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Immunity to *Staphylococcus aureus*: Implications for Vaccine Development

RICHARD A. PROCTOR
University of Wisconsin, Medical Microbiology/Immunology, Madison, WI 53705

ABSTRACT Cell-mediated immunity seems to be critical for prevention and resolution of invasive *S. aureus* infections, but an imbalance in this immunity may also produce SIRS and death or an inadequate protective response with prolonged bacteremia and death. This dysregulation is likely at the heart of mortality and severe disease in humans. Anti-toxin antibodies may also come into play in reducing the severity of *S. aureus* infections, but these antibodies might also address superantigen-induced immune dysregulation. Thus, while changing intrinsic T cell responses may be therapeutically difficult, monoclonal antibodies against superantigens may have utility in addressing dysfunctional immune responses to *S. aureus*. The models above are hypotheses for examining, and potentially dramatically improving immune response to and safety of *S. aureus* vaccines.

INTRODUCTION

Most adult humans have high levels of circulating antibodies against many staphylococcal antigens, indicative of prior subclinical infections, but these antibodies are generally not protective, and clinically significant infection with *S. aureus* fails to provide protective immunity. Multiple vaccines have been developed for the prevention of *S. aureus* infections, but none were proven efficacious in the human trials reviewed in references 1–4. All of the vaccine candidates functioned well in animal models, mostly murine models, but also in rabbits and primates. The reliance on murine models can be related to the extensive data available about murine immunity. Based on the large number of failures, a reasonable conclusion is that murine immunity and human preventive immunity against *S. aureus* are significantly different. The divergence of human and murine immunity has been detailed in the recent literature (1–6).

Clearly, one major hurdle in producing an *S. aureus* vaccine is the lack of detailed information about the human protective immune response to *S. aureus* (1–4). Several vaccine candidates that target surface antigens and produce opsonizing antibodies have reached clinical trials, but they have failed to protect or attenuate infections in humans. All of these antigens produced robust humoral immunity that provided protection in animal models. These data indicate that antibodies based on opsonophagoctyic activity are not protective in humans. While these results were very disappointing, they were not entirely surprising, because patients with B cell defects do not show increased frequency or severity of *S. aureus* diseases (2–4). Information from immune defects, clinical trials, and studies of human sepsis are providing important information about the immune

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Correspondence: Richard A. Proctor, rap@wisc.edu

response to *S. aureus* in humans, underlining the importance of cellular immunity. This information is examined here.

IMMUNE DEFECTS AND RECURRENT *S. AUREUS* INFECTIONS

The inborn and acquired immune defects that increase the incidence of *S. aureus* help to define the cells and pathways that provide protective immunity, and these are summarized in Table 1. Overall, evidence is mounting that helper T (T_H) cells plus polymorphonuclear neutrophils (PMNs), dendritic cells, and macrophages are important for a protective immune response (7–14).

Vitamin D Deficiency and Dendritic Cell Failure

Patients with vitamin D deficiency have increased numbers of *S. aureus* infections (15, 16). This may relate in part to decreased bactericidal activity of their dendritic cells (17). Indeed, some strains of *S. aureus* were able to reside within bone marrow dendritic cells and macrophages because they expressed high activity of the Agr quorum-sensing system and escaped from phagosomes by producing the lytic proteins phenol-soluble modulins (18). Therefore, having adequate vitamin D levels may help dendritic cells to express maximal bactericidal activity against *S. aureus* as well as to release mediators to activate the immune system.

Mutations in NGFβ and Its Receptor NTRK1 Reduce Phagocyte Activation

Mutations causing loss of nerve growth factor β (NGFβ) or its receptor have been associated with recurrent *S. aureus* infections in humans in skin, joints, bones, and the oral cavity (19). *S. aureus* factors such as peptidoglycan, protein A, α-hemolysin, and phenol-soluble modulins stimulate macrophages through nucleotide-binding oligomerization domain-like receptors to produce NGFβ (19). NGFβ is both a chemoattractant for and an activator of phagocytes. NGFβ activation of neutrophils and macrophages results in enhanced killing of *S. aureus*. Deletion of NGFβ or its receptor NTRK1 results in more severe *S. aureus* infections in animal models (19). Of note, the ability to activate macrophages to produce NGFβ is limited to *S. aureus* because not even *Staphylococcus epidermidis* causes the release of NGFβ. Patients deficient in NGFβ demonstrate the critical importance of phagocytes in the control of *S. aureus* infections.

IRAK-4/MyD88 Deficiency

Defects in interleukin-1 receptor-associated kinase-4 (IRAK-4) or myeloid differentiation factor 88 (MyD88) impair Toll-like receptor 2 (TLR-2)-mediated and interleukin-1 (IL-1) receptor-mediated immunity such that macrophages fail to produce inflammatory cytokines such as IL-1β, IL-6, IL-8, interferons (IFNs), and tumor necrosis factor alpha (TNF-α) (20–23). Without these cytokines, there is a failure to activate a specific subset of T-helper cells known as T_H17 cells, which are critical for the activation of polymorphonuclear neutrophils (PMNs). These deficiencies manifest soon after birth with recurrent *S. aureus*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* infections. Prophylactic antibiotics and early aggressive antibiotic therapy are required to treat babies with these defects. While intravenous immunoglobulin is often used, with respect to pneumococcal infection, there is no correlation between the presence or absence of antipneumococcal antibodies and the occurrence of invasive pneumococcal disease

TABLE 1 Immune defects that increase the incidence of *S. aureus* infections[a]

Immune defect	Biological basis	Clinical presentation	References
Failure of dendritic cells	Vitamin D required for activation	Recurrent and more severe infections	15, 16
Failure to activate macrophages	Mutations in NGFβ and its receptor, NTRK1	Recurrent and more severe *S. aureus* infections	19
Failure to activate PMNs	IRAK-4 or MyD88 deficiency	Failure of PMNs to kill *S. aureus*, *S. pnumoniae*, and *P. aeruginosa* despite Abs; invasive and skin infections; resolving in teenage years	20–23
Failure to differentiate naive T cells into T_H17 cells	IL-6 autoantibodies or IL-6 deficiency	Recurrent *S. aureus* infections	14
Failure of T_H17 cells to recruit PMNs	STAT-3 defect	Recurrent *S. aureus* skin and mucosal infections, starting in neonates	8, 10, 13
T-cell defects, e.g., with HIV or prednisone treatment	Reduced activation of T cells	Recurrent *S. aureus* infections, especially mucocutaneous	34–36
MAIT cell exhaustion (T cell exhaustion)	10–45% of lymphocytes Inactive after SAg exposure	Increased severity and frequency of infections in intensive care units with reduced MIAT cells	39–44, 48

[a]IRAK-4, interleukin-1 receptor-associated kinase-4; MAIT, mucosal-associated invariant T; MyD88, myeloid differentiation factor 88; NGFβ, nerve growth factorβ; STAT-3, signal transducer and activator of transcription 3; T_H17, T helper cell-17.

in patients with these deficiencies. This demonstrates the critical importance of T_H17 cells and PMNs in the outcome, even though it is well known that anticapsular antibodies are important in host defense against the pneumococcus (20–23). Those children that survive until their teenage years have a resolution of frequent invasive infections.

IL-6 Autoantibodies

A patient described by Puel et al. with recurrent *S. aureus* infections had normal immunoglobulins, suggesting that his infections could not have been the result of immunoglobulin deficiency. Instead, this patient was found to lack the proinflammatory cytokine IL-6 due to anti-IL-6 antibodies (14). The absence of IL-6 causes an immunodeficiency state, which can be assumed to be responsible for his recurrent *S. aureus* infections. IL-6 is normally produced in response to *S. aureus* interactions with macrophages, dendritic cells, and γδ-T cells. IL-6, in conjunction with transforming growth factor β (TGF-β), helps to direct the conversion of naive CD4 T cells to T_H17 cells (24) and the proliferation of T_H1 and T_H2 cells, among many cell types (25). IL-6 is also important for blocking regulatory T cell (Treg) development and for stimulating B cells to produce antibodies (24). Overly active Tregs can produce immunosuppression by reducing T_H1 and T_H17 cellular activation of the bactericidal activity of phagocytes. On the one hand, activation of T_H17 cells is critical for the control of *S. aureus* infections (26); on the other hand, the suppression of Tregs may allow for an overly exuberant inflammatory response to *S. aureus* infections (27, 28). Indeed, loss of Tregs can result in fatal inflammatory disease (29). Thus, IL-6 plays a key role in regulating T_H17/Treg balance so as to control immunity and immunopathology.

Job's Syndrome, a T_H17/STAT3 Defect

Patients with autosomal-dominant hyper-IgE, or Job's syndrome, have dominant-negative mutations in signal transducer and activator of transcription 3 (STAT3) (8, 10, 13), and mutations in STAT3 have a strong association with frequent and severe *S. aureus* mucocutaneous infections, including staphylococcal pneumonia, empyema, and "cold" skin abscesses. STAT3 is an intracellular signal transduction factor in T_H17 cells, which links surface receptors to the activation of genes (30, 31). Activation by IL-6 of its receptor on T_H17 cells plays a key role in the differentiation of naive T cells into T_H17 cells. T_H17 cells are critical for controlling *S. aureus* infections because they release IL-17, which recruits PMNs to the site of infection and helps to activate the PMNs for killing *S. aureus* (31). A key role for PMNs in the protection from *S. aureus* infections has also been established by the observation of recurrent *S. aureus* infections in patients with chronic granulomatous disease (primary defect in the production of reactive oxygen species by their PMNs) (32). However, the role of STAT3 may extend beyond PMNs because STAT3 is also involved in expression of host antimicrobial peptides in keratinocytes (31) and in the production of Reg3γ, an antimicrobial peptide produced by respiratory epithelial cells, whereby these respiratory mucosal cells become bactericidal for *S. aureus* (33). *S. aureus* interaction with respiratory epithelial cells activates them through STAT3 for the production of Reg3γ. Thus, while STAT3 is important for controlling systemic invasion by *S. aureus* by recruiting and activating PMNs, it also plays an important role in activating mucosal and skin cells. Hence, this defect is associated with recurrent *S. aureus* mucocutaneous infections.

Corticosteroids and AIDS

Patients with reduced cell-mediated immunity have an increased incidence of *S. aureus* infections. This can be due to an underlying disease such as systemic lupus erythematosus, AIDS infection, or the use of corticosteroids (34–37). Even moderate-dose prednisone therapy increases the risk of serious *S. aureus* infection (36). While we frequently think of viral infections as being associated with reduced cell-mediated immunity, the link to *S. aureus* infections comes from the reduced T_H17 cell-PMN axis in prednisone-treated patients (38).

Mucosal-Associated Invariant T (MAIT) Cells, Superantigens, and T Cell Exhaustion

MAIT cells represent up to 10% of T cells in blood and up to 35% in liver and some mucosal sites (39–44), and they may be considered the first T cell responders to invading bacteria because they are activated during the early stages of bacterial infection and act as a bridge between the innate and adaptive immune systems by recognizing bacterial byproducts derived from riboflavin metabolism (42). However, unlike the situation with humans, MAIT cells are infrequent in laboratory mouse strains such as C57BL6, thereby limiting the utility of murine models without humanization (39). MAIT cells have been implicated in protecting the host from multiple species of bacteria (40–42, 44, 45). However, recent studies have shown that they also respond to superantigens (SAgs), such as staphylococcal enterotoxin B (SEB), and have been identified as extremely potent and fast-acting producers of proinflammatory cytokines (39).

To quote from Taylor et al. (39), "We have identified a population of innate T-like cells, called MAIT cells, as the most powerful source of proinflammatory cytokines after exposure to SAgs." In addition to being involved in immunopathogenic activity, MAIT cells may also be involved in "a novel mechanism of SAg-associated immunosuppression in humans" (39) wherein widespread activation of MAIT cells by SAgs results in their inability to respond to future challenges. Sandberg et al. (43) report that subsequent to such SAg activation, the MAIT cells remain unresponsive to stimulation with conventional bacterial antigens. This concept of immune exhaustion is supported by the observation that intensive care unit patients with reduced MAIT cells were more vulnerable to severe and subsequent bacterial infections during their stay in the intensive care unit (46). Equally, ill patients' normal MAIT numbers did not show increased bacterial infections (46). Thus, SAg-producing *S. aureus* hijacks MAIT cells by inducing the cytokine storm and leaves them functionally impaired. A mechanism for this is based on the occurrence of anergy via upregulation of inhibitory receptors such as lymphocyte-activation gene 3 (39, 44, 47).

T Cell Exhaustion is Manifested in Humans by Low Levels of IL-2

SAgs induce other modifications to T cells (see Fig. 2). A marker of T cell exhaustion is low levels of IL-2 (39, 43, 48). IL-2 production increases dramatically in SEB-challenged MAIT cells compared to conventional T cells in peripheral blood mononuclear cells (39). This is in contrast to *E. coli* exposure to MAIT cells where IL-2 was not produced (49). These observations are consistent with previous findings where SEB and other SAgs delete or anergize T cells (50, 51). Moreover, exposure of human $CD4^+CD25^-$ T cells to SEA induces proliferation and is followed by a switch to a $CD25^+FoxP3^+$ Treg phenotype that secretes IL-10 but not IL-2 (39). SEA also activates αβT cells (52). SEB activates αδT cells and stimulates the conversion of Treg to T_H17-like cells (11, 39, 52–57). In summary, SAgs can induce a cytokine storm, but they are also potent immunomodulators of the T cell immune response. These effects would be anticipated to change during the course of *S. aureus* sepsis.

Summary of Immune Defects and *S. aureus* Infections

In summary, the inborn and acquired immune defects that are associated with an increase in the incidence of *S. aureus* infections show that the macrophage-T cell axis is critical for the activation of phagocytes to control *S. aureus* invasive infections. Conspicuously absent is the need for opsonic antibodies for protection against *S. aureus*, because children with agammaglobulinemia do not show increased numbers of *S. aureus* infections (1–5). The innate activation of macrophages and dendritic cells, as well as the surface factors that activate complement, seem sufficient to control *S. aureus* without opsonization. On the other hand, antibodies against *S. aureus* toxins have been shown to reduce the severity and mortality of *S. aureus* toxin-mediated diseases (6, 58–61). As discussed below, staphylococcal SAgs can play a major role in the modulation of T cell development; therefore, antitoxin antibodies may be crucial in the maintenance of a balanced macrophage-T cell axis.

STAPHYLOCOCCAL SEPSIS AND CYTOKINE PRODUCTION

Some information is emerging about anti-*S. aureus* immunity that is based on studies of patients with sepsis, especially *S. aureus* bacteremia, and this is summarized in Table 2. In septic patients, the profile of cytokines produced during infection is a reflection of the cells that are activated (Table 2). Normally, interaction of invasive *S. aureus* with macrophages and dendritic cells causes the release of proinflammatory cytokines such as IL-1, IL-2, IL-6, IFN-γ, and TNF-α. This is later followed by IL-10, which downregulates the immune response. However, this normal pattern of immune response is not seen in patients that have worse outcomes from *S. aureus* sepsis. Thus, mortality is associated with dysregulation of the immune system in apparently normal individuals. As detailed in Table 2, mortality or more severe disease is associated with low IL-1, IFN-γ, and TNF-α but high IL-6 and IL-10.

A dramatic example of immune dysfunction during *S. aureus* infection came from the V710 staphylococcal vaccine trial, where increased mortality occurred in vaccinated patients (62). V710 was a recombinant *S. aureus* surface protein, IsdB (iron surface determinant protein B), and was given to subjects prior to cardiovascular surgery. Patients that received the vaccine and subsequently developed invasive *S. aureus* infection during the postoperative period showed increased mortality. The cause of the increased mortality was systemic inflammatory response wherein control of the immune response was lost. Posttrial investigation found that low levels of IL-2 were observed not only during sepsis but even before patients received the V710 vaccine (63). There was a 5-fold increased mortality in vaccinees that

TABLE 2 Cytokines, sepsis, and survival in *S. aureus* infection

Study	Type of infection[a]	Survival or less complicated course	Death or complicated course
Söderquist et al. 1992 (84)	65 patients with sepsis	Rapidly dropping IL-6	Persistently elevated IL-6
van Dissel et al. 1998 (67)	Sepsis	High IL-1 and TNF-α with low IL-10	Low IL-1 and TNF-α with high IL-10
Rose et al. 2012 (68), Rose et al. 2017 (69)	*S. aureus* bacteremia	High IL-1 and low IL-10	Low IL-1β and IFN-ϒ; high IL-10
V710 vaccine trail Fowler 2013 (62); McNeely 2014 (63)	Invasive infections after cardiothoracic surgery	High IL-1, IL-2, and IL-17	Low IL-2 and IL-17 preoperatively and all postoperative testing
McNicholas et al. 2014 (85)	61 patients with SAB[a]	Low levels of IL-6 predict better outcome	High levels of IL-6 predict worse outcome
Gupta et al. 2016 (65)	Posttrauma sepsis (mix of bacterial pathogens)		High IL-4, IL-10, TGF-β, T_H17, and T_H17/Treg Low IL-2 and IFN-γ
Minejima et al. 2016 (66)	196 patients with SAB	Low TNF-α and IL-10; low IL-17A in all patients	High TNF-α and IL-10; low IL-17A in all patients
Chantratita et al. 2017 (86)	327 patients with SAB	Low IL-6 and IL-8 had less respiratory failure	High IL-6 and IL-8 had more respiratory failure

[a]SAB, *S. aureus* bacteremia.

had low prevaccination levels of IL-2. Thus, low baseline levels of IL-2 could predict a tragic outcome when vaccinees developed a postoperative infection. These patients also showed low levels of IL-17. These unanticipated results show that excess mortality was related to a dysregulated immune response even before the vaccine was given. Because IL-2 is critical for the survival of Tregs (64), one can postulate that the loss of these cells that modulate the immune response may have played a role in the mortality of these vaccinees. IL-2 is complex in that it produces both pro- and anti-inflammatory effects by downregulating T_H17 but upregulating T_H1 cells. Although increased numbers of T_H17 cells were found in *S. aureus* sepsis in several studies (9, 65), this is usually not accompanied by an increased blood concentration of IL-17 (12, 62, 65, 66) and may help to explain why IL-17 levels were low in clinical studies when one would anticipate higher T_H17 activity. It also raises the possibility that T_H17 cells may act locally rather than systemically (Fig. 1).

The data outlined in Table 2, suggesting that immune dysregulation correlates with more severe disease and mortality, are considered here. IL-1 is released from macrophages and dendritic cells (among other cells) when *S. aureus* is first met while invading tissues (12). However, patients that show low levels of IL-1 have worse outcomes during invasive *S. aureus* infections (67–69). Of the many functions that IL-1 has, perhaps a very important one for invasive *S. aureus* infections comes in directing T_H17 differentiation and activation (70), because T_H17 cells are critical for protection against *S. aureus* infections (10, 13). Therefore, it is striking that patients with *S. aureus* circulating in their bloodstream and interacting with macrophages would fail to produce IL-1, and this is an obvious sign of immune dysregulation.

Another cytokine released early in the course of *S. aureus* infection is IL-2 (71), and low levels have correlated with poor outcomes (62, 65). Broadly speaking, IL-2 ± TGF-β reduces inflammation by directing reduction of T_H1, T_H2, and T_H17 differentiation and increasing Treg expansion (72). The importance of IL-2 in directing cells toward a moderated inflammatory response is underscored by the increased deaths in patients receiving the V710 *S. aureus* vaccine (62), wherein low prevaccination IL-2 levels correlated very strongly with a systemic inflammatory response syndrome (SIRS) response in these patients when an invasive *S. aureus* infection occurred. Moreover, IL-2 levels remained low during the infection. These observations are consistent with data from Gupta et al. (65), who studied sepsis in trauma patients, wherein death was associated with low level of IL-2 in culture supernatant of peripheral blood mononuclear cells from these patients. Of course, severe trauma itself causes changes in the immune response, so the immune dysregulation noted in this study is less clear cut than in the *S. aureus* vaccine study.

Also consistent with the IL-2 data for immune dysregulation are the observations from several studies that strongly correlate high levels of IL-10 with poor outcomes (65, 67–69). IL-10 downregulates the inflammatory response to *S. aureus* invasion. The increased mortality suggests that the balance between pro- and anti-inflammatory responses is incorrect. *S. aureus* itself may actively alter this balance by stimulating production of IL-10 directly. Quantitatively, *S. aureus* interactions with monocytes and macrophages via TLR-2 interactions produce 4- to 20-fold more IL-10 than interactions

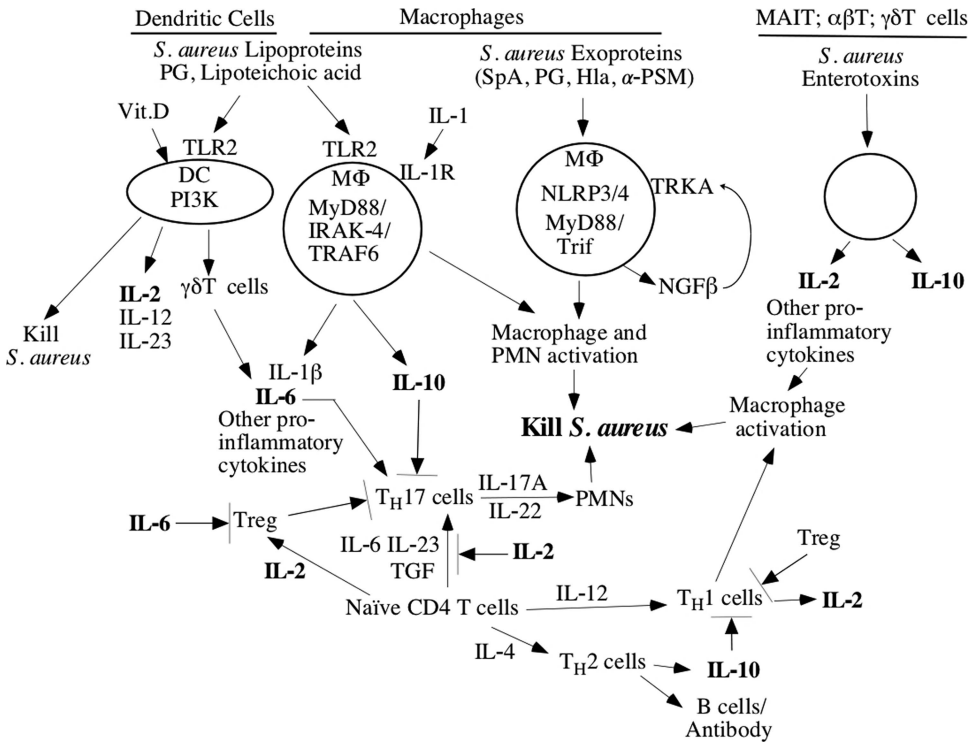


FIGURE 1 Model for human immunity to *S. aureus* based on immune defects and cytokines in sepsis.

with dendritic cells (58). Thus, more IL-10 is produced during bacteremia than in cutaneous infections. While the downregulatory effects following interactions of *S. aureus* ligands with the TLR-2 on T cells, monocytes, macrophages, and dendritic cells may be critical for balancing the host response to SAgs (73–76), overly vigorous suppression of the immune response may lead to continued bacteremia, whereas inadequate suppression may result in death due to SIRS. Engagement of TLR-2 on macrophages can also produce the proinflammatory cytokine, IL-1, but in dendritic cells IL-2 is produced. IL-2 production is needed for the development and maintenance of Tregs, which suppress immune responses produced by T_H17 cells (56). In some cases, T_H17 cells, which are not thought of as IL-10 producers, can convert to IL-10 production when given a second *S. aureus* challenge (70), which might relate to the first challenge being vaccination and the second challenge being invasive infection (63). Hence, the inhibitory activity of IL-2 on T_H2 and T_H17 cells and stimulatory activity on Treg cells might be lost when IL-2 levels are low during sepsis and allow for increased IL-10 production. High IL-10 would decrease PMN activation and killing of *S. aureus* (70, 77–81), reduce T_H17 proliferation (78, 82), and reduce Treg activity (78, 82, 83).

A balance between too low and too high IL-10 levels in response to *S. aureus* infections has been suggested as needed to avoid an overly vigorous response (SIRS) or an incomplete activation (persistent bacteremia) (78, 82, 83).

Another consistent finding is that persistently elevated IL-6 correlates with death and/or with another worse outcome with *S. aureus* sepsis (84, 85, 86). IL-6 is produced by macrophages and dendritic cells shortly after *S. aureus* products bind to TLR-2 (14, 24, 27, 30, 81). IL-6 causes differentiation of naive T cells into T_H17 and regular Tregs into proinflammatory Tregs that produce IL-17, IFN-γ, and TNF-α (14, 24, 27, 56). Thus, persistently elevated IL-6 may be linked to an overactive proinflammatory response that damages the host more than it protects it.

Finally, noninterleukins have also been examined during *S. aureus* sepsis in humans. Low levels of IFN-γ correlate with death (65, 68, 69). Early interactions of *S. aureus* with macrophages via TLR-2 lead to IFN-γ release (83). Similarly, when *S. aureus* interacts with dendritic cells via TLR-2, this results in dendritic-cell-mediated activation of T_H1 and γδT cells to produce IFN-γ (18, 87). IFN-γ activates macrophages to kill *S. aureus* (83). MAIT cells can also produce IFN-γ after

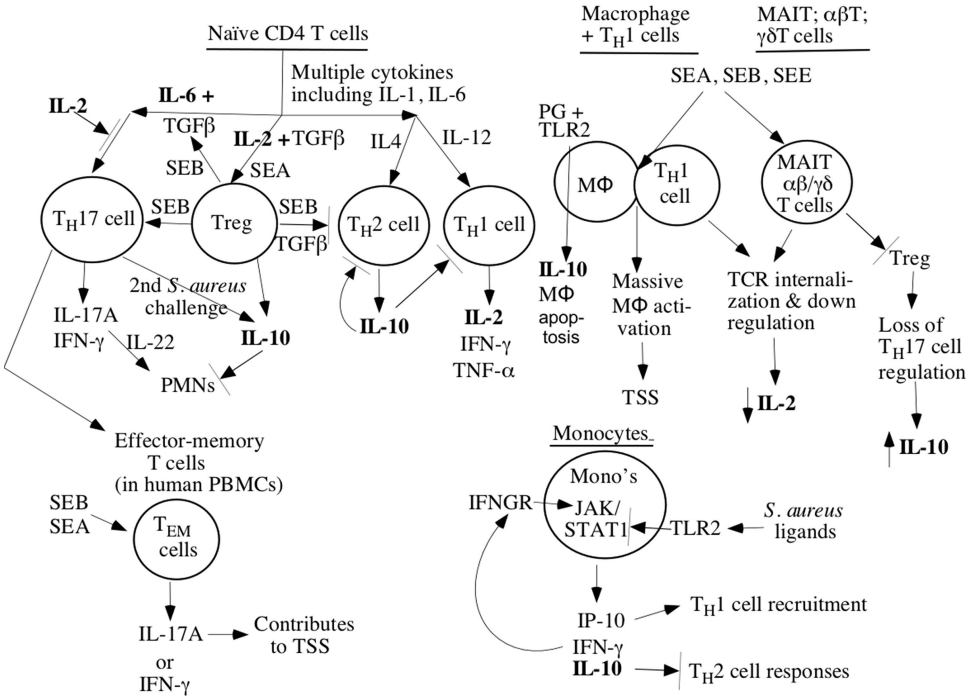
interactions with SEB (39). Clearly, low levels of IFN-γ might result in poor clearance of *S. aureus* by macrophages. Of interest, immunization of C57Bl/6 mice with killed *S. aureus* resulted in CD4 T-cell-dependent production of high IFN-γ levels with *S. aureus* bacteremia challenge that produced death (88). This provides another example where human and murine immunology diverge.

In contrast to IFN-γ levels, TNF-α levels yielded inconsistent results because high levels of TNF-α were associated with increased (66) or decreased (67) mortality from *S. aureus* bacteremia. TNF-α is important for activation of phagocytes, but it has also been associated with SIRS and death. More studies will be needed to sort this out. Nevertheless, the available studies of cytokine release during *S. aureus* sepsis provide strong evidence for immune dysfunction that leads eventually to death or more severe disease.

IMMUNE DYSREGULATION AND DEATH

Immune dysregulation, either over- or under-activation, of the immune response can be associated with mortality and/or more severe disease. This raises the question of why so many humans have a nonprotective response to *S. aureus* infections that is clearly related to immune dysregulation. We are familiar with *Mycobacterium leprae* and *Trypanosoma cruzi* as causing immunosuppression of the host, and hence one hypothesis is that the balance between the host and *S. aureus* has become lost. This might be due to the production of superantigens (SAgs) that can alter the responses of antigen-presenting cells and T cells (39, 43, 47, 50–53, 57, 74, 89–96). Observations from these papers are summarized in Fig. 2 and are offered as enterotoxins redirecting T cell differentiation. For example, SEB has many interactions with the human immune system. SEB can cause Tregs to develop a T_H17 phenotype and to produce TGF-β (91). The TGF-β enhances naive T cells to differentiate into T_H17 cells, and it inhibits T_H2 cell activation. SEA, SEB, and SEE can activate T_H1 and MAIT cells as superantigens that result in massive macrophage activation and toxic shock (39, 43, 46, 47, 49). After such activation, the T cells and MAIT cells downregulate and fail to respond to further stimulation, leaving the host immunocompromised for days to weeks (39, 46). In addition, SAgs can even inhibit the primary interactions between staphylococcal products and TLR-2 (89, 90). Thus, SAgs have a very large number of interactions with the human immune system, especially T cells and macrophages (Fig. 2). Notably, cutaneous infections and vaginal toxic shock syndrome with *S. aureus* do not reliably provoke

FIGURE 2 *S. aureus* enterotoxin modifications of immune response.



durable, protective immune responses (58, 97), thereby opening the possibility for SAgs and other toxins to influence the immunity response; yet seemingly, they have provoked no immune response. These interactions may underlie failures of humans to respond with protective immunity against *S. aureus* because continued exposure to SAgs is not inhibited without the presence of antitoxin antibodies.

COMMENTS ON THE MODELS

Gaps exist in our knowledge of the construction of the models of human immunity against *S. aureus* presented in Fig. 1 and 2, but these generate testable hypotheses. A major breakthrough for the development of an *S. aureus* vaccine that could prevent disease and death, or at least reduce the severity of infections, would be the discovery of a biomarker. Examples of vaccine biomarkers are anti-hepatitis B viral surface antigen and antimeningococcal capsular antibodies whose presence correlates with protection from infection. Our lack of a biomarker that predicts protection from *S. aureus* infections relates directly to our lack of understanding of protective immunity against *S. aureus*. Many successful bacterial vaccines against *S. pneumoniae*, *H. influenzae*, *Neisseria meningitidis*, and *Clostridium tetani* have been developed when the mechanism of immune protection was known and a biomarker was followed during clinical trials.

While cytokines provide some indication of which cells are activated, the precise cells being activated are not defined because cytokines can be produced by multiple cells and pathways. There is limited information concerning the timing and precise pathways in *S. aureus* human infections, which are not well replicated by murine models (1, 4, 6, 59, 60, 88). Moreover, cytokines may be released just locally, not systemically, so blood levels are not helpful. Finally, the relative balance between T cell subsets may be critical to the outcome. For example, our current state of knowledge does not allow us to know whether T cell exhaustion, reduced action of Tregs, or overactivation of T_H17 cells cause death with multiorgan failure during invasive *S. aureus* infections. In addition, the immune reactions to cutaneous/mucosal invasion versus systemic (bacteremic) infection are probably distinct, wherein γδT and T_H17 cells (IL-17A) are more important for skin and respiratory infections, whereas T_H1 (IFN-γ) responses are more important for survival during bacteremia (12, 98–100). We can see that sustained high levels of IL-10 correlate with death from *S. aureus* infections, yet it is not clear whether this is due to oversuppression of the immune response or a manifestation of the host attempt to reduce an overly exuberant immune response. When human peripheral blood mononuclear cells were differentiated into dendritic cells by culturing with granulocyte-macrophage colony-stimulating factor + IL-4, they produced a primarily T_H1/T_H17 stimulatory response, whereas when they were differentiated with macrophage colony stimulating factor, this triggered primarily an IL-10 response in response to TLR-2 activation by peptidoglycan or lipoteichoic acid (101). Hence, it is conceivable that the high levels of IL-10 during persistent *S. aureus* bacteremia come from continued activation of macrophages; however, it is also conceivable that the high levels of IL-10 downregulate the immune response needed to clear the bacteria.

Similarly, the data from the V710 vaccine trials, wherein low prevaccination IL-2 was strongly associated with SIRS, could be due to be overexpansion of or overly active T_H17 cells, e.g., by reduced Treg activity and loss of suppressive effects on T_H17 cells. Another hypothesis that springs out of Fig. 2 is that some patients may have T cell exhaustion and altered immune response due to colonization with superantigen-producing *S. aureus* strains (especially SEB), which can downregulate T cell receptors (92). For example, if superantigens led to MAIT cell downregulation, then low levels of IL-2 might prime the host for poor Treg and high T_H17 responses when *S. aureus* invasion occurred. It would be anticipated that these patients might be colonized with SEB-producing strains, lack anti-SEB antibodies, and have low levels of IL-2. Low levels of IL-2 result in reduced Treg and increased T_H17 activity, perhaps adding to an imbalanced immune response to invasive *S. aureus* infections as seen in the V710 clinical vaccine trial. Finally, patients with immunodeficiencies tend to have local infections that rarely develop spillover bacteremia (102), but we have little knowledge about the factors involved in protection from primary *S. aureus* bacteremia. Contrasting the immune responses to bacteremia to cutaneous infections may shed light on the context for T cell activation.

The models for human immune responses to *S. aureus* are really hypotheses (Fig. 1 and 2), and much more detail is needed about the types of T cells being activated, the balance between T cell types, the timing of T cell activation and inactivation, the impact of antibodies, and the correlations to outcomes. Given the multiple possible interpretations of changes in cytokines, a detailed analysis of the types of T cells produced, their state of activation, the time course of activation, and the rel-

ative balance between the different T cell subsets prior to and during *S. aureus* invasive infections should shed light on which pathway(s) are critical for immunity to *S. aureus* infections. In addition, prospective data on the types of antibodies being produced (opsonic versus toxin-neutralizing), especially during *S. aureus* bacteremia versus cutaneous infections, that are correlated with outcome will help to inform us about the relative value of these antibodies. Animal models do not substitute for human data. This basic knowledge will be critical as *S. aureus* vaccine trials are designed because patients should be stratified in future clinical trials to evaluate the impact of therapeutic interventions.

SUMMARY OF HUMAN IMMUNITY AGAINST *S. AUREUS*

Cell-mediated immunity seems to be critical for the prevention and resolution of invasive *S. aureus* infections, but an imbalance in this immunity may also produce SIRS and death or an inadequate protective response with prolonged bacteremia and death. This dysregulation is likely at the heart of mortality and severe disease in humans. Antitoxin antibodies may also come into play in reducing the severity of *S. aureus* infections, but these antibodies might also address superantigen-induced immune dysregulation. Thus, while changing intrinsic T cell responses may be therapeutically difficult, monoclonal antibodies against superantigens may have utility in addressing dysfunctional immune responses to *S. aureus*. The models above are hypotheses for examining, and potentially dramatically improving, the immune response to and safety of *S. aureus* vaccines.

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