Histol Histopathol (2017) 32: 761-766

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Role of cytokines in host defense against *Staphylococcus aureus* skin infection

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Summary. Wound infection caused by *Staphylococcus aureus* (*S. aureus*) is a critical clinical problem due to long hospitalization times, significant morbidity and mortality, as well as considerable medical resource consumption. With the emergence of methicillin-resistant *S. aureus* (MRSA) strains, current antibiotic treatments are becoming ineffective in combatting *S. aureus* infection. Thus, a novel therapeutic strategy is required. Recent studies discovered that several cytokines in the infected wound area play protective roles against *S. aureus* infection. This review summarizes recent discoveries regarding the role of cytokines-mediated responses in host defense against *S. aureus* skin infection, and discusses their implications for future immunotherapy and vaccine development.

Key words: Wound, Infection, *Staphylococcus aureus*, Cytokine

Introduction

Wound infection is one of the most common complications after severe trauma, burn or surgery, and it prolongs hospitalization, causes significant morbidity and mortality, and expends a considerable amount of medical resources. A previous study reported that the reduction of the overall wound infection rate from 4.2% to 2.5% at a single medical center over a 10-year period saved approximately $3 million in hospital costs (Olson and Lee, 1990).

Notably, *Staphylococcus aureus* (*S. aureus*) accounts for the majority of bacterial wound infections (Kim et al., 2015). *S. aureus* is also responsible for many other skin and soft tissue infections in humans, including impetigo, folliculitis, cellulitis, and infected ulcers. More concerning is the fact that *S. aureus* skin infection can progress to invasive and life-threatening infections, such as bacteremia, abscesses, pneumonia and sepsis (Klevens et al., 2007). Several therapeutic strategies are used to combat infection by *S. aureus*, including antibiotic-based treatments, antibiotic-free treatments, immunotherapy, therapeutic vaccines and occasionally, combinations of the above options. However, the use of antibiotics is highly effective and constitutes the traditional first-line treatment (Dou et al., 2016). Unfortunately, the indiscriminate use of antibiotics has led to the development of *S. aureus* strains increasingly resistant to multiple antibiotics, such as methicillin-resistant *S. aureus* (MRSA) strains. The widespread emergence of MRSA strains is becoming a global health problem. For example, epidemiological data from a burn center in Iran showed that MRSA strains were detected in approximately 60% of 128 *S. aureus* isolates that were collected from wound infections of burn patients (Motallebi et al., 2016). In other countries, the prevalence of MRSA varies from 23% to about 70% (Naqvi et al., 2007; Carvalho et al., 2010). Due to the spread and diffusion of MRSA, classic antibiotics have become less efficient against *S. aureus* infections.

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DOI: 10.14670/HH-11-867

Although the U.S. FDA (Food and Drug Administration)'s reboot of antibiotic development has contributed to the development of a few novel antibiotics effective in preventing and controlling MRSA wound infections (Shlaes et al., 2013), their efficacy is also bound to decrease after widespread use (Taubes, 2008). Due to this rapidly rising epidemic, and the increasingly serious issue of antibiotic resistance, novel therapeutic strategies beyond antibiotic treatment are required. Skin has its own defensive mechanisms against bacterial infections (Percival et al., 2012), such as its innate immune system and microenvironment. Thus, enhancing the skin's inherent antimicrobial/anti-infective abilities may constitute a valid alternative therapeutic option.

Recently, several cytokines located in the skin or wounds have been shown to be able to promote cutaneous immune responses, thus enhancing antimicrobial defense against *S. aureus* infection. In this article, we review recent advances in understanding the role of cytokine-mediated responses in host defense against *S. aureus* skin infection, and discuss their implications for future immunotherapy and vaccine development.

Interleukin-33 (IL-33)

IL-33 is a novel member of the IL-1 family of cytokines. In structure, it is most similar to IL-18 and IL-1β, another two classic IL-1 family members. The mature IL-33 protein is formed through the cleavage of a 31-kDa precursor by caspase-1. Similar to other members of the IL-1 cytokine family, IL-33 plays a dual role in various inflammatory diseases. IL-33 was found to combine with its receptor ST2, subsequently activate nuclear factor kappa beta (NF-κB) and mitogen-activated protein kinase (MAPK), and drive the production of pro-inflammatory cytokines. Moreover, IL-33 has been shown to be constitutively expressed in the nucleus of endothelial and epithelial cells in normal human tissues (Moussion et al., 2008), and may function as an endogenous alarmin molecule; it is released into the extracellular space after tissue damage and alerts the immune system about the tissue injury or infection (Moussion et al., 2008). In tissues with infectious wounds, IL-33 expression was observed to increase rapidly, primarily localized in epidermal keratinocytes and dermal macrophages (Yin et al., 2013; Li et al., 2014). Our recent work showed that peptidoglycan and lipoteichoic acid, major cell wall components of *S. aureus*, can stimulate the production of IL-33 in macrophages through the toll-like receptor 2-MAPK-AKT- signal transducer and activator of transcription 3 (TLR2-MAPK-AKT-STAT3) signaling pathway. Notably, addition of exogenous IL-33 obviously inhibited MRSA colonization and accelerated wound healing (Yin et al., 2013). These actions are mediated by several mechanisms. First, the increase of IL-33 expression in the early stages of infection can enhance the proliferation and the bactericidal activity of neutrophils, which boosts the clearance of infected skin wounds from bacteria. In addition, IL-33 can upregulate C-X-C chemokine receptor 2 (CXCR2) expression (Alves-Filho et al., 2010; Fang et al., 2016), which plays a major part in augmenting the migration of neutrophils -key effector cells in innate immunity, which are involved in phagocytosis and bacterial killing- to sites of infection (Verdrengh and Tarkowski, 1997; Burg and Pillinger, 2001; Rigby and Deleo, 2012). Finally, IL-33 binds to its receptor ST2, activating AKT-β-catenin and the inducible nitric oxide synthase (iNOS), which results in the release of nitric oxide (NO) (Li et al., 2014). NO, a reactive oxygen radical, has been reported to exhibit antimicrobial activities against a variety of bacteria, including *S. aureus* (Ghaffari et al., 2006, 2007).

IL-17

IL-17 (also called IL-17A) was discovered in 1993 (Yao et al., 1995), and it is the archetype of the IL-17 family of cytokines, which contains five other members (IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F). In addition to being generated by activated T cells (Th17 cells), IL-17 is produced by other cells including γδ T cells, NK cells, eosinophils and neutrophils. It mediates its biological effects via binding to its receptor IL-17R, which is a ubiquitously expressed cell surface receptor (Aggarwal and Gurney, 2002). IL-17 is a pro-inflammatory factor and acts on multiple cell types to induce the expression of cytokines, chemokines, and metalloproteinases. Moreover, it plays a critical role in innate immunity against cutaneous infections by *S. aureus*. In vivo experiments showed that IL-17-deficient mice were more susceptible to bacterial and fungal infections than wild type mice (Ye et al., 2001; Shibata et al., 2007; Kagami et al., 2010; Maher et al., 2013). Reduction of IL-17 production is responsible for the fact that mice deficient in resident epidermal γδ T cells, which are the main producers of IL-17 during *S. aureus* infections (Maher et al., 2013), had substantially larger skin lesions with higher bacterial counts and impaired neutrophil recruitment compared with wild type mice, while administration of exogenous recombinant IL-17 can alleviate immunodeficiency. In addition, IL-17 is capable of promoting protective immunity against recurrent *S. aureus* skin and soft tissue infections. Exposure to *S. aureus* preferentially expands a population of IL-17-secreting memory γδ T cells, which confers protective immunity against recurrent infections by the bacterium (Murphy et al., 2014). The presence of some strains of *S. aureus* around an infected wound can activate IL-1β production via Nlrp3-mediated signaling, subsequently inducing γδ T cells to produce IL-17. Moreover, certain strains can activate IL-1β production independently of Nlrp3, via the formation of non-Nlrp3-dependent inflammasomes as well as through non-inflammasome-mediated pathways. These alternative mechanisms induce the production of IL-17, even in the absence of Nlrp3. Furthermore, the production of IL-17 by skin γδ T cells depends on IL-1R/MyD88 signaling,

TLR2/MyD88 signaling, and IL-23. These findings suggest that immunomodulatory therapy aimed at promoting IL-17 responses in the skin may be a valid therapeutic strategy against *S. aureus* skin infection (Cho et al., 2010a). In addition to being involved in innate immunity, IL-17 is also a key cytokine for the recruitment, activation, and migration of neutrophils (Borsche and Lewinsohn, 1999; Aggarwal and Gurney, 2002; Moseley et al., 2003). It can stimulate the expression and release of C-X-C chemokines, thus promoting the recruitment of neutrophils, which is the most important step in the clearance of some pathogens.

IL-1

IL-1α and IL-1β are products of different genes, whose translation leads to the formation of pro-IL-1α and pro-IL-1β, respectively. Both precursor proteins are expressed in keratinocytes; however, pro-IL-1β is mainly produced by immune cells, such as monocytes/macrophages, dendritic and Langerhans cells. After being released into the extracellular environment upon cell death or lysis, pro-IL-1α is cleaved into mature IL-1α by cell membrane-associated calpain proteases as well as extracellular proteases. In contrast, production of active and secreted IL-1β is hydrolysed from pro-IL-1β by caspase-1, upon activation of the inflammasome. In several in vitro experiments, the processing of pro-IL-1β into active IL-1β was largely dependent on ASC/ nod-like receptor family, domain containing 3 (ASC/NLRP3) inflammasome activation (Craven et al., 2009; Muñozplanillo et al., 2009; Cho et al., 2012), indicating that this inflammasome plays a critical role in the activation of IL-1β. Both IL-1α and IL-1β contribute to host immune defense against infections by activating IL-1R and the subsequent MyD88/IRAK/NF-ϰB signaling pathways (Kupper and Fuhlbrigge, 2004; Miller et al., 2006; Miller and Cho, 2011). These induce the production of chemokines such as C-X-C chemokine ligand 1 (CXCL1), CXCL2, CXCL8, which promote neutrophil recruitment and abscess formation at skin regions infected by *S. aureus* (Krishna and Miller, 2012). IL-1β mainly promotes the recruitment of neutrophils in cases of deeper intradermal *S. aureus* infection, whereas IL-1α plays a predominant role in superficial *S. aureus* infection (Cho et al., 2010b).

IL-22

IL-22 is a member of the IL-10 family of cytokines, which is produced by activated Th1, Th17, and NK cells. IL-22 signals through the IL-22 receptor that is highly expressed on epithelial cells of skin, lungs, kidneys, and gut (Wolk et al., 2004). The IL-22 receptor is a protein complex that consists of IL-22R1 (interleukin 22 receptor, alpha 1) and IL-10BR (interleukin 10 receptor, beta), the latter being a subunit also shared by the receptor complex for interleukin 10. IL-22 has no influence on immune cells because of the absence of IL-22R1 expression from both resting and activated immune cells (Wolk et al., 2004); however, it has been detected in various tissues including skin, as well as their corresponding cell lines, and is believed to function as a mediator that directly promotes the innate, nonspecific immunity of these tissues (Boniface et al., 2005). Upon local bacterial skin infection, the expression of IL-22 is elevated in memory Th cells. Moreover, IL-22 stimulated keratinocytes constitutively express high levels of β-defensin, thus contributing to immune reaction against the skin infection by killing invading pathogens. Simultaneously, β-defensin defends against the invasion of further pathogens, including agents for which specific immune responses have not been established. In addition, IL-22 can induce production of other antimicrobial proteins capable of suppressing the growth of *S. aureus*, including psoriasin (S100A7) and CAP18/LL37, at the sites of skin inflammation (Liang et al., 2006). In a mouse model, mechanical skin injury was shown to induce a rapid burst of IL-22 mRNA expression and IL-22 release from γδ T cells, which is important for the expression of neutrophil chemo-attractants and neutrophil recruitment in mechanically injured skin as well as the containment of S aureus infection (Malhotra et al., 2016). Recently, IL-22 was found to enhance SLURP1 expression via STAT3 signaling, reportedly (Moriwaki et al., 2015); SLURP1 is effective in inhibiting the proliferation of *S. aureus*. Taking the above findings together, immune therapy and vaccination targeting IL-22 may prove an attractive alternative strategy in combating *S. aureus* (including MRSA) skin infections.

Interferon-γ (IFN-γ)

IFN-γ is a well-known mediator with a wide range of anti-bacterial, anti-viral, anti-tumor, and immuno-modulatory activities (Shpacovitch et al., 2011). However, IFN-γ in *S. aureus* infection can be beneficial or harmful, depending on the stage of the infection and the cell type involved in pathogenesis. Sasaki et al. (2006) reported that wild type mice immunized against *S. aureus* showed a remarkable decrease in bacterial growth, but this effect was diminished in IFN-γ knock-down mice, suggesting that IFN-γ is essential for an acquired resistance against *S. aureus* infection. However, IFN-γ produced in response to the challenge cannot influence secondary antibody responses. In addition, Sasaki et al. reported that even though IFN-γ plays a protective role early in *S. aureus* infection, its effect during the late stage of pathogenesis is detrimental, as IFN-γ knockdown mice displayed increased survival rates, decreased bacterial numbers, and improved kidney histological findings compared with normal mice (Nakane et al., 1995; Sasaki et al., 2000). Moreover, Satorres et al. (2009) found that IFN-γ can induce neutrophil-mediated nasal mucosal injury, facilitating *S.*

aureus colonization. With respect to its positive effects, IFN-γ is the downstream effector of IL-4- and IL-10-induced enhancement of host resistance to *S. aureus* infection. In a recent study, IFN-γ reportedly enhanced the antibacterial response of human mast cells to *S. aureus* by increasing intracellular and extracellular ROS production. In another study, IFN-γ was found to play a significant role in protecting human keratinocytes from the lethal effects of the *S. aureus* alpha toxin through apolipoprotein L1 (ApoL1)-induced autophagy (Brauweiler et al., 2016). In addition, IFN-γ is a critical regulator of neutrophil recruitment in *S. aureus* wound infection, and neutrophils are known to be the first line of host defense against infections by this bacterium. However, it is necessary to maintain a balanced neutrophil activation and immune response. Mc Loughlin et al. found that T cell-derived IFN-γ was able to generate a neutrophil-rich environment that promoted *S. aureus* pathogenesis by facilitating bacterial survival within the neutrophils (Mcloughlin et al., 2008).

Conclusions

In conclusion, recent discoveries involving cytokines that enhance defense against *S. aureus* have helped us further understand the protective immune responses against skin infection caused by this bacterium. This knowledge should assist the design of immune-based antibacterial therapies to combat such infections. In addition to detection of *S. aureus* by pattern recognition receptors, production of antimicrobial peptides and antibody-mediated immune responses, cytokine responses promoting the recruitment of neutrophils to regions of infection and subsequent abscess formation are also essential for *S. aureus* clearance (Krishna and Miller, 2012). Neutrophils are the major cellular component of the innate immune system; they are capable of engulfing bacteria through phagocytosis, and killing them through the activity of NADPH oxidase and myeloperoxidase (Beavers, 2016; Mcguinness et al., 2016). In this review, we describe several cytokines, secreted by resident cells at sites of infection, which participate in the defense against *S. aureus* by contributing to the production of chemotactic factors, which recruit neutrophils to the site of infection. These insights provide a rationale for future efforts directed at targeting local cytokine-mediated responses through novel treatment regimens. Notably, phagocytes, like neutrophils, could facilitate *S. aureus* infection. Dysregulation of stimulated neutrophils can create an environment that promotes the intracellular survival of *S. aureus* to the detriment of the host (Gresham et al., 2000). Furthermore, *S. aureus* has the ability to produce many molecules that directly inhibit neutrophil functions such as recruitment and phagocytosis (Mcguinness et al., 2016). Therefore, it is vital that appropriate antibacterial therapies are in place to coordinate the timely recruitment of neutrophils to the infection site, and their subsequent clearance from it (Mcloughlin et al., 2008).

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Accepted January 12, 2017