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Genetic basis of host innate immune response in mastitis caused by *Staphylococcus aureus*

ADRIANNA PAWLIK, GRAŻYNA SENDER, RAFAŁ STARZYŃSKI, AGNIESZKA KORWIN-KOSSAKOWSKA

Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Jastrzebiec, Poland

Abstract

The review briefly describes chosen genes coding for the host innate immunity to staphylococcal infections. There is little known about pathogen – host interactions in such infections. We focus our attention on particular proteins connected with an innate immunity to Staphylococcus aureus during its fundamental steps – pathogen recognition, chemotaxis and immune response regulation process as well as intracellular persistence. Of particular importance is to describe whether mutations, localized in genes, involved in a response to gram-positive bacteria can underlay development of a persistent infection.

Key words: *bovine mastitis, innate immunity, Staphylococcus aureus.*

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Staphylococcus aureus (*S. aureus*) is the most important and prevalent contagious mammary gland pathogen in the world's population of dairy cattle. Mastitis etiological agent plays a crucial role in the udder inflammation process. Authors suggest that *Escherichia coli* (*E. coli*) mastitis process is being mainly determined by host factors [1], which seem to be an effect of pathogen toxicity and host immune system rapid reaction. In contrast, *S. aureus* mastitis infection course is mainly dependent on pathogen characteristics. Many studies confirmed different immune responses in *S. aureus* and *E. coli* infections [2-6]. Frequent subclinical infection occurrence and less severe immune reaction due to delayed neutrophil migration [7] are factors that confer to the prevalence of the staphylococcal mastitis. Mastitis caused by these bacteria is mainly subclinical, persistent, and often transfers into a chronic infection. Strong induction of the pro-inflammatory interleukin 8 (IL-8) and tumor necrosis factor α (TNF-α) genes expression, therefore – polymorphonuclear leukocytes (PMNs) activation and recruitment is being observed after experimental udder infection with *E. coli* but not with *S. aureus* [8].

There is little known about pathogen – host interactions in staphylococcal infections. Of particular importance is to describe whether mutations, localized in genes, involved in an innate immune response can underlay development of a persistent infection. Hypothesis that *S. aureus* strains are starting to transit into the intracellular pathogens is striking and of great significance both for dairy industry and for veterinarians. Animals carrying intracellular pathogens are not only more prone to develop a recurrent inflammation but are latent infection source in herd also. Statement that normal *S. aureus* phenotype can change into its intracellular variant (SCV) after an exposure to antibiotics has been formed regarding human strains and is probable for bovine strains too. This review will try to shed light on host immune genes whose mutations may be possibly involved in metamorphosis of pathogen into its intracellular form. We focus our attention on particular proteins connected with an innate immunity to *S. aureus* during its fundamental steps – pathogen recognition, chemotaxis and immune response regulation process as well as intracellular persistence. Chosen proteins are as follows: Toll-like receptors (TLRs), nucleotide binding oligomerization domains (Nods), peptidoglycan recognition proteins (PGRPs), interferon γ (IFN-γ) and natural killer cells (NK).

Innate response comprises for the vast majority of overall immune response and direct adaptive immunity in diverse ways. Mechanisms of innate immunity can be divided into two groups: first represents host perceiving an infection, second – host dealing with it [9]. Cellular innate immu-

Correspondence: Prof. Grażyna Sender, Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Jastrzębiec, 05-552 Magdalenka, Poland, phone: +48 22 736 71 27, fax: +48 22 756 14 17, +48 22 756 16 99, e-mail: g.sender@ighz.pl

nity comprises of neutrophils, macrophages, natural killer and dendritic cells [10]. From an early stage of infection, macrophages act as factors signaling pathogen presence in the udder. They secrete chemoattractants for neutrophils, inducing their migration from bloodstream to milk. Control of bacterial growth in acute *S. aureus* infection is supported by an effective neutrophils recruitment which is important for changing infection course from acute to persistent [11]. Mammary epithelial cells (MEC) are able to secrete chemokines that attract neutrophil and pro-inflammatory cytokines. Most of the studies upon MEC activity were made on the lipopolisaccharide (LPS) or *E. coli* challenged cells [12, 13]. Stimulation of MEC with heat inactivated *E. coli* resulted in up-regulation of the 30% of immune relevant genes of epithelial cells in comparison with the 17% up-regulated genes of entire udder [12], which indicates a decisive role of MEC during mastitis. It is well known that genes up-regulated after LPS challenge of MEC are different from those, up-regulated after gram-positive components challenge. It has been shown that gram-positive bacterial components provoke immunomodulatory genes expression in MEC to the lower extend than LPS [14]. Regarding *S. aureus* infections Pfaffl *et al.* [15] proved that although mammary tissue abundance of TNF-α mRNA is significantly higher in high – somatic cell quarters in comparison to low – somatic cells and control quarters, the main source of TNF-α mRNA in the udder are neutrophils. It is on the contrary to lactoferrin, for which the mammary tissue mRNA levels are 20 fold higher than somatic cells mRNA levels [15].

Interactions between the host immune response and an infectious agent are complex; they rely on the interactions between many cell types and their proteins. Mediators secreted in the infection site and their effectiveness in the induction of neutrophils migration are important for pathogen neutralisation. In staphylococcal mastitis this neutralisation is often incomplete and leads to development of the chronic infection. Resident macrophages (RM), always present in the udder are the first cell type that interferes with bacteria after crossing teat canal physiological barrier. Resident macrophages and dendritic cells express pathogen recognition receptors (PRRs), needed for chemoattractants release and neutrophil influx to the inflammation site. Resident macrophages can also gain ability to kill and degrade bacterial cells by IFN-γ and TNF-α mediated activation. Macrophages and dendritic cells present antigen via major histocompatibility complex (MHC) class II cells and trigger an adaptive immunity. Due to the supporting role of innate immunity, any disturbance in its functions can markedly decrease the host ability to fight infection.

Interactions between circulating PMNs and vascular endothelial cells are needed for neutrophils migration to the infection site. Complement activation, phagocytosis and inflammatory response are mechanisms used by the host to neutralise extracellular bacteria. Results of the complement activation are as follows: opsonisation and enhanced phagocytosis of bacteria and production of substances recruiting and activating of lymphocytes [16, 17]. Phagocytes (neutrophils, macrophages) use wide range of surface receptors to recognize opsonised bacteria. Major class of receptors binds conserved bacterial ligands called pathogen-associated molecular patterns. Toll-like receptors are the main group of danger signal detectors. Toll-like receptor 4 ligands are: LPS and lipoteichoic acid (LTA) [18], and formerly proposed TLR-2 ligands were: peptidoglycan (PG) and LTA. However, recent studies pointing out that above mentioned cell wall components might not be ligands for TLRs [19]. Undoubtedly ligands for both TLR-2 and TLR-4 are present in heat killed, unfractioned bacteria [8, 19]. The problem appears in contamination of LTA preparations that are responsible for TLR activity assignment. The main component of staphylococcal cell wall that is responsible for TLR-2 activation is lipoprotein [20]. Existence of a weak immune response to *S. aureus* infections may be associated with the fact that although TLRs are activated by LTA or heat – inactivated bacteria, no further nuclear transcription factor κB (NF-κB) activation in MEC was observed. In addition, macrophages, neutrophils, and probably mammary epithelial cells [14] express CD14 surface receptor that improves binding of the bacterial ligands to TLRs. Toll-like receptors mediate transmembrane signalling, resulting in pro-inflammatory cytokines gene expression via activation of activated protein 1 (AP1) and NF-κB. In MEC TLR pathway components are being expressed even without previous pathogen stimulation, thus there is a suggestion that TLRs in MEC are immediately ready to response [14]. Genetic mutations in TLRs signalling pathway are responsible for several human diseases, including asthma and artherosclerosis [21]. More over that great variability in TLRs genes sequence is known [22]. For TLRs role, mechanisms of action and genetic variants see e.g. Mills [23], Seo *et al.* [24], Hard and Tapping [25]. Toll-like receptor system works almost perfectly detecting pathogens at the cell surface or lysosome/endosome membranes, while pathogens that have invaded cytosol are recognized by various cytoplasmic pattern recognition receptors (PRRs). Nod-LRR receptors (or NBS-LRR for nucleotide-binding site and leucine-rich repeat) are the proteins with nucleotide binding oligomerization domain and caspase recruitment domain (CARD) at their N-terminus, responsible for signalling initiation [18, 26]. Nod2 protein is a sensor of the smallest portion of peptidoglycan (PG) known for triggering an immune response – muramyl dipeptide (MDP). It is known to interact both with gram-positive and gram-negative bacteria. Genetic variation of Nod2 protein is responsible for severe inflammatory bowel disease (Crohn's disease) in humans (302insC frameshift mutation in *Nod2* gene). Some alleles and haplotypes of *Nod2* gene are associated with paratuberculosis in cattle (Johne's disease, caused by *Mycobacterium avium* subsp. paratuberculosis

(MAP) [27, 28]. As shown by Bercot *et al.* [29] one of Nod2 genetic variants (Leu1007fsinsC SNP) was linked with impaired neutrophil responses in woman with granulomatous mastitis related to Corynebacteria, probably due to decreased MDP sensing and impaired synergy with TLRs. It is probable that Nod2 and TLR-2 pathways cross-react [26]. Recent study on bMEC, pointed out that Nod1 ligands – peptydoglycan fragments are recognized by MEC cells during *E. coli* experimental infection [30].

Peptidoglycan of gram-positive bacterial cell wall is a potent antigen and can be detected by the host with use of PGRPs. This family of proteins is conserved from insect to mammals. Peptidoglycan can be bound to membrane, stored in vesicles or secreted into an extracellular space. Recent paper by Atilano *et al.* [31] described interaction between bacterial cell wall teichioc acids (WTA) and PG. They proved on Drosophila model that the WTA limits PG binding to PGRP. In humans and cattle there are 4 PGRPs: S, L, I-α and I-β. Peptidoglycan recognition proteins (PGRP-1) is stored in tertiary granules of neutrophils. This protein attenuates growth of gram-positive bacteria and induces an intracellular killing [26]. Bovine PGRP-1 is the only PGRP that is capable of bacteria killing. Peptidoglycan recognition protein 1 shows destructive activity to bacteria that expose PG like *S. aureus*, bacteria with buried PG (*Salmonella typhimurium*) and even those without PG (*Cryptococcus neoformans*). Therefore PGRP1 may be considered as a germicidal protein independently from PG recognition. It is unclear whether PGRP-1 is secreted out of cell or acts exclusively intracellular. Tydell *et al.* [32] suggested that PGRP1 is secreted from neutrophils upon bacterial stimulation, and enter phagolysosome bond to antigen. Peptidoglycan recognition proteins DNA sequence are conserved in wide range of organisms, though Dziarski *et al.* [33] suggested that only sequences coding for pathogen recognition, in contrary to those coding for microbicidal activity are conserved from insects to mammals.

Seabury *et al.* [34], analyzed diversity and evolution of the 11 innate immune genes in cattle, including TLR-2 and PGRP1, as there is a suggestion that strong selection on cattle performance might have led to the forming of particular haplotypes connected to the performance type and/or disease susceptibility. Mentioned authors concluded however, that none of the haplotypes analyzed can be assigned to either particular performance type (dairy/beef) or even subspecies (Bos taurus taurus/Bos taurus indicus).

Pathogen stimulation of the white blood cells and other cell types, results in production of the pro-inflammatory and immunomodulating proteins, called cytokines. Interleukin 12 production increases in sepsis, IL-8 increases via stimulation with TNF-α. Interleukin 1 (α – intracellular, and β – extracellular) activates T-cells and induces growth factors and inflammatory mediators. Interleukin 6 plays role in B cells differentiation and immunoglobulin secretion, IL-8 is chemotactic for neutrophils, IFN-γ is involved in macrophages activation [35]. Exact time course of cytokines expression is still unclear since it differs regarding an experiment [8, 14, 36, 37]. Major cytokines produced during *S. aureus* infection are: TNF-α, IL-1, IL-6, IL-8, IL-12 and IFN-γ. Systemic cytokine response was observed by some authors, with the late peak of cytokines production (50-75 h after *S. aureus* challenge) in comparison to *E. coli* (peak in 1-5 h after challenge). Other authors observed sustained IL-1b, TNF-α, IL-8, CXCL6 and GRO-α production in MEC and noted it as typical for *E. coli* infections and rapid but short peak (in 3 hours post infection) in pro-inflammatory cytokines production after *S. aureus* challenge [14, 37].

Polymorphisms, found in *IL-8* gene [38] or in gene coding for IL-8 receptor B (CXCR2, present on neutrophil surface) [39-41] are likely to be the functional mastitis markers. The authors mentioned above shown significant association between milk somatic cell count and gene variants. In addition bovine *IL-8* gene is mapped to BTA6 (Bos taurus autosome 6), where the probable QTL (quantitative trait locus) for performance trait is localized; supporting that IL-8 genetic variation can influence performance [38]. Study by Rambeau and Pighetti [42] proved an impaired neutrophil migration in cattle of CXCR2 +777 CC genotype. Lahouassa *et al.* [43] found a new IL-8 receptor (named nIL-8R) in cattle which is an equivalent of human CXCR2, and is a potent chemotaxis mediator. In *S. aureus* infections the level of IL-8 expression is lower than in *E. coli* infections (probable immunosuppressive pathogen function) [44]. Watanabe *et al.* [45] showed that inflammatory reaction, mediated by IL-8 can be of particular importance when udder inflammation progresses from subacute to the chronic state.

GRO proteins, formerly known as melanoma growth factors, along with IL-8 belong to ELR+ CXC chemokine family. They play role in neutrophils chemotaxis and leukocytes activation [46]. Proteins from GRO family that could be of special concern, regarding staphylococcal mastitis are GRO-β and GRO-γ. These protein mRNAs are found in MEC after staphylococcal challenge, which confirms the role of epithelial cells in neutrophil chemotaxis during mastitis [37].

Natural killer cells are a subset of bone-marrow origin lymphocytes, different from B or T cells. Natural killer cells secrete IFN-γ and can kill infected cells by direct lytic mechanisms. They secrete also IL-15 and IL-18 that favour CD8+ cells development and enhance lysis of *M. tuberculosis* in monocytes, via CD8+ cells [47]. Natural killer cells possess MHC-independent activity and are crucial for intracellular pathogens killing. These cells after stimulation can release toxins from saposin-like family [4].

Interferon γ is one of the major cytokines in both innate and acquired immune response to intracellular pathogens. It is considered as key element of an early response to the intracellular pathogens due to its inhibitory effect on pathogen replication and promotion of TH1 type response

[48]. It also acts as an activator of stem cells to produce immune system cells. Interferon γ promotes a long-term repopulating of hematopoietic stem cells proliferation *in vivo* [49]. Listeria monocytogenes is the best described intracellular pathogen considering IFN-γ role in immune response. Probably multiple pathways take part in IFN-γ production during Listeria infection [50-52]. Lots of cells have the ability to produce IFNs, and it is known that memory CD8 T cells produce this cytokine in response to IL-12 and IL-18, produced by Listeria – infected macrophages. Disorders of IFN-γ mediated immunity can be caused by the deficiency in its receptors (IFN-γR1 and IFN-γR2) and this leads to the increased risk of mycobacterial diseases in humans [53].

Chosen proteins important for *S. aureus* invasion in dairy cows were described in this paper. Mutations, localized in genes, coding for these proteins can cause a severe distraction in animal innate immune response, therefore – they can create a favourable environment for a pathogen persistence in the udder. If such a connection is proved, described genes can function as *S. aureus* mastitis genetic markers.

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