The Innate Immune Response Against *Staphylococcus aureus*

Isabelle Bekeredjian-Ding, Christoph Stein and Julia Uebele

Abstract The innate immune system harbors a multitude of different receptor systems and cells that are constantly prepared to sense and eliminate invading microbial pathogens. *Staphylococcus aureus* enters the body on its exposed epithelial surfaces, e.g., on skin and mucosa. The initial interaction with epithelial cells is governed by Toll-like receptor (TLR)-2-mediated local production of soluble mediators, including cytokines, chemokines, and antimicrobial peptides. The overall goal is to achieve a steady state of immune mediators and colonizing bacteria. Following cell and tissue invasion clearance of bacteria depends on intracellular microbial sensors and subsequent activation of the inflammasomes. Tissue-resident mast cells and macrophages recruit neutrophils, macrophages, and NK cells. This inflammatory response supports the generation of IL-17 producing NKT, γδ T cells, and T helper cells. Local dendritic cells migrate to the lymph nodes and fine-tune the adaptive immune response. The scope of this chapter is to provide an overview on the major cell types and receptors involved in innate immune defense against *S. aureus*. By segregating the different stages of infection from epithelial barrier to intracellular and systemic infection, this chapter highlights the different qualities of the innate immune response to *S. aureus* at different stages of invasiveness.

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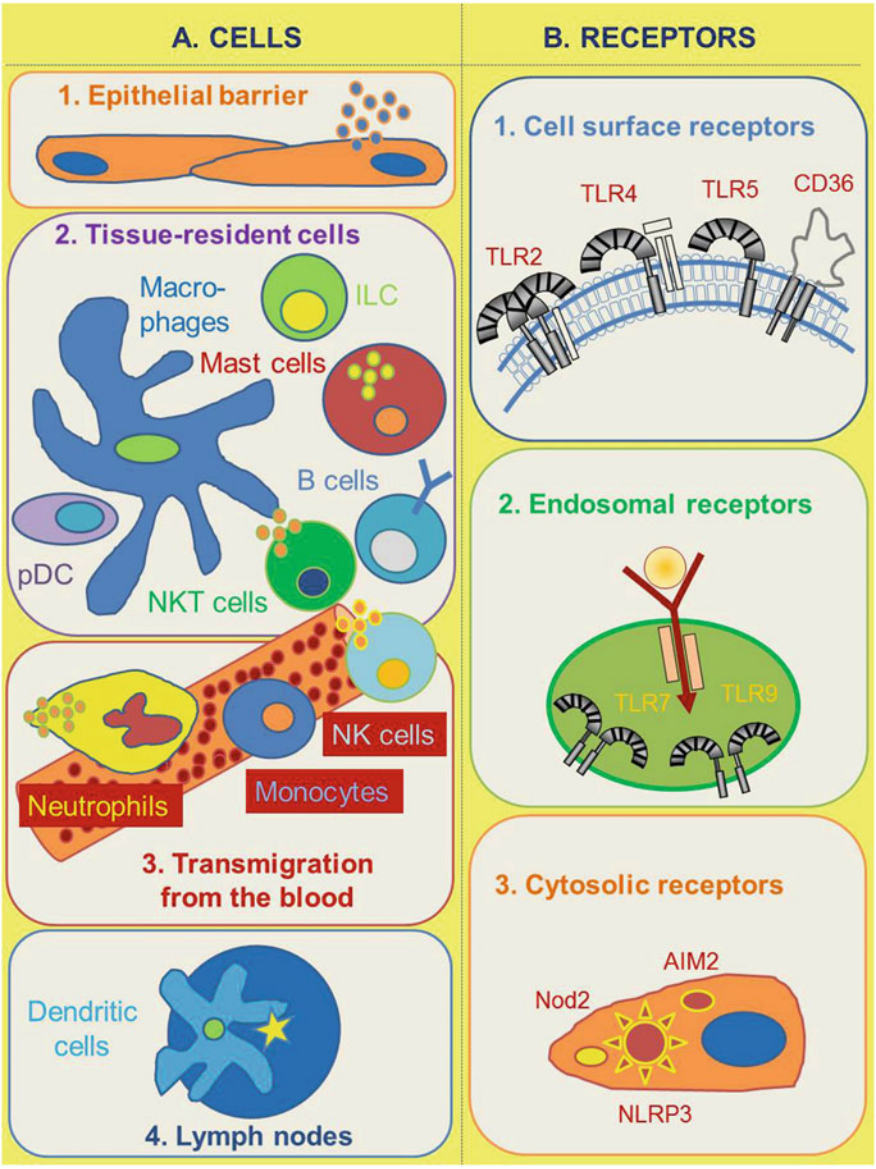
1 Introduction

In the last two decades, our understanding of the cellular and molecular mechanisms regulating innate immune defense has been refined. The researchers working in this field have not only cloned and described a broad variety of receptors responsible for the sensing of microbial pathogens but we have also learned how the different immune cell subsets contribute to immune defense and shape the effector function of the adaptive immunity. Despite all of these efforts, we have only started to understand how all of these cells and receptors integrate to mount a pathogen-specific protective immune response and which factors determine the differences in the outcome and quality of the immune response observed among individuals.

Numerous studies have dealt with the innate immune response against *S. aureus*. They have defined the receptors and cells required for innate immune protection against infection with this pathogen. It has even been postulated that clearance of *S. aureus* infection can solely rely on the innate immune system (Schmaler et al. 2011; Josefsson and Tarkowski 1999). By contrast, activation of adaptive immune cells in *S. aureus* infection has rather been associated with exacerbated inflammation and development of arthritis (Josefsson and Tarkowski 1999) and is most likely due to aberrant activation of B and T lymphocytes by *S. aureus* superantigens (reviewed in Broker et al. 2014). Nevertheless, a multitude of studies also highlighted that *S. aureus* also possesses a broad variety of virulence factors that promote its superb ability to adapt to a hostile environment and successfully evade the innate immune defense (reviewed elsewhere in this volume).

This chapter provides an overview on the innate immune mechanisms involved in physiological recognition and immune defense against *S. aureus* in carriers and local and systemic infections. Unfortunately, to date, there are no studies available that systemically compare the immune response to colonizing, invasive, and


A. CELLS
B. RECEPTORS
1. Epithelial barrier
2. Tissue-resident cells
Macro-
phages
ILC
Mast cells
B cells
pDC
NKT cells
NK cells
Neutrophils
Monocytes
3. Transmigration
from the blood
Dendritic
cells
4. Lymph nodes
1. Cell surface receptors
TLR4
TLR5
CD36
TLR2
2. Endosomal receptors
TLR7
TLR9
3. Cytosolic receptors
AIM2
Nod2
NLRP3

◀ **Fig. 1** The different layers of innate immune defense. **A**: **Antibacterial defense on a cellular level**: **1**. **Epithelial barrier**: keratinocytes and mucosal epithelial cells are the first to encounter bacteria. Bacteria are sensed by surface receptors and intracellular pattern recognition receptors (*PRRs*). These cells produce antimicrobial peptides (*blue*) and cytokines in response to stimulation of TLR2 or Nod-like receptors in response to *S. aureus* lipoproteins and/or peptidoglycan. **2**. **Tissue-resident cells**: mast cells, tissue-resident macrophages, innate lymphoid cells (*ILCs*), plasmacytoid dendritic cells (*pDCs*), NKT, and innate B cell subsets present in the tissues are prepared to fight invading pathogens. They express a broad variety of scavenger receptors and PRR that enable bacterial recognition, phagocytosis, and release of chemokines and proinflammatory cytokines, which attract leukocytes from blood. **3**. **Transmigration of cells from blood**: neutrophils, monocytes, and NK cells immigrate from blood and participate in phagocytosis and clearance of bacteria and abscess formation. **4**. **Lymph nodes**: Cell migration from the infected site initiates the antigen-specific adaptive immune response. Dendritic cells migrate to lymph nodes and present antigen to T cells. Neutrophils and macrophages interact with B cells. **B**: **Cellular levels of innate immune receptors**. **1**. **Surface receptors** on epithelial cells and leukocytes mediate the recognition of bacterial cell wall components. TLR2 recognizes staphylococcal lipoproteins and plays a central role in phagocyte activation. Scavenger receptors such as CD36 and SR-A recognize *S. aureus* and promote phagocytosis and bacterial clearance. **2**. **Endosomal TLRs** recognize microbial nucleic acids. They are activated upon degradation of the bacterium and acidification of the phagosome. **3**. **Cytosolic receptors** sense liberated bacterial degradation products such as peptidoglycan and microbial DNA. In infections with *S. aureus,* they activate the NLRP3, NLRC5, and AIM2 inflammasomes and promote caspase-1-dependent activation of IL-1β and IL-18, thus driving the formation of IL-17-producing T cells

intracellularly persisting *S. aureus* strains. The authors have, therefore, defined different layers of antibacterial immune defense on a cellular (Fig. 1A) and a receptor level (Fig. 1B) and assigned these to the different stages and types of infection.

2 The Encounter at the Epithelial Barrier

When encountering the body surfaces, *S. aureus* cells interact with and adhere to epithelial surfaces in skin and mucosa. The presence of adherent bacterial cells is sensed by epithelial surface receptors that recognize microbial components derived from the bacterial cell wall. These include wall teichoic acid (WTA), lipoteichoic acid (LTA), peptidoglycan (PG), and lipoproteins (Lpp). Additionally, secreted bacterial toxins such as alpha toxin, beta hemolysin, and Panton-Valentine leukocidin (PVL) are neutralized by preformed IgA present in the mucosa (Verkaik et al. 2009). Notably, to date, there is nearly no information available that allows a comparison of the epithelial and leukocyte responses upon initial encounter of the pathogen to those maintained in chronic colonization with *S. aureus*.

2.1 The Sentinel Function of Toll-like Receptor-2: Permitting Colonization and Preventing Invasion

The major surface receptor implicated in epithelial recognition of Gram-positive commensals such as *S. aureus* is Toll-like receptor (TLR)-2, a pattern recognition receptor (PRR) expressed on cells of epithelial, endothelial, and leukocyte origin. It senses di- and triacylated bacterial Lpp by forming heterodimers together with TLR6 and TLR1, respectively (Jin et al. 2007; Kang et al. 2009). Its engagement by *S. aureus*-derived TLR2 ligands contributes to the integrity of the epithelial barrier by supporting tight junctions and skin wound repair (Kuo et al. 2013). In vivo studies demonstrated that mice lacking TLR2 (or the central TLR adaptor molecules MyD88 and IRAK4) are highly susceptible to *S. aureus* infection (Takeuchi et al. 2000; Kielian et al. 2005; Yimin Kohanawa et al. 2013; Suzuki et al. 2002). In infection with this pathogen, these mice exhibit reduced cytokine responses and a higher bacterial burden in the affected organs. Well in line with these findings, patients with genetic mutations in the *irak4* and *myd88* loci display increased frequencies with pyogenic infections, among them *S. aureus* (reviewed in von Bernuth et al. 2012). However, the requirement for TLR2 in the human is less clear.

Staphylococcal Lpp account for approximately 2 % of the proteome and function as regulators of the iron transport through the cytoplasmic membrane (Schmaler et al. 2010; Babu et al. 2006; Maresso and Schneewind 2006). *S. aureus* expresses more than 50 lipoproteins, among them SitC or the tandem lipoproteins encoded in the pathogenicity island vSaα (Stoll et al. 2005; Hashimoto et al. 2006; Kurokawa et al. 2011; Nguyen et al. 2015). Maturation of Lpp involves several steps of posttranslational modification, the most important one being the transfer of a diacylglycerol group by the phosphatidyl glycerol diacylglyceryl transferase (*lgt*) (Sankaran et al. 1995; Sankaran and Wu 1995). This modification is essential for recognition via TLR2 (Stoll et al. 2005; Hashimoto et al. 2006; Kurokawa et al. 2011; Schmaler et al. 2009).

Activation of TLR2 on keratinocytes leads to the release of antimicrobial peptides (AMP) and proinflammatory cytokines and neutrophil-attracting chemokines (Niebuhr et al. 2010a; Wanke et al. 2011; Olaru and Jensen 2010). Well in line with a central role of TLR2 in the recognition of *S. aureus* in the skin, unresponsiveness of keratinocytes from patients with atopic dermatitis to TLR2 stimulation might contribute to colonization of affected skin with *S. aureus* (Niebuhr et al. 2011).

Similarly, expression of TLR2 protected against nasal colonization with *S. aureus* (Gonzalez-Zorn et al. 2005). Moreover, deficient secretion of nasal AMP and *S. aureus*-triggered downregulation of TLR2 have been proposed to support *S. aureus* nasal carriage (Gonzalez-Zorn et al. 2005; Nurjadi et al. 2013; Zanger et al. 2011; Quinn and Cole 2007) and adherence of *S. aureus* on bronchial epithelial cells that express low to absent levels of TLR2 (Mayer et al. 2007). Furthermore, recent reports proposed that *S. aureus* induces expression of TLR2 on salivary epithelial cells (Negrini et al. 2014) and triggers the release of the chemoattractant cytokine IL-8 from colonic epithelial cells in a TLR2-dependent manner (Kang

et al. 2015), a finding important in light of the gastrointestinal tract serving as an important reservoir for colonizing *S. aureus* strains (Nowrouzian et al. 2011; Gries et al. 2005; Kato-Matsunaga and Okonogi 1996; Bhalla et al. 2007; Klotz et al. 2005).

Notably, sensing via TLR2 cannot distinguish between viable and dead bacteria. Furthermore, TLR2 activity is subject to strain variation, e.g., it varies depending on the proliferative and metabolic state (Hilmi et al. 2014). TLR2 recognition, therefore, exerts an immune stimulatory effect on epithelial cells and a broad range of immune cells, but it is not solely responsible for bacterial clearance or containment of adherent *S. aureus* on the epithelial surfaces. Not surprisingly, it was, thus, not possible to prove an association of single nucleotide polymorphisms in the *tlr2* gene with either *S. aureus* carriage and/or associated rhinopolyposis (Sachse et al. 2010; Tewfik et al. 2008) or infection with *S. aureus* (El-Helou et al. 2011; Moore et al. 2004).

Keeping in mind that sensing of TLR2-active lipoproteins is coupled to bacterial proliferation and loss of cell wall integrity that uncover the cytoplasmic membrane (Hilmi et al. 2014; Wolf et al. 2011), the central role of TLR2 sensing might be attributed to two key determinants: Firstly, TLR2-dependent induction of AMP that degrade bacterial cells achieves a steady-state condition in the quantity of colonizing bacterial cells, thus making further recruitment and activation of phagocytes unnecessary: This principle has been described in drosophila but very probably is also valid for mammalian immune defense (Zaidman-Remy et al. 2006). Secondly, TLR2 exerts an important priming effect on epithelial cells and immune cells, thus preparing these cells to recognize invading *S. aureus* via intracellular sensors that subsequently induce its elimination by intracellular bacterial lysis in phagocytes or death of infected epithelial cells.

These events prepare the grounds for the polarization of T cell responses, most importantly the generation of Th17 cells in *S. aureus* skin infections, which are reviewed in Miller and Cho (2011). Nonetheless, *S. aureus* and diacylated TLR2 Lpp derived thereof also induce thymic stromal lymphopoietin (TSLP) (Takai et al. 2014; Vu et al. 2010), a cytokine expressed by human epidermal keratinocytes and mucosal epithelial cells that favors Th2 cell responses and blocks Th1/Th17 differentiation (Ziegler et al. 2013). In addition, *S. aureus* and TLR2 ligands have been implicated in the promotion of tolerance established via TLR2-dependent IL-10-mediated suppression of T cell responses induced by *S. aureus* or TLR2-dependent infiltration of colonized skin with myeloid suppressor cells (Skabytska et al. 2014; Chau et al. 2009).

Altogether, these findings highlight the central role of TLR2 in the recognition of *S. aureus* on epithelial cells from different body origins. Notably, the stimulatory function of TLR2 on epithelial cells is supplemented by its effects on professional phagocytes, which are discussed later in this chapter. The current findings further illustrate that TLR2 balances pro- and anti-inflammatory immune responses, thus permitting colonization but preventing infection.

2.2 Bacterial Invasion: Immune Defense Relies on Intracellular Sensors and Inflammasome Activation

Upon invasion of epithelial cells (or endosomal escape in professional phagocytes), cytosolic pattern recognition receptors (PRRs) secure immune detection of invading pathogens. In this context, recognition of *S. aureus* occurs via peptidoglycan binding by Nod receptors. The Nod1 receptor senses meso-diaminopimelic acid (*meso*DAP) in PG, which is present in peptidoglycan of Gram-negative species; the Nod2 receptor recognizes the muramyl dipeptide present in peptidoglycan of Gram-positive and Gram-negative organisms (Girardin et al. 2003). Nod2$^{-/-}$ cells were irresponsive to *S. aureus* PG (Volz et al. 2010). Nevertheless, one report claimed that both Nod receptors contribute to the recognition of *S. aureus* (Kapetanovic et al. 2007). A central role of Nod2 in vivo was demonstrated in a skin infection model using in *nod2*-deficient mice (Hruz et al. 2009). In this study, production of α-toxin facilitated Nod2 recognition by promoting access to the cytosol through pore formation in the plasma membrane.

TLR2 stimulation represents an important costimulus for Nod2-dependent recognition of peptidoglycan and vice versa (Volz et al. 2010; Schaffler et al. 2014). Furthermore, staphylococcal lipoteichoic acid (LTA) enhances recognition of TLR2 ligands and PG by a, so far, ill-defined mechanism. Additionally, Nod2 ligand MDP enhances LTA-triggered induction of cyclooxygenase-2 in macrophages (Ahn et al. 2014), which increases bactericidal activity against *S. aureus* (Bernard and Gallo 2010).

Notably, recognition of PG is greatly facilitated by uncovering the minimal PG recognition motifs: PG digestion by PG recognition proteins (PGRP) facilitates Toll signaling in drosophila and phagocytosis of *S. aureus* in human cells (De Marzi et al. 2015; Garver et al. 2006). Moreover, PG digestion by lysozyme is an important prerequisite for efficient activation of the NLRP3 inflammasome (Shimada et al. 2010). However, the PG-hydrolyzing activity of the major autolysin (*atl*) and D-alanylated wall teichoic acid interferes with recognition of *S. aureus* PG by drosophila PGRP (Kurokawa et al. 2011; Atilano et al. 2011, 2014) and O-acetylation of muramic acid (*oat*) typically found in *S. aureus* makes PG resistant to the hydrolytic activity of lysozyme (Shimada et al. 2010; Bera et al. 2007). This results in a pathogenicity factor-mediated suppression of proinflammatory cytokine production and subsequent inflammasome activation, facilitates colonization of skin and mucosa, and enables prolonged intracellular persistence. Relevance of these mechanisms was further provided by studies on *S. aureus* mutants with minimized PG synthesis, i.e., absence of nonessential peptidoglycan binding proteins, which rendered *S. aureus* less virulent while more susceptible to antibiotics and resulted in better bacterial clearance in infection (Reed et al. 2015).

Subsequent to engagement of cytosolic PRR, *S. aureus* induces activation of the inflammasomes. These cytosolic molecular complexes mediate the activation of caspase-1, which triggers the release of biologically active IL-1β and IL-18 and cell death. Notably, next to TLR activation, inflammasome activation depends on the

presence of ATP, which is required for the induction of an intracellular potassium flux (Franchi et al. 2007; Arlehamn et al. 2010; Petrilli et al. 2007). *S. aureus* establishes this intracellular potassium gradient via *agr*-dependent expression of pore-forming toxins, e.g., α-hemolysin, Panton-Valentine leucocidin (PVL), and phenol-soluble modulins; this results in NLRP3 (NACHT, leucine-rich repeat (LRR), and pyrin domain-containing protein 3)-dependent caspase-1 activation in a variety of cell types, ultimately leading to pyroptosis and secretion of IL-1β and IL-18 (Soong et al. 2015; Accarias et al. 2015; McGilligan et al. 2013; Holzinger et al. 2012; Perret et al. 2012; Craven et al. 2009; Munoz-Planillo et al. 2009; Chi et al. 2014; DuMont and Torres 2014; Queck et al. 2008; Bocker et al. 2001; Gurcel et al. 2006). By contrast, the absence of *agr* and/or pore-forming toxins promotes intracellular persistence and survival of *S. aureus* by inducing autophagy, a process counteracting NLRP3 and caspase-1 activation and associated pyroptosis and IL-1β production (Soong et al. 2015). Nevertheless, the role of autophagy and Nod/NLRP3 activation in immune recognition of intracellularly persisting metabolically inactive small colony variants has not been sufficiently addressed to date.

Moreover, an earlier study suggested that low MOIs of *S. aureus* promote IL-1β and IL-18 cleavage via activation of NLRC5 (Davis et al. 2011). In addition, a recent study suggested a specific role of the DNA-activated absent in melanoma-2 (AIM2) inflammasome in IL-1β-mediated bacterial immune defense in *S. aureus* CNS infection (Hanamsagar et al. 2014). To date, however, there is no evidence for involvement of the cytosolic RNA-sensing RIG-I-like receptors (RLR) in immune defense against *S. aureus*.

Notably, in murine *S. aureus* infection models, neutrophil recruitment, cutaneous abscess formation, and clearance of *S. aureus* in pneumonia were shown to be dependent on IL-1β levels (Labrousse et al. 2014; Cho et al. 2012; Miller et al. 2007). However, based on a murine model of α-toxin-dependent severe necrotizing pneumonia, pharmacological intervention with NLRP3 activation was also discussed to ameliorate the course of disease (Kebaier et al. 2012). Moreover, a study in patients with atopic dermatitis suggested that the Th2-derived cytokines IL-4, IL-5, and IL-13 counteract activation of *S. aureus* α-toxin-induced activation of NLRP3 and ASC (Niebuhr et al. 2014). This finding supported the hypothesis that susceptibility of Th2-prototypical DBA/2 mice to *S. aureus* infection could be attributed to the failure to activate the NLRP3 inflammasome, while *S. aureus*-resistant C57BL/6 mice with an inherent Th1-profile clear *S. aureus* by activating the inflammasome (Accarias et al. 2015).

2.3 *Linking Inflammasomes to Protective T Cell Responses: The Role of NLRP3 in Th17 Differentiation*

Interestingly, a recent study proposed that NLRP3/IL-1β-dependent recruitment of IL-17-producing γδ-T cells is required for recruitment of neutrophils to the infection site (Maher et al. 2013). Further in vitro studies showed that IL-1β and IL-23

support a T cell receptor and CD1d-dependent IL-17A response to heat-killed *S. aureus* in invariant NK T cells (Doisne et al. 2011). This T cell subset expresses a T cell receptor that recognizes lipid antigens in a CD1d-restricted manner and NK cell markers. It is typically found in barrier tissues where it assumes a protective role in colonization with *S. aureus* (Nieuwenhuis et al. 2009) and a murine *S. aureus* sepsis model (Kwiecinski et al. 2013). Alternatively, induction of Th17 cells was reported to be induced by dendritic cells; here, IL-1β production and IL-23 production were triggered by dual activation of surface TLRs (TLR2/4/5) and concomitant engagement of FcγRIIA by staphylococcal immune complexes with IgG (den Dunnen et al. 2012).

Taken together, these findings argue for the coexistence of redundant innate immune mechanisms for the induction of Th17-mediated immune defense. Future work is needed to understand whether certain mechanisms are more relevant in distinct disease entities.

3 Professional Phagocytes and Their Effector Functions

3.1 Phagocytosis: Linking Intracellular Lysis to Antigen Presentation

Engulfment, ingestion, and phagosomal degradation of microorganisms by processes such as acidification and enzyme digestion are essential for killing of the microbes and are required for activation of cells of the adaptive immune response via antigen presentation by MHCII molecules. This process is initiated by cellular recognition of *S. aureus* PAMPs and opsonins. One important opsonin is mannose-binding lectin (MBL), a collection that contributes to bacterial recognition and mediates activation of complement and innate immune cells. Its binding to *S. aureus* facilitates phagocytosis by enhancing opsonization by complement components and synergy with TLR2/6 ligands in the phagosome (Neth et al. 2000, 2002; Ip et al. 2008). Survival of mice lacking MBL is severely impaired after intraperitoneal injection of *S. aureus* (Shi et al. 2004). MBL has been shown to increase uptake of *S. aureus* via upregulation of the scavenger receptor SR-A (Ono et al. 2006). However, strain-specific differences in MBL binding have been attributed to differences in the surface carbohydrate structures (Shang et al. 2005).

It should, however, not be disregarded that the processes of internalization and phagosome maturation are important prerequisites for MyD88/TLR-dependent recognition of *S. aureus* (Wolf et al. 2011; Ip et al. 2010). Albeit TLR2 itself does not mediate phagocytosis, sensing of *S. aureus* and induction of the proinflammatory cytokine response only occur upon recruitment of TLR2 to the phagosome (Underhill et al. 1999). Degradation of bacteria in the phagosome facilitates recognition of PG via Nod receptors and, thus, activation of the inflammasome (Wolf et al. 2011; Shimada et al. 2010; Ip et al. 2010; Sokolovska et al. 2013;

Kaplan et al. 2012). Interestingly, inflammasome-mediated activation of caspase-1 not only activates IL-1 and IL-18 precursors but also participates in the acidification of the phagosome (Sokolovska et al. 2013), which enables recognition of microbial nucleic acids by TLRs (Parcina et al. 2008, 2013).

Staphylococcal ribosomal (23S) RNA is recognized in a sequence-specific manner by TLR13 expressed in murine conventional $CD8_{HIGH}$ DC but not plasmacytoid dendritic cells (pDCs) (Oldenburg et al. 2012). This receptor is not expressed in humans, but staphylococcal RNA was recently shown to mediate human monocyte activation by TLR8 (Bergstrom et al. 2015). By contrast, in human B cells, pDC activation by *S. aureus* is blocked by inhibitory oligonucleotides blocking TLR7 and TLR9, the only TLRs expressed in these cell types (Parcina et al. 2008, 2013; Hornung et al. 2002).

Further support for a role of phagocytosis in cellular defense against *S. aureus* is provided by the importance of scavenger receptors in infection. These receptors mediate recognition and clearance of *S. aureus* and are typically expressed on phagocytes:

Most prominently, mice lacking CD36, a receptor expressed in macrophages, monocytes, endothelial, and epithelial cells, are highly susceptible to *S. aureus* infections (Hoebe et al. 2005; Stuart et al. 2005; Blanchet et al. 2014). Of note, mice with a double deficiency in CD36 and SR (scavenger receptor)-A, another scavenger receptor required for phagocytosis of *S. aureus* (Amiel et al. 2009), died of pneumonia but were protected from *S. aureus* peritonitis (Blanchet et al. 2014).

Interestingly, CD36 has been implicated in the recognition of phosphatidylserine on apoptotic cells (Fadok et al. 1998). The same receptor specifically recognizes *S. aureus* via the diacylglycerol moiety in LTA and acts as a coreceptor for TLR2 (Hoebe et al. 2005; Nilsen et al. 2008; Baranova et al. 2008). Supporting its association with TLR2, expression of CD36 was higher in patients with atopic dermatitis carrying a TLR2 polymorphism (R753Q) that leads to reduced TLR2 reactivity (Niebuhr et al. 2010b; Mrabet-Dahbi et al. 2008).

Moreover, PIR-B (paired immunoglobulin-like receptor) was also found to bind *S. aureus* LTA (Nakayama et al. 2012). A protective function in *S. aureus* pneumonia was found to be due to suppression of the inflammatory response (Banerjee et al. 2010).

Notably, CD36 and $\alpha_5\beta_1$ integrin, the receptor for vitronectin, a plasma protein that binds to apoptotic cells, collaborate in apoptotic cell recognition (Fadok et al. 1998). *S. aureus* binds vitronectin via extracellular adherence protein (Eap) (Hussain et al. 2008). It is, therefore, likely that cells involved in apoptotic cell clearance also participate in the recognition of *S. aureus.* Well in line with the tolerogenic response induced by apoptotic cells, in murine peritonitis the presence of Eap on *S. aureus* had an anti-inflammatory effect that led to a reduction in infiltrating neutrophils (Chavakis et al. 2002).

3.2 Tissue-resident Phagocytes

3.2.1 Mast Cells: Well-prepared Guardians of Skin and Mucosa

Mast cells are important sentinels in the skin and mucosa. These phagocytic cells are prepared to kill bacteria with intracellular ROS or release extracellular traps and AMP. They further have the unique ability to rapidly release cytoplasmic granules storing preformed vasoactive and immune stimulatory mediators, e.g., histamine, TNF, and the proteases tryptase and chymase into the extracellular environment. In bacterial infections, they have mainly been implicated in defense against respiratory pathogens in pneumonia (reviewed in Urb and Sheppard 2012). Since they predominantly reside at sites where encounters with invading pathogens are to be expected due to constant contact with the exterior environment, it should not be over interpreted that mast cells were not required for bacterial clearance or host survival in an in vivo *S. aureus* peritonitis model (Ronnberg et al. 2014).

Mast cells contribute to the elimination of *S. aureus* by release of extracellular traps, proinflammatory cytokines, and AMP (Abel et al. 2011; Rocha-de-Souza et al. 2008; von Kockritz-Blickwede et al. 2008a). *S. aureus*-derived PG, LTA, protein A, and TLR2 ligands have been implicated in mast cell activation (Jawdat et al. 2006; Matsui and Nishikawa 2002, 2005; Terada et al. 2006; McCurdy et al. 2003). Degranulation was recently postulated to be specifically induced by *S. aureus* δ-toxin, which links colonization to allergic reactions in atopic dermatitis (Nakamura et al. 2013). However, recent studies highlight that *S. aureus* evades these bactericidal effects by invading mast cells via $\alpha_5\beta_1$ integrin, a reaction demonstrated in mucosal tissue from nasal polyposis (Abel et al. 2011; Hayes et al. 2015).

3.2.2 Macrophages: Tissue-Specific Vigilants Balancing the Local Immune Response

Macrophages are professional phagocytes that are either resident in the tissue or develop from monocytes that enter the tissue from the blood vessels. Their major function is the clearance of invading pathogens from the site of infection and antigen presentation to T cells in the periphery and in the lymphatic organs. Tissue-resident macrophages are often highly specialized on their specific environment, e.g., marginal zone macrophages in the spleen, microglia in the brain, alveolar macrophages, and macrophages in the thymus are each equipped to fulfill their specific tasks.

Again, TLR2 plays a central role in the release of soluble mediators mediating bacterial defense and in bacterial killing, e.g., in macrophages, staphylococcal lipoproteins induce proinflammatory cytokines, nitric oxide (NO), and reactive oxygen species (ROS) (Nguyen et al. 2015; Kim et al. 2015; Nandi et al. 2015; Bishayi et al. 2014). Moreover, in brain abscesses of TLR2-deficient mice,

secretion of proinflammatory cytokines and NO was abrogated, but IL-17 production was increased (Kielian et al. 2005). Furthermore, expression of *S. aureus*-binding scavenger receptor, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) (Shimaoka et al. 2001), and murine macrophage scavenger receptor (MSR)-AI/II was increased in response to *S. aureus* and TLR2 ligands in microglia arguing for a specific role of TLR2 and these scavenger receptors in CNS infection (Kielian et al. 2005).

By contrast, a recent study claimed that neither TLR2 expression on macrophages nor proinflammatory cytokine production by macrophages is essential for immune defense against *S. aureus* (Yimin Kohanawa et al. 2013). Nevertheless, the importance of macrophages in antistaphylococcal immune defense was recently demonstrated in a murine post-influenza pneumonia model where resistance to *S. aureus* infection was achieved by GM-CSF-mediated influx of neutrophils and alveolar macrophages and mainly established by the production of reactive oxygen species (ROS) in macrophages (Subramaniam et al. 2014). In an additional study, MyD88-dependent activation of dermal macrophages and their interaction with neutrophils was shown to be required for control of neutrophil-mediated inflammation in cutaneous *S. aureus* infection (Feuerstein et al. 2015).

In addition, several studies reported binding and uptake of *S. aureus* cells in marginal zone (MZ) macrophages (Palecanda et al. 1999; van der Laan et al. 1999; Westerberg et al. 2008; Birjandi et al. 2011). It was further suggested that in vivo uptake was mediated by macrophage receptor with collagenous structure (MARCO) (Palecanda et al. 1999; van der Laan et al. 1999). This receptor might, therefore, play a central role in MZ macrophage-mediated removal of *S. aureus* from the bloodstream.

Notably, the currently available studies do not differentiate between pro- and anti-inflammatory monocyte and macrophage subsets. However, macrophage polarization is highly dependent on the microenvironment, e.g., GM-CSF, TLR2 ligands, and Fcγ receptors differentially affect macrophage function (reviewed in Martinez and Gordon 2014). Contradictory findings, might therefore, arise from the tissue- and/or mouse strain-specific milieu and the predominance of functionally distinct subpopulations.

3.3 Blood-Derived Phagocytes

Both epithelial cells and tissue-resident innate immune cells release chemokines and cytokines upon bacterial encounter. These soluble mediators provoke transmigration of cells from the blood circulation. Activation induces differentiation peripheral blood monocytes to inflammatory monocytes, macrophages, and dendritic cells that transmigrate into the tissue and participate in bacterial clearance.

3.3.1 Neutrophils: Recruited to Resolve Uncontrolled Spread of Infection

Neutrophils are recruited to the site of infection and represent the hallmark of early antistaphylococcal defense in the invaded tissue (reviewed in Rigby and DeLeo 2012). They further participate in abscess formation, an event that is supported by *S. aureus*-derived toxins and their ability to induce a specific form of programmed cell necrosis (necroptosis) (reviewed in Kobayashi et al. 2015; Greenlee-Wacker et al. 2015). Indeed, phagocytosis and subsequent intracellular lysis of *S. aureus* in neutrophils are often prevented by staphylococcal virulence factors, and infected neutrophils containing viable bacteria evade efferocytosis by macrophages via an upregulation of CD47 expression, the phosphatidylserine "don't eat me" signal (Greenlee-Wacker et al. 2014).

Nevertheless, neutrophils are essential for antistaphylococcal innate immune defense, a fact that was demonstrated in mice depleted of neutrophils (Kohler et al. 2011; Robertson et al. 2008; Verdrengh and Tarkowski 1997) but can also be derived from increased susceptibility to *S. aureus* seen in neutropenic patients and in patients with genetic defects in neutrophil function, i.e., chronic granulomatosis disease (CGD) (Hartl et al. 2008; McNeil 2014) and mouse models thereof (Kohler et al. 2011; Pizzolla et al. 2012). Furthermore, increased mortality in *S. aureus* septicemia after depletion of complement was mainly attributed to insufficient recruitment of neutrophils (Sakiniene et al. 1999). In addition, in mice, MyD88-dependent IL-1 and IL-18 signalings are required for mobilization of neutrophils and resolution of staphylococcal skin abscesses (Miller et al. 2006) and post-burn infection (Kinoshita et al. 2011). Therefore, neutrophils remain central cells in immune defense against *S. aureus* and other compensatory mechanisms such as the release of bactericidal antimicrobial peptides most likely govern neutrophil-dependent first-line immune defense against *S. aureus*.

Despite their synthesis in many different types of phagocytes, e.g., monocytes, macrophages, and DC, the highest levels of defensins as HNP1-3 are expressed by neutrophils (Ryu et al. 2014). AMP, such as cathelicidin (LL-37) and α-defensin, contribute to bacterial killing and degradation in the phagosome (Jann et al. 2009), neutralize toxins (Cardot-Martin et al. 2015), induce the production of cytokines (Chaly et al. 2000), exert chemotactic activity (Yang et al. 2001), and facilitate the formation of neutrophil extracellular traps (NETs) (Neumann et al. 2014). However, again, *S. aureus* virulence factors shield the pathogen from AMP. This occurs through AMP-inactivating enzymes (Braff et al. 2007; Jin et al. 2004; Sieprawska-Lupa et al. 2004) and modification of charge of surface structures, e.g., via D-alanylation of WTA and LTA (Collins et al. 2002; Peschel et al. 1999; Simanski et al. 2013).

A recent study further highlights that in vivo recruitment of neutrophils to the site of infection occurs in two waves, e.g., initially from the blood, and secondly, they are mobilized from the bone marrow (Kamenyeva et al. 2015). The authors propose that in *S. aureus* infection, neutrophils enter the lymph node medulla and interfollicular areas where they interact with B cells to interfere with antibody

production (Kamenyeva et al. 2015). The significance of these findings remains unclear but is well compatible with a previously described anti-inflammatory role of neutrophils in staphylococcal arthritis (Verdrengh and Tarkowski 1997). Concomitant with the release of neutrophil myeloid-related proteins (MRP) -8 and -14 into the bronchoalveolar fluid exerts an additional protective effect in pneumonia by mediating transmigration of neutrophils, this phenomenon might be necessary for resolution of inflammation (Achouiti et al. 2015).

3.4 Dendritic Cells: Orchestrating the Adaptive Immune Response in Tissue and Lymph Nodes

3.4.1 Myeloid Dendritic Cells: Expert Control of T Cell Responses

Dendritic cells regulate the T cell response in infection via presentation of antigen and concomitant expression of T cell polarizing costimulatory ligands and release of cytokines and other soluble mediators.

Myeloid dendritic cells (mDCs) are specialized cells whose major function is to present antigen to T cells after migration to the local lymph nodes. They play a key role in the clearance of *S. aureus,* and their depletion increases mortality in an in vivo model of bacteremia (Schindler et al. 2012). Furthermore, Jin et al. highlighted that mDCs expressing the C-type lectin BDCA1+ are highly responsive to *S. aureus* and support differentiation of T cells into IFNγ-producing CD4+ (Th1) and CD8+ (Tc1) cells (Jin et al. 2014). Interestingly, this property was attributed to high expression levels for TLR2 and the scavenger receptor SR-A whose expression levels were low on mDCs with a BDCA3+ CD16+ phenotype.

Another study differentiated the effects of *S. aureus* Lpp and PG on monocytes and on in vitro generated monocyte-derived dendritic cells: While PI3K-dependent production of anti-inflammatory IL-10 is induced on monocytes, production of Th1/Th17 polarizing cytokines IL-12 and IL-23 is triggered in monocyte-derived dendritic cells (Frodermann et al. 2011). Well in line with this report, it was demonstrated that IRAK4 reverts IL-10-dominated tolerogenic MyD88-dependent signaling in *S. aureus*- or TLR2/4-stimulated human monocytes from PKB/Akt/mTOR-dependent IL-10 to Th1-promoting IL-12 secretion (Over et al. 2013). However, release of phenol-soluble modulins by *S. aureus* results in the loss of T cell priming capacity and the induction of T regulatory cells (Schreiner et al. 2013).

In the skin, *S. aureus* is phagocytosed by Langerhans cells, a specialized DC subset found in dermis (Reis e Sousa et al. 1993). Furthermore, in a murine atopic dermatitis model, dual activation of DC via TLR2 ligands and IL-4 induced the progression of self-limited Th2-mediated dermatitis to chronic cutaneous inflammation (Kaesler et al. 2014).

Myeloid-derived suppressor cells, on the contrary, suppress T cell responses and thereby contribute to the persistence of *S. aureus* in chronic infections (Tebartz et al. 2015). They further halt monocyte and macrophage-mediated clearance of *S. aureus* biofilm (Heim et al. 2014), and once induced by TLR2/6 ligands are recruited to *S. aureus* colonized skin where they suppress T cell responses to the pathogen (Skabytska et al. 2014).

3.4.2 Plasmacytoid Dendritic Cells and Type I Interferons: Fine-Tuning of Innate and Adaptive Immune Responses

Plasmacytoid dendritic cells are considered to be DC of lymphoid origin. They represent the major producers of systemically active interferon-α in the human body and have been implicated in tolerance to oral antigens (Goubier et al. 2008). They are present in the blood, in the lymphatic organs, and probably all peripheral tissues. *S. aureus* induces pDC-derived secretion of IFN-α, TNF, and IL-6 (Parcina et al. 2008; Michea et al. 2013). However, depending on the tissue environment, soluble mediators such as prostaglandins and TGF-β alter pDC-derived cytokine secretion panels and their function (Michea et al. 2013; Bekeredjian-Ding et al. 2009; Contractor et al. 2007). Their role in infection, particularly *S. aureus* infection, was extensively reviewed in Bekeredjian-Ding et al. (2014).

One of their most important characteristics is the expression of Fcγ receptor IIA and Fcε receptor that exert positive and negative regulatory effects, respectively, on pDC activation and release of IFN-α. Therefore, pDC most likely orchestrate the secondary immune response to *S. aureus* (Parcina et al. 2008), and their presumptive role in first-line immune defense is limited to invasion by protein A-bearing *S. aureus* strains and pDC-mediated support of polyclonal B cell activation (Parcina et al. 2013).

Additionally, pDC might be involved regulation of the antistaphylococcal immune response by type I interferon. In vivo, induction of IFN-α production in pDC by TLR9 ligand CpG ODN was protective against *S. aureus* pneumonia in a hemorrhagic shock model (Roquilly et al. 2010) and IFN-α-mediated resistance of host cells against *S. aureus* alpha toxin (Lizak and Yarovinsky 2012). Similarly, IFN-β increased clearance of *S. aureus* from murine BMDC and human monocytes in vitro and in an cutaneous infection model in vivo (Kaplan et al. 2012), and deficiency in IFN-α/β receptor or TLR9 expression resulted in improved clearance of bacteria from mice with *S. aureus* pneumonia (Parker and Prince 2012). However, IFN-β production was associated with increased inflammation and cellular necrosis in murine skin infection (Kaplan et al. 2012).

Notably, several studies showed that IFN-α- and IFN-α-inducing TLR7/9 agonists suppressed the formation of Th17 cells under healthy conditions, in infection, and autoimmune disease (Cui et al. 2014; Hirohata et al. 2010; Liu et al. 2011; Meyers et al. 2006; Vultaggio et al. 2011). The inhibitory effect of IFN-α on Th17 responses can be attributed to the induction of the IL-17-suppressing cytokine IL-27 (reviewed in Goriely et al. 2009). In accordance with these findings, lack of IL-27

receptor expression increases Th17 cell numbers and decreases the bacterial burden in post-influenza *S. aureus* pneumonia (Robinson et al. 2015).

Moreover, a recent report showed that *S. aureus*-induced expression of osteopontin in DC was responsible for increased Th17 induction (Salvi et al. 2013). Upregulation of osteopontin occurred upon TLR2 activation and concomitant absence of IFN-β induction, which was observed with Gram-negative bacteria after engagement of LPS/TLR4 and subsequent recruitment of TRIF (Salvi et al. 2013). Notably, *S. aureus*-induced IFN-β release is further prevented by lysozyme resistance of *S. aureus* and its resistance to degradation in the phagosome (Kaplan et al. 2012). Nevertheless, protective effects of IFN-I-mediated suppression of Th17 responses on DC have also been described: In a murine EAE model, IFN-I suppressed the expression of an intracellular translational isoform of osteopontin (iOPN) in myeloid DC; this enabled IL-27 synthesis and, in turn, decreased Th17-mediated inflammation, which ultimately slowed down the progression of EAE (Shinohara et al. 2008; Guo et al. 2008).

Furthermore, generation of monocyte-derived dendritic cells in the presence of IL-27 resulted in increased suppression of intracellular growth of *S. aureus*, upregulation of MHC II, and increased IL-12 secretion that shifted the T cell response to a Th1 phenotype (Jung et al. 2015). IL-27 further induced the synthesis of IFN-α and IFNλ1 in PBMC and DC derived from healthy donors, thus promoting an autoregulatory negative feedback loop (Cao et al. 2014). Thus, intertwined regulation of IFN-α and IL-17 determines the polarization of CD4+ T cell responses, the efficacy of bacterial clearance, and the degree of inflammation in autoimmune disease and infection. A fine-tuned balancing of these two cytokines is, therefore, most likely very critical for the resolution of *S. aureus* infection and immunopathology.

4 The Last Frontiers Before Adaptive Immunity

4.1 Innate Immune B Cells: Rapid Supply of Antibacterial Antibodies

In murine peritonitis and sepsis, rapid accumulation of IgM-secreting plasmablasts is observed within 48 h after bacterial challenge (Martin et al. 2001). The cells responsible for this early IgM secretion are B cell subsets that express B cell receptors that recognize thymus-independent (TI) antigens, e.g., bacterial PAMPs such as capsular polysaccharides, LPS, and phosphocholine and phosphatidylserine, which are also present on apoptotic cells. Together with PRR, stimulation targeting of these B cell receptors elicits B cell proliferation and differentiation to plasmablast in a T cell-independent manner. Release of these antibacterial IgM molecules (also called natural IgM) enables bacterial opsonization and subsequent complement activation. It has further been postulated that cellular uptake of *S.*

aureus immune complexes with IgM is promoted by an Fcα/μ receptor (Shibuya and Honda 2006).

Among these, specialized B cell subsets are CD5-positive B1a and CD5-negative B1b cells that reside in the peritoneal and pleural cavities in mice. B1b cells are capable of phagocytosis of *S. aureus*, intracellular bacterial killing, and antigen presentation to T cells (Gao et al. 2012). Albeit this response is weaker than in macrophages, it underlines the phylogenetic relationship of innate immune B cells and macrophages.

Notably, *S. aureus* targets V_H3+ B cells via protein A, which results in long-term depletion of the B1a and MZ B cell pools (Goodyear and Silverman 2004; Viau et al. 2005). In the presence of pDC and costimulation via TLR2-active Lpp and endosomal TLRs, protein A-activated B cells are not directly harmed by programmed cell death but undergo differentiation to IL-10-secreting B regulatory cells and IgM-producing plasmablasts (Parcina et al. 2013; Bekeredjian-Ding et al. 2007). This process enables IL-10-mediated suppression of T cell responses before ultimately resulting in cell death due to the physiologically short life span of plasmablasts and, again, extinction of these B cell subsets.

4.2 *Natural Killer Cells: Neglected Sensors for Intracellular Persisting* S. aureus*?*

NK cells have mainly been studied in viral infection and malignancy. They are attracted to the infected tissue and enter by transmigration from the bloodstream. Their ability to recognize infected and damaged cells independent of MHC-restricted antigen presentation of antibodies makes them very flexible and invaluable cells for the rapid defense against invading pathogens. Upon encounter of suspicious cells, the release of IFNγ and granules containing cytotoxic proteases (granzymes) and perforine induces apoptosis of the encountered cell.

Although resistance Rag2-IL2R$\gamma^{-/-}$ C57BL/6 mice against *S. aureus* infection suggested that NK cells are not essential for innate immune defense against *S. aureus* (von Kockritz-Blickwede et al. 2008b), the interaction of natural killer cells with alveolar macrophages was shown to be beneficial in murine *S. aureus* pneumonia models (Zhao et al. 2014; Small et al. 2008). Similarly, upon exposure to *S. aureus* interaction with monocytes was required for activation of human NK cells in vitro (Haller et al. 2002). A protective role of NK cells was further described in the development of *S. aureus* arthritis (Nilsson et al. 1999). Detection of NK cells in human joint infections caused by chronically persistent *S. aureus,* indeed, argues for a potential role of NK cells at the site of infection (Wagner et al. 2006). Nevertheless, the obvious role of NK cells in the detection intracellularly persisting *S. aureus* and the elimination of infected cells have not yet been demonstrated.

4.3 *Innate Lymphoid Cells: Confinement of* S. aureus *to Its Niche?*

In tissues exposed to the environment and colonized by commensals, innate lymphoid cells (ILCs) prevent bacterial translocation beyond the epithelial barrier, trigger mucosal IgA production, and function as important regulators of immune homeostasis (reviewed in Philip and Artis 2013; Tait Wojno and Artis 2012; Diefenbach et al. 2014). Notably, commensals trigger the development of ILC, and ILCs phenotypically and functionally adapt to changes in the composition of the local microbiome (Tait Wojno and Artis 2012). NK cell receptors (NCR) such as NKp44/46 and expression of TLR2 and its coreceptors enable binding and sensing of the local microbiota (Philip and Artis 2013).

Three different classes of murine ILC have been defined by the expression of prototypical transcription factors and T helper cell-like cytokine secretion profiles, e.g., Tbet+ ILC (group 1) produce IFNγ, GATA3+ ILC (group 2) secrete IL-5, IL-9, and IL-13 and RORγt+ ILC (group 3) release IL-17A, IFNγ, and IL-22 (Diefenbach et al. 2014; Robinette et al. 2015). Notably, NK cells have recently been allocated to group 1 ILC (Philip and Artis 2013; Robinette et al. 2015; Monticelli et al. 2012). In the human, similar ILC subsets have been described, including different group 2-like ILCs in the respiratory tract and skin or different CD127+ group 3-like ILCs in tonsils, appendix, and Peyer's patches (Tait Wojno and Artis 2012; Monticelli et al. 2012; Mjosberg and Eidsmo 2014). Nevertheless, despite their presence at the main sites of *S. aureus* colonization, at present there is no available information on their role in preventing invasion. We can only speculate that in chronic carriers, ILC might confine *S. aureus* to its niche, thus preventing systemic immune responses.

5 Conclusion

A broad variety of receptor systems cooperates in sensing *S. aureus* and regulating the host immune response to this pathogen (see Table 1 for summary). TLR2-dependent recognition of *S. aureus* by epithelial cells limits the spread of colonizing *S. aureus* on the skin and mucosal surfaces. Upon cell and tissue invasion activation of resident innate immune cells by *S. aureus* fosters a proinflammatory environment that attracts neutrophils, NK cells, and monocytes from the blood. Notably, degradation of bacteria in the phagosomes is essential for bacterial recognition via TLR, activation of the inflammasomes, and subsequent bacterial clearance. However, evolution has selected *S. aureus* strains that are resistant to these processes.

At present, we know that innate immune cells and PRR also participate in the resolution of *S. aureus* infections. However, the exact mechanisms involved remain to be investigated and are potentially exploited by *S. aureus* to promote tolerance.

Table 1 Staphylococcal recognition motifs in innate immunity

Cellular level	Receptor system	PRR	Cell type	Staphylococcal recognition motif	Species	References
Soluble molecules	Collectins	Mannose-binding lectin (MBL)	S	Mannose-fucose spacing[a]	Mouse	Ip et al. (2008), Shi et al. (2004)
					Human	Neth et al. (2000, 2002), Shang et al. (2005)
	Antimicrobial peptides (AMP)	α-defensin, LL-37[b]	E, M	Surface structures such as lipids and wall teichoic acid	Human	Cardot-Martin et al. (2015), Yang et al. (2001), Neumann et al. (2014)
Surface receptors	Integrins	$\alpha_5\beta_1$ integrin	M, L, E	Surface proteins (MSCRAMMs, i.e., FnBP)	Mouse	Abel et al. (2011)
					Chronic rhinosinusitis patients	Hayes et al. (2015)
	Toll-like receptors (TLR)	TLR2	M, L, E	di- and triacylated lipoproteins	Mouse	Takeuchi et al. (2000), Kielian et al. (2005), Yimin Kohanawa et al. (2013), Stoll et al. (2005), Hashimoto et al. (2006), Nguyen et al. (2015), Schmaler et al. (2009), Underhill et al. (1999), Kim et al. (2015), Nandi et al. (2015), Bishayi et al. (2014)
					Human	Nguyen et al. (2015), Hilmi et al. (2014)
					patients with atopic dermatitis	Niebuhr et al. (2010), Mrabet-Dahbi et al. (2008)
	Scavenger receptors	CD36[a]	M, E	Lipoteichoic acid (LTA)	Mouse	Hoebe et al. (2005), Stuart et al. (2005), Blanchet et al. (2014)
		PIR-B	L, M	Lipoteichoic acid (LTA)	Mouse	Nakayama et al. (2012)
		SR-A	M, E	Broad but ill-defined specificity	Mouse	Ono et al. (2006), Stuart et al. (2005), Jin et al. (2014)
		MARCO	M, E		Mouse	Nakayama et al. (2012)

(continued)

Table 1 (continued)

Cellular level	Receptor system	PRR	Cell type	Staphylococcal recognition motif	Species	References
		(MSR)-AI/II[a]	M		Mouse	Kielian et al. (2005)
		LOX-1[a]	M, En		Hamster and Bovine cell lines	Shimaoka et al. (2001)
Endosomal receptors	Endosomal Toll-like receptors (TLR)	TLR8	M	Ribosomal RNA	Human	Bergstrom et al. (2015)
		TLR13	M	Ribosomal RNA	Mouse	Oldenburg et al. (2012)
		TLR9	M, L, E	DNA	Mouse	Roquilly et al. (2010), Lizak and Yarovinsky (2012), Parker and Prince (2012)
					Human	Parcina et al. (2008, 2013)
Cytosolic receptors	NLR	NOD1	M, L, E	Peptidoglycan (*meso*DAP)	Mouse	Kapetanovic et al. (2007)
		NOD2[a]	M, L, E	Peptidoglycan (muramyl dipeptide)	Mouse	Girardin et al. (2003), Volz et al. (2010), Kapetanovic et al. (2007), Hruz et al. (2009), Schaffler et al. (2014)
		NLRP3	M, L, E	α-hemolysin, Panton-Valentine-leukocidin	Mouse	Shimada et al. (2010), Soong et al. (2015), Accarias et al. (2015), McGilligan et al. (2013), Holzinger et al. (2012), Perret et al. (2012), Craven et al. (2009), Munoz-Planillo et al. (2009), Chi et al. (2014), DuMont and Torres (2014), Bocker et al. (2001), Gurcel et al. (2006), Kebaier et al. (2012), Niebuhr et al. (2014), Maher et al. (2013), Sokolovska et al. (2013)
		NLRC5	M, L	α-hemolysin	Human	Davis et al. (2011)
		AIM2	M, L	DNA	Mouse	Hanamsagar et al. (2014)

Cell types: *M* (myeloid), *L* (lymphoid), *E* (epithelial), *En* (endothelial); *S* (serum)
[a]Synergism with TLR2; [b]Synergism with TLR9

Finally, future work is needed to clarify the role of innate immunity and, in particular, NK cells in the recognition of intracellular persisting *S. aureus* and the role of ILC in immune homeostasis in chronic carriage.

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