity (Stadnicki and Colman, 2003). Neutrophil degranulation releases PGLYRP-1 that, multimerized with itself or complexed with PGN, potently activates TREM-1 causing pro-inflammatory cytokine release (Cho, 2006). As PGN is a cell wall component of all bacteria, activation of TREM-1 cells by PGLYRP-1 or PGN complexes in bacteria-rich environments potently amplifies inflammation.

Here, the ability of an anti-TREM-1 antibody to dampen the release of pro-inflammatory cytokines by colon lamina propria cells (LPCs) from patients with IBD is investigated and correlated with PGLYRP-1 levels (Du *et al*., 2017). Moreover, PGLYRP-1+ myeloperoxidase is a potential biomarker for predicting the effect of anti-TREM-1 therapy (Subramanian *et al*., 2006). These studies open the possibility for a new treatment for IBD and offer insight into PGLYRP-1 (Tanaka, 2008), combined with a neutrophil marker such as MPO, as biomarkers to predict patients who would benefit from anti-TREM-1 therapy (Vermeire and Rutgeerts, 2005).

ST-elevation myocardial infarction (STEMI)

Acute myocardial infarction (AMI) is largely categorized into two categories: ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI) (Al Shehri and Youssef, 2016). Among the most easily accessible bio-fluids is the whole blood, containing leukocytes with informative transcripts used in their first line of immune defense and sentinels for many disease processes (Alkuraishy and Al-Gareeb, 2015). Using peripheral blood in clinical applications can also provide early and accurate information before development of the disease (Andjic *et al*., 2015). Accordingly, it is the potential method to be informative in disease status and of the underlying diverse disease mechanisms by the blood gene expression profiling (Bilal *et al*., 2015).

Blood gene expression profiling reflects the status of diseases, and characteristic molecular signature provides a novel window on gene expression preceding acute coronary events (Andrechuk and Ceolim, 2015). Fortunately, the correlation results have indicated that PGLYRP1, IRAK3 and VNN3 are more specific and sensitive diagnostic biomarkers for STEMI than traditional CK-MB or troponin by a simple ELISA method. Ironically, they are the most sensitive STEMI biomarkers, none has been reported for cardiovascular disease or cardiac markers.

Atherosclerosis

The thiazolidinedione medications (TZDs), pioglitazone and rosiglitazone, improve a number of inflammatory markers associated with cardiovascular disease (CVD) and have favorable effects on imaging intermediates of atherosclerosis including carotid intima-media thickness (Milasan *et al*., 2015), vascular inflammation, restenosis following stent implantation (Aydin *et al*., 2015), and de novo coronary artery disease progression. Although rosiglitazone favorably affects myriad intermediate markers of atherosclerosis (Hong *et al*., 2015), it appears to increase myocardial infarction (MI) risk.

Some studies have found that rosiglitazone has a unfavorable effects on three novel inflammatory biomarkers previously shown to independently associate with atherosclerosis (LTβR, PGLYRP-1, and CCL23) and a favorable effect on another novel biomarker (Ling *et al*., 2015), sRAGE, which previously studies have been shown to be inversely associated with atherosclerosis (Lubrano *et al*., 2015).

PGN is detectable in varying levels in the circulation and has been identified by immunohistochemical staining in human atherosclerotic specimens. PGN may promote

localized inflammation in non-mucosal sites by stimulating the production of PGRPs. Among four known human subtypes of PGRP, PGLYRP-1 is expressed primarily in PMN granules, likely functioning as an antibacterial protein. Plasma levels of PGLYRP-1 may represent the systemic response to bacterial exposure, possibly underpinning the observed associations between bacterial infection and exposure with coronary heart disease.

Rheumatoid arthritis (RA)

RA is a chronic inflammatory and autoimmune disease characterized by inflammation of the synovial membrane leading to the destruction of affected joints (Takamatsu *et al*., 2016). The study of polymorphisms of genes differentially expressed may lead to the identification of putative causal genetic variants in multifactorial diseases such as RA (Adtani and Malathi, 2015). The list of genes to explore is established on the basis of the differential expression in RA vs controls, and included four up-regulated genes (*S100A8*, *PGLYRP1*, *RNASE2*, and *LY96*) and two down-regulated genes (*RUNX3* and *IL2RB*) (Ataee *et al*., 2015). The hypothesis is that the differentially expressed genes are associated with RA, using family-based methodology (Bougea *et al*., 2015).

Recent studies have shown that PGRPs influence host-pathogen interactions through their pro-inflammatory or anti-inflammatory properties, which are independent of their antibacterial activities, modulating the balance between inflammatory T-helper (Th)17 cells and regulatory T cells. Taking into consideration the potential role of bacteria in the pathogenesis of RA, an up-regulation of *PGLYRP1* in the context of the *HLA-DRB1* shared epitope (SE) may influence the onset of the disease affecting inflammatory circuits, cytokine production, and possibly antigen presentation (Boughrara *et al*., 2015).

Skin melanoma and renal carcinoma

During the last decade novel approaches for cancer treatment have been developed. Anti-tumor vaccination is considered to be one of the most promising of these (Goncalves *et al*., 2015). One of the possible ways to induce specific immune response is the use of tumor rejection antigens discovered during recent years (Goncalves *et al*., 2015). Clinically important results of vaccinotherapy are achieved in patients with melanoma and renal carcinoma in a number of studies (Kao *et al*., 1992). The results with this treatment are comparable to chemotherapy and immunotherapy.

Recently, a novel gene, tag7 is identified, also known as *PGRP-S*. A phase I/II trial has been undertaken to define the feasibility, safety and anti-tumor effects of the autologous vaccine prepared by transferring *tag7*/*PGRP-S* gene into malignant melanoma and renal cell carcinoma cells. Related findings have indicated that vaccinotherapy of patients with skin melanoma and renal carcinoma with the *tag7*-modified autologous tumor cells is safe and do not have any significant side-effects. The use of genetically modified autologous tumor cells will be a promising approach for cancer therapy in the future.

DISCUSSION

Human PGLYRP1 plays a role in innate immunity in the context of neutrophils by contributing to the killing of intracellular and extracellular bacteria. PGLYRP-1 have Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria. Besides, the requirement for Zn^{2+} can only be partially replaced by Ca^{2+} for killing of Gram-positive bacteria but not for killing of Gram-negative bacteria and also influence host-pathogen interactions through their pro-inflammatory and anti-inflammatory properties.

Moreover, the PGLYRP1 dimer in human serum and polymorphonuclear cells is detected, from where it is secreted after degranulation; these cells being a possible source of serum PGLYRP1; these cells being a possible source of serum PGLYRP1. In addition, all PGRP protect cells from PGN-nduced apoptosis. PGRP increase THP-1 cell proliferation and enhance activation by PGN. PGLYRP1–PGN complexes increase the membrane expression of CD14, CD80 and CD86, and enhance secretion of interleukin-8, interleukin-12 and tumor necrosis factor-α, but reduce interleukin-10, clearly inducing an inflammatory profile.

Recent findings indicate that the adaptive arm of immunity is governed by the innate immunity mechanisms that control co-stimulatory signaling of antigen-presenting cells (APCs) (Fang *et al*., 2015). The combination of cytokines effecting both innate and acquired immune response taken together with tumor antigens may significantly improve overall efficiency of anti-tumor vaccination.

Although many functions of human PGLYRP1 have been identified, it is still possible that human PGLYRP1 have other unidentified functions, because many mammalian proteins have evolved to have multiple functions. In addition, it is still not clear how PGLYRP1 affects the cytokines in human various diseases.

Statement of conflict of interest

The authors in the paper showed no potential conflicts of interest.

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