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Regulation of helper T cell responses to staphylococcal superantigens

Abstract

Staphylococcal superantigens (sAgs) including toxic shock syndrome toxin-1 (TSST-1) and related enterotoxins are exoproteins with unique immunobiological properties. They bind to major histocompatibility complex (MHC) class II molecules of antigen-presenting cells outside the peptide groove, and induce massive proliferation of T cells bearing specific Vb determinants. This tri-molecular interaction leads to uncontrolled release of various proinflammatory cytokines especially interferon-g (IFN-g) and tumor necrosis factor-a (TNF-a), the key cytokines causing sAg-mediated shock. The effector T cells involved in this hyper-immune response are predominantly of the T helper-

1 (Th1) phenotype. There is also some evidence that polarization to a Th2 response with the production of classical anti-inflammatory cytokines (such as interleukins IL-4 and IL-6) also occurs. Moreover, the emergence of a novel regulatory T cell (Tr1) subset, producing mainly IL-10 but little or no IL-2 and IL-4, has recently been described following repeated sAg stimulation. In this review, the current knowledge regarding the regulation of T helper cell subsets in response to staphylococcal sAgs is critically evaluated, and the role of various cytokines which directly influence T cell differentiation and polarization is summarized. Particular emphasis is directed towards pro-inflammatory as well as anti-inflammatory and regulatory effector functions during toxic shock. Based on this review, we propose that a delayed production of IL-10 by Tr1 cells may be the most prominent driving force in the down-regulation of the Th1 hyper-immune response, and the critical determinant for the eventual recovery of the host.

Full text

INTRODUCTION

Staphylococcal exotoxins, including toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins (SEs) A, B, C_{1-3}, D, E, G-K and others [1], belong to a family of structurally related proteins known as superantigens, and are the causative agents of toxic shock syndrome [2-5] They are also implicated in a wide variety of other human diseases including rheumatoid arthritis, psoriasis, multiple sclerosis [6], and the sudden unexpected nocturnal death syndrome [7]. These superantigens bind to the major histocompatibility complex (MHC) class II molecules on the antigen-presenting cells (APCs), and to the T cell receptor- (TCR) bearing specific Vbeta elements [8]. This tri-molecular interaction leads to massive proliferation of T cells, and the uncontrolled and systemic release of proinflammatory cytokines, including interleukins IL-1, IL-6, interferon-gamma (IFN-gamma), tumor necrosis factor (TNF), and others [9-11]. It is believed that the massive release of these pro-inflammatory cytokines, particularly TNF-alpha, is the key step leading to life-threatening toxic shock syndrome [12-15]. The effector T cells involved in this hyper-immune response are predominantly of the T helper-1 (Th1) phenotype. There is also some evidence that polarization to a Th2 response with the production of classical anti-inflammatory cytokines (such as IL-4 and IL-6) also occurs. Moreover, the emergence of a novel regulatory T cell (Tr1) subset, producing mainly IL-10 but

little or no IL-2 and IL-4, has recently been described following repeated sAg stimulation [16].

In this review, the current knowledge regarding the regulation of T helper cell subsets in responses to staphylococcal sAgs is critically evaluated, and the role of various cytokines which directly influence T cell polarization or differentiation is summarized. Particular emphasis is directed towards pro-inflammatory as well as anti-inflammatory and regulatory effector functions during toxic shock. Although bacterial sAgs from other sources, particularly streptococcal pyrogenic exotoxins A and C, have been shown to induce similar immune responses [17-20], they will not be included in this review. Furthermore, for the sake of brevity, the term "sAgs" used in this review refers specifically to staphylococcal sAgs commonly associated with TSS (*i.e.* TSST-1, SEA, SEB and SEC), unless explicitly indicated otherwise.

CLINICAL FEATURES AND EPIDEMIOLOGY OF STAPHYLOCOCCAL TSS

Staphylococcal TSS is characterized by the abrupt onset of fever, diarrhea, diffuse skin rash followed by desquamation, hyperemia of the mucous membranes, and hypotension or shock. Other organ systems, including hepatic, renal, muscular, cardiopulmonary, hematological, and central nervous systems may also be involved. Published estimates of the incidence of TSS vary (5-15 cases per 100,000) [21]. Although initially described primarily in menstruating women in association with tampon use [22], non-menstrual cases associated with post-surgical *Staphylococcus aureus* infections are increasingly recognized [14]. Among 1,069 TSS cases reported in the United States during 1987-1996, approximately 41% were non-menstrual in origin [21]. The overall fatality remains high (4.1%; 3% for menstrual cases and 5% for non-menstrual cases) [21], and recurrence is frequent [14, 23, 24].

LIMITATIONS IN IMMUNOBIOLOGICAL STUDIES OF STAPHYLOCOCCAL sAgs

To place this review in proper perspective, it is useful to first consider some limitations in the interpretation of published studies concerning the immunobiological properties of staphylococcal sAgs. Much of our knowledge of sAgs has been derived from *in vitro* studies of human peripheral blood mononuclear cells (PBMC) from healthy donors, perhaps because the mode of action of T cell stimulation seems similar, though not identical, to conventional

antigens [20]. There have been very few studies of human PBMC obtained from patients during acute TSS or convalescence. There are severe limitations in the interpretation of results from such studies. Firstly, it is clear that *in vitro* observations of the biological properties of sAgs may not parallel *in vivo* results. For example, Vbeta-specific T cells that appeared to be anergic *in vitro* following sAg re-stimulation may in fact be functional *in vivo* [25]. Secondly, the MHC class II DR allele isotype or the presence of antibodies to various sAgs in the healthy donors are seldom known or reported. It is not clear whether these variables may influence the cytokine profiles or kinetic responses following sAg stimulation. Finally, the source and purity of the sAgs being studied may be an important source of variability. We and others previously demonstrated that commercial sources of staphylococcal sAgs may contain impurities which may produce biological effects that are absent when compared to purified preparations or recombinant counterparts [10, 26]. The use of Coomassie blue or silver staining after sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) may not be adequate as the sole criterion for determining the purity of sAgs under study [27]. More sensitive techniques such as immunoblotting with polyclonal antiserum raised against the crude culture supernatant used for sAg purification may be required to detect minute quantities of co-purified products [10]. Thus, observations obtained from *in vitro* studies must be interpreted with caution.

To investigate toxic shock syndrome *in vivo,* the rabbit model of subcutaneous sAg infusion described by Parsonnet *et al.* [28] has been most commonly studied. While this rabbit model accurately reproduces most of the hemodynamic and clinical manifestations of human TSS, the lack of immunological reagents and cytokine gene knock-out constructs precludes a detailed dissection of different T cell subsets and lymphokine responses to sAgs in this animal species. For this reason, the murine model of sAg-mediated lethal shock is commonly used for *in vivo* studies of TSS [29-37]. Since mice have a natural resistance to sAg-induced shock, D-galactosamine, an amino-sugar isolated from chondroitin sulphate and an inhibitor of transcription in the liver [38, 39], is required to sensitize mice to the lethal effect of bacterial sAgs. While this model system does not perfectly replicate human TSS, it has been an acceptable model to examine some of the *in vivo* immunobiological effects of sAgs. Furthermore, treatment with D-galactosamine alone does not appear to greatly affect T cell activation or the cytokine profiles either qualitatively or quantitatively [33]. Occasionally, surgical adrenalectomy or administration of

RU-38486, a glucocorticoid receptor antagonist [40], has also been used to sensitize mice and counteract the natural resistance to sAg-mediated lethal shock. Interestingly, the absence of IL-10, accomplished either by neutralization with anti-IL-10 monoclonal antibodies [41] or by IL-10 gene targeting [42], also confers enhanced sensitivity to sAg-induced lethality without the need for chemical or surgical sensitization. The basis for this interesting property of IL-10 will be further discussed in this review.

T CELL ACTIVATION AND EFFECTOR FUNCTIONS DURING TOXIC SHOCK

Both MHC class II-expressing APC and T cells bearing Vbeta-specific determinants are required for sAg-mediated T cell activation and cytokine secretion, similar to conventional peptide antigens [43]. However, sAg presentation by the APC does not require prior processing, and is not MHC-restricted. Furthermore, cell-to-cell contact of the APC and the TCR appears critical for the induction and secretion of sAg-mediated pro-inflammatory cytokines [44]. sAgs bind to a relatively conserved portion of the TCR Vbeta chain [43, 45], causing "false recognition" of irrelevant antigens displayed on MHC class II molecules [46]. This results in the activation of both the T cell and the APC, followed by uncontrolled cytokine release, clonal expansion and massive proliferation of activated T cells that constitute 5-20% of the total T cell population. The critical requirement for T cells in sAg-mediated shock is demonstrated by the lack of responsiveness in SCID mice and in cyclosporin A-treated mice, both of which lack a functional T cell signaling pathway (notably the Ras/MAP kinase pathway) for the formation and activation of the essential transcription factor AP-1 [33]. In addition, SCID mice could be made susceptible to toxic shock following immune reconstitution with functional T cells [32]. In addition to the tri-molecular interaction of cross-bridging by sAgs between MHC class II and Vbeta-specific TCR, the strength of co-stimulatory signals also appear pivotal in sAg-mediated T cell activation and cytokine induction. The co-stimulatory molecules implicated include the CD80/86 (also known as B7.1/B7.2) on the APC which interacts with CD28 on the T cell [47, 48], CD40 on the APC which interacts with CD154 (CD40 ligand) on activated T cells [49, 50], and adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) and lymphocyte-function-associated antigen-1 (LFA-1) [51-53].

sAgs induce proliferation and cytokine production in both $CD4^+$ and $CD8^+$ T cells *in vitro* and *in vivo* [20, 54]. However, $CD4^+$ or T helper (Th) cells are preferentially

activated by sAgs due to their high-affinity binding to MHC class II molecules [46]. $CD8^+$ cytotoxic T cells also respond to sAg stimulation following presentation by MHC class I molecules, resulting in enhanced production of both IFN-gamma and IL-12 [55]. The polyclonal stimulation of Th cells by sAgs results in a large number of effector cells which are responsible for the systemic release of both pro- and anti-inflammatory cytokines [56]. This exaggerated and systemic T cell response, rather than the more controlled local response to conventional antigens, is the hallmark of sAg-mediated TSS.

A WORKING MODEL OF T CELL POLARIZATION DURING TSS

Helper T lymphocytes have classically been divided into Th1 and Th2 subsets based on their cytokine production profiles [56]. Th1 effector cells typically produce large quantities of IL-2, IFN-gamma, TNF-alpha and TNF-beta. Th2 effector cells produce little or no IL-2 (although this cytokine produced from other sources assists their outgrowth) [57], but large amounts of IL-4, IL-5, IL-6, IL-10 and IL-13 [58, 59]. In addition to their cytokine production profiles, Th subsets can also be distinguished on the basis of their expression pattern of cytokine and chemokine receptors and other cell surface markers. Th1 cells have lost cell surface expression of IFN-gammaR2, whereas the expression of IL-12Rbeta2 and IL-18R is absent on Th2 cells. Effector Th cell subsets regulate the activity of one another. Thus, the production of IFN-gamma by Th1 effector cells inhibits Th2 cell differentiation and proliferation, whereas the Th1 cells themselves have lost responsiveness to IFN-gamma at the receptor level. The production of cytokines by Th1 differentiated cells is inhibited indirectly by the production of IL-10 by Th2 effector cells, which acts on the APC compartment [58-61]. Antigen-naive Th cells (Th0) represent an intermediate phenotype capable of producing both Th1 and Th2 cytokines in response to antigenic challenge [59]. Whether polarized Th1 and Th2 cells are derived through the differentiation of Th0 cells that produce both Th1 and Th2 cytokines, or whether Th0 cells represent a separate, stably differentiated T cell population, remains unclear [59].

Recently, another subset of helper T cells that produce mainly IL-10, some TGF-beta, and little or no IL-4 has been described [62]. This subset has been called regulatory T cells (Tr1) because of its prominent ability to down-regulate Th1 responses. A comparison of the cytokines that are implicated in the polarization of various helper and regulatory T cells following superantigen stimulation is

shown in Table 1. There is evidence for the presence and activity of each of these T helper cell subsets during the immune response to sAgs [16, 33, 40, 41, 63-66]. The inter-relationship of these T helper cell subsets and their cytokines will be briefly reviewed here. While many cytokines are induced by superantigens, this review will focus only on those lymphokines which directly influence T helper cell polarization. Thus, the role of the monokines IL-1beta and IL-8 will not be further discussed in this review.

The special case of interleukin-2 (IL-2)

Superantigens induce the proliferation of a large number of effector T cells *via* polyclonal activation [54]. IL-2, a T cell mitogenic cytokine, is consistently produced at high concentrations by all staphylococcal sAgs [19], and is responsible for the early clonal expansion and proliferation by activated T cells of naive (Th0) as well as polarized Th1 and Th2 subsets [56, 57]. Curiously, whereas primary stimulation by sAgs *in vitro* [18, 19, 65] and *in vivo* [32, 41] leads to massive production of IL-2 by activated T cells, subsequent re-challenge with the same sAgs results in an inhibition of IL-2 production [16, 63, 67]. This lack of IL-2 induction following repeated sAg stimulation, is accompanied by clonal deletion and programmed cell death (apoptosis) of some but not all activated T cells, and is associated with an absence of both T cell proliferation and IL-2 responsiveness (tolerance or anergy) [16, 63, 68]. The finding that only some activated T cells undergo programmed cell death points to more than one mechanism for the induction of anergy or non-responsiveness by sAgs. In this regard, Florquin *et al.* [69] showed that some anergic T cells made deficient in IL-2 production by repeated exposure to SEB *in vivo*, are, in fact, primed for IL-10 secretion in mice. There is also *in vitro* evidence that re-stimulation results in the up-regulation of IL-2Ralpha [70], and exogenous IL-2 reversed this sAg-induced anergic state or activation-induced deletion [71]. Thus, the non-responsiveness of sAg-induced anergic T cells is not absolute. This sAg-induced non-responsiveness is not simply due to sAg presentation in the absence of co-stimulation on non-professional APCs, since presentation of SEB on highly purified dendritic cells during the primary response did not prevent the induction of non-responsiveness [70]. Furthermore, this sAg-induced non-responsiveness is not due to the preferential induction of a Th1 phenotype, since skewing towards a Th2 phenotype by adding IL-4 and antibodies to IFN-gamma did not prevent the induction of non-responsiveness by SEB [70]. It appears that while early stages of IL-2 inhibition are due to a synergistic action

of TGF-beta and IL-10, inhibition of IL-2 at later stages arise from downstream signaling pathways [63].

Th1

Based on the profile of cytokine production, $CD4^+$ T cells rapidly differentiate into effector Th1 cells following sAg stimulation [43, 56], producing high levels of pro-inflammatory cytokines including IL-2, IFN-gamma, TNF-alpha and TNF-beta [33, 64, 65]. Concurrently, activated APCs also produce high levels of TNF-alpha [33], IL-1 [72], IL-8 [73], IL-10 [74] and IL-12 [66]. TNF-alpha and TNF-beta appear to be the key pro-inflammatory cytokines in the pathogenesis of sAg-induced lethality [33, 72].

Secondary challenge with sAgs also induces an increase in both IFN-gamma and TNF-alpha production, likely due to the induction IL-12 [16, 75-77]. As a result, the immediate cytokine response to sAgs can be considered to reflect an acute Th1 response.

*Interferon-gamma (IFN-*gamma*)*

Production of IFN-gamma, the cytokine most strongly associated with Th1 responses [56], is well documented in toxic shock syndrome [16, 33, 37, 78, 79]. *In vivo*, initial production of this pro-inflammatory cytokine is detectable within half an hour of sAg exposure [33], and serum concentration is high in murine models of toxic shock [16]. This is consistent with an early and differentiated Th1 effector cell response to sAg stimulation.

IFN-gamma contributes significantly to the pathogenesis of toxic shock syndrome in the murine model. This is demonstrated by the protective effects of anti-IFN-gamma mAb on SEB-induced toxicity in mice [31, 80]. This might be expected since TNF release was found to be reduced when IFN-gamma was neutralized [66], and since direct neutralization of TNF has been shown to reduce lethality in animal models of toxic shock [32]. It is important to note that studies of IFN-gamma neutralization have not consistently resulted in a reduction in sAg-induced lethality. For example, when low doses of D-galactosamine were used to sensitize mice to sAgs, IFN-gamma neutralization did impart a protective effect [79]. However, when higher doses of D-galactosamine were used for sensitization, IFN-gamma neutralization only

reduced certain systemic manifestations of illness such as weight loss and hypoglycemia, but not mortality [31]. These apparently disparate results raised the possibility that D-galactosamine sensitization itself could augment the lethal effects of IFN-gamma [31]. Nevertheless, the importance of IFN-gamma in mediating sAg-induced toxicity is further supported by results in an animal model that does not require D-galactosamine sensitization. When mice were sensitized to toxic shock by prior treatment with specific anti-IL-10 antibodies, in the absence of D-galactosamine, complete protection from SEB-induced lethality was achieved following neutralization of IFN-gamma [41].

Tumor necrosis factor (TNF)

High levels of the pro-inflammatory cytokine TNF-alpha are released systemically during TSS [33]. Based on *in situ* mRNA induction in splenocytes isolated from sAg-treated mice, the initial production of TNF-alpha appears to originate primarily from activated T cells and/or dendritic cells, whereas macrophages produce the majority of TNF-alpha later in the response [78]. This is not surprising since dendritic cells have been shown to be 50 times more potent in stimulating T cells during toxic shock when compared to other APCs [81]. Abundant expression of both MHC class II and co stimulatory molecules on the vast cell surface of dendritic cells may contribute to this strong stimulatory signal.

sAg-mediated toxic shock also results in the production of TNF-beta, mainly by activated Th1 cells [64]. This is in contrast to LPS-mediated shock, where TNF-beta production is absent. Thus, the total amount of TNF (both alpha and beta) induced following maximal sAg stimulation of human PBMC is greater than that induced by maximal LPS stimulation [64]. TNF-beta, like TNF-alpha, is a pro-inflammatory cytokine capable of inducing the acute phase response in the liver [82]. The contribution of TNF-beta in the pathogenesis of TSS is often overlooked, since many commercially available TNF-alpha antibodies in fact have significant cross-reactivity with TNF-beta [32].

In vivo, the kinetics of TNF induction is rapid, achieving peak serum levels 1 hour after sAg exposure in rabbits [32-34]. Neutralization of total TNF (-alpha and -beta) *in vivo* has been shown to completely abrogate sAg-mediated lethality in several animal models [32, 34, 72]. Conversely, soluble 55 kDa TNF receptor is effective in neutralizing the deleterious effects of TNF overproduction during

toxic shock [83]. Therefore, TNF is considered the key effector cytokine in the pathogenesis of toxic shock syndrome [34].

Interleukin-12 (IL-12)

IL-12 is produced by activated APCs, and is required for the priming of activated T cells to produce IFN-gamma [84]. In murine models of LPS-induced shock, IL-12 production is strongly induced, resulting in vigorous Th1 activation [85]. A similar response mediated by IL-12 occurs in toxic shock induced by staphylococcal sAgs [66]. In human PBMC stimulated with TSST-1, peak IL-12 production is not observed until at 48 h after exposure (Kum WWS, Chow AW, unpublished data). This delayed production of IL-12 is probably responsible for the second phase of the biphasic production of IFN-gamma in human PBMC following TSST-1 stimulation. Neutralization of IL-12 has been shown to inhibit sAg-induced IFN-gamma by 60% [66]. Therefore, it could be hypothesized that treatment with IL-12 would exacerbate the immune response to sAgs through up-regulation of IFN-gamma and subsequent TNF production. Unexpectedly, pre-treatment with IL-12 has been shown to rescue mice from the lethal effects of toxic shock [37]. This apparent paradox may be explained by the observation that exogenous IL-12 also up-regulates the anti-inflammatory cytokine IL-10, which serves as a negative feedback for IL-12-induced IFN-gamma production (see further discussion under IL-10) [86-88].

Interleukin-18 (IL-18)

IL-18, formerly known as interferon-gamma-inducing factor (IGIF), is a recently described, APC-derived pro-inflammatory cytokine [89]. It has been shown to induce IFN-gamma production by Th1 cells, either alone or synergistically with IL-12, and is an important cofactor in enhancing the cytotoxic activity and proliferation of natural killer (NK) cells [90]. Whether IL-18 significantly enhances the production of sAg-induced IFN-gamma production *in vivo* and contributes to the lethality of TSS is unclear. Recent studies by Hochholzer *et al.* [90] revealed that in the D-galactosamine-sensitized murine model of SEB-induced shock, targeted disruption of the IL-18 gene had neither an effect on lethality nor on the induction of IFN-gamma. In contrast, LPS-induced IFN-gamma production was abrogated and lethality was reduced in these IL-18 knockout mice. This finding by itself is far from conclusive because it has been suggested that sAg-mediated lethality in D-galactosamine-sensitized animal

models may be less dependent on IFN-gamma production than is the case in LPS-induced models [31, 90]. Of note, in our own studies, TSST-1 failed to induce detectable IL-18 in human PBMC, even at 72 hours after stimulation, suggesting that this cytokine may not play a critical role in IFN-gamma induction during TSS (Kum WWS, Chow AW, unpublished data).

Th2

Th2 cells are considered to be the classical antagonists to a Th1 phenotype. sAg-activated Th2 cells induce a humoral immune response and down-regulate the cellular Th1 effector function by producing various anti-inflammatory cytokines including IL-4 [16, 19, 33, 67], IL-6 [31, 34] and IL-10 [16, 41, 42, 63, 67, 75-77]. These Th2-like cytokines have been shown to be induced by various sAgs both *in vivo* and *in vitro,* although the level of IL-4 expressed has been variable for different sAgs in different studies [19, 91]. The Th2 response is particularly prominent following chronic sAg stimulation [67]. Both IL-4 and IL-10 are capable of suppressing IFN-gamma through direct and indirect mechanisms, while still stimulating B cell differentiation [58, 92]. However, exogenous IL-4 is less effective than IL-10 in inhibiting IFN-gamma and other Th1 cytokines induced by SEA and SEB [93]. Additionally, there is compelling data indicating that IL-10 production in response to repeated sAg stimulation originates from a unique subset of T helper cells known as T regulatory (Tr1) cells that are distinct from classical Th2 cells. Furthermore, as discussed later in this review, IL-10 (along with TGF-beta) plays a pivotal role in down-regulating the Th1 hyperimmune response induced by sAgs and is believed to be critical for the eventual recovery from toxic shock. This regulatory cytokine along with TGF-beta will be further discussed under the section of T regulatory (Tr1) cells.

Interleukin-4 (IL-4)

The production of IL-4, an anti-inflammatory cytokine [56], can be detected both *in vitro* [19] and *in vivo* [16, 33, 67] following primary exposure to various sAgs, although variable results have been reported by different authors and with different sAgs. IL-4 plays a critical role both as a promoter of B cell differentiation [94] and a suppressor of IFN-gamma, as well as TNF-alpha production [92]. Suppression of sAg-induced IFN-gamma and TNF-alpha by exogenous IL-4 has been well demonstrated by Krakauer *et al.* [91]. This anti-inflammatory response to exogenous IL-4 may be mediated either by increasing the production of IL-10

or inhibition of IL-12 [95]. Evidence for an extended IL-4 response following repeated sAg stimulation is lacking, however. While secondary superantigenic challenge may prime for a more enhanced IL-4 response [16, 67], this is not always observed [76]. In addition, extended treatment with sAgs seems to abrogate the IL-4 response almost completely [16, 63]. This may be due to the production of immunosuppressive cytokines, such as TGF-beta [63] which can down-regulate both IL-4 production [96] and other Th2 responses [97].

Interestingly, although the induction of IL-4 mRNA in human PBMC can be readily detected following primary treatment of all staphylococcal sAgs [19, 98], the detection of IL-4 in stimulated culture supernatants has been variable for different sAgs, and in different studies for the same sAgs. For example, Krakauer was unable to detect IL-4 in culture supernatants of human PBMC stimulated with either TSST-1 [91], SEA or SEB [93]. Similarly, Assenmacher *et al.* [99] reported that expression of IL-4 in murine splenocytes following *in vitro* stimulation with SEB was undetectable either by intracellular staining or by ELISA (detection limit 0.2 ng/ml). Rink *et al.* [19] also reported that the induction of IL-4 by all staphylococcal sAgs in human PBMC was "very low" or undetectable. In contrast, Lagoo *et al.* [98] reported significant levels of IL-4 following primary stimulation of human T cells and monocytes with SEA and SEB. The reason for this discrepancy is unclear. One possible variable to account for these disparate results from different laboratories could be the purity of the sAgs used in these studies. In our own studies with recombinant TSST-1 that are devoid of potential contaminants, IL-4 production is consistently undetectable by ELISA (sensitivity limit 8 pg/ml) following primary or repeated stimulation, either in human PBMC or in an *in vivo* murine model system (WWS Kum, SB Cameron, AW Chow, unpublished data).

In contrast to *in vitro* stimulation, both Florquin *et al.* [67] and Bourrie *et al.* [100] were able to detect serum levels of IL-4 in mice following primary or repeated injection with SEB. Sundstedt *et al.* [16] observed that mice challenged repeatedly with SEA at 4-day intervals produced a transient elevation in serum IL-4 levels that subsequently became suppressed following the third SEA injection. This was temporally correlated with a sustained level of serum IL-10. Neutralization with anti-IL-10 antibody in these animals resulted in an enhanced production of IL-4 in comparison to untreated control animals, suggesting that perhaps the expression of IL-4 *in vivo* may be under negative feedback control by IL-10.

Interleukin-6 (IL-6)

IL-6 is produced by both activated T cells and monocytes following sAg stimulation. It has both pro-inflammatory and anti-inflammatory effects, depending on the particular system being studied [101]. While IL-6 can function as a pro-inflammatory agent and induce an acute phase response in the liver, it can also induce B cell differentiation leading to a Th2-type humoral immune response. More recently, Xing *et al.* [102] demonstrated conclusively, by the use of IL-6 gene knock-out mice, the anti-inflammatory and homeostatic nature of endogenous IL-6, in both local and systemic acute inflammatory responses induced by LPS. In addition, treatment of naïve T cells with IL-6 during initial priming promotes the production of IL-2 which is required for Th2 outgrowth, and thus can directly or indirectly influence IL-4 production by naïve Th0 precursor cells [57]. Therefore, IL-6 appears to drive Th2 differentiation in a similar fashion to the way that IL-12 drives Th1 differentiation [103].

There is conflicting data regarding the role of IL-6 in the pathogenesis of TSS. While initially considered to act synergistically with TNF-alpha in inducing shock [34], other evidence appears to indicate that pretreatment of mice with antibodies to IL-6 in fact increased mortality [31]. It has been suggested that pretreatment of mice with anti-IL-6 may actually increase the circulating levels of IL-6 due to the formation of IL-6 immune complexes [104, 105]. However, the finding that exogenous IL-6 protects against lethality during sAg-mediated shock supports the contention that IL-6 may have anti-inflammatory effector functions [29]. The mechanism for this protection has not yet been elucidated, but it is possible that this protective effect is mediated through Th2 cells. It is therefore conceivable that Th2 cells have the ability to suppress the presence and/or function of sAg-activated Th1 cells, although whether this actually occurs *in vivo* is currently unclear.

Tr1

Groux *et al.* [62] described a unique subset of effector $CD4^+$ T cells generated after repeated antigenic stimulation of naïve $CD4^+$ T cells in the presence of IL-10, or a combination of IL-4 and IL-10. These T cell clones, designated T regulatory (Tr1) cells, displayed low proliferative capacity and a cytokine profile distinct from that of the classical Th2 phenotype in that high levels of IL-10 were produced with low levels of TGF-beta, while levels of IL-4 or IL-2 were

undetectable. Since then, a number of workers have confirmed the existence of this novel subset of regulatory T cells in a variety of model systems [106, 107]. Tr1 cells grow slowly *in vitro* and are often characterized as "anergic" due to their inability to produce IL-2 upon antigenic stimulation [62]. Tr1 cells are antigen-specific and require TCR engagement by the antigen/MHC complex for activation despite the finding that their low proliferative capacity could be overcome by neutralization of IL-10 and TGF-beta [62]. Furthermore, the growth and proliferative response of Tr1 cells is itself dependent on IL-10.

The origin, or cell lineage of Tr1 cells is currently unclear, as it is not yet understood whether they are derived by a further differentiation from Th0, Th2 or Th1 cell types, although there is some evidence in support of the latter following SEB stimulation [99]. Using intracellular immunofluorescent staining techniques, Assenmacher *et al.* [99] elegantly showed the sequential production of IL-2, IFN-gamma and IL-10 in T helper cells following primary and. repeated stimulation by SEB. As expected from naïve T cells, primary exposure to SEB rarely induced the co-expression of any combination of these cytokines in a given activated T cell. However, following repeated stimulation, IL-2-enriched Th cells were seen to sequentially and preferentially express IFN-gamma, while IFN-gamma-enriched Th cells were seen to sequentially and preferentially express IL-10. In contrast, IL-2 and IL-10 were rarely co-expressed. These data suggest that Tr1 cells may have developed from Th1 precursors.

The induction of Tr1 cells is antigen-specific, while the suppressor function of these regulatory T cells, once activated, appears to be antigen non-specific [108]. Such non-specificity is likely due to a "bystander effect" of the paracrine action of the immunosuppressive cytokines induced. This regulatory T cell subset has been implicated in both peripheral tolerance [109-114], and mucosal tolerance mechanisms [115, 116].

The induction of regulatory T helper cells following repeated sAg stimulation was first reported by Sundstedt *et al.* [16]. Following successive subcutaneous injection with high-dose SEA (10 mug) in mice, a hyporesponsive state was induced characterized by clonal deletion and anergy of the remaining SEA-reactive T cells. These anergic T helper cells characteristically produced high levels of IL-10, but little or no IL-4, while the production of Th1 cytokines, including IL-2, IFN-gamma and TNF, was markedly inhibited. The IL-10 production was sustained with further sAg stimulation in the complete absence of IL-2, IL-4

and IFN-gamma. Pretreatment of mice with neutralizing anti-IL-10 mAb before the SEA challenges, substantially enhanced IFN-gamma and TNF serum levels, and led to an increase in IL-4, but not IL-2 production. These data suggest that IL-10 may provide negative feedback to control the accumulation of Th1 and perhaps even Th2 effector responses. Since the production of IL-10 in these T helper cells did not seem to be linked to IL-4 production, it was proposed that this sAg-induced immunosuppressive effect was not due to the shift to a classical Th2 response, but represented a novel T regulatory phenotype. We believe that this Tr1 subset plays a profound, down-regulatory role in suppressing the potentially harmful Th1 immune response induced by sAgs.

Interleukin-10 (IL-10)

IL-10 is the regulatory cytokine most consistently identified in human PMBC or murine splenocytes following repeated staphylococcal sAg stimulation [16, 41, 42, 63, 67, 75-77]. While IL-10 can be produced by both macrophages and T cells, it is mainly produced by $CD4^+$ T cells in toxic shock models, as demonstrated using $CD4^+$-depleted [41] or $CD4^+$ knock-out mice [16], and in macrophage-depleted mice [16]. sAg activation of $CD4^+$ T cells results in both up-regulation of IL-10 mRNA [76] and IL-10 production [16, 41, 42, 16, 75-77], which is detectable in mice 4 hours after a single injection of SEB [41]. Scheffold *et al.* [117] demonstrated, by high-intensity immunofluorescence, that IL-10 is expressed on the surface of $CD4^+$ cells following SEB stimulation, and in a conformation that may bind its appropriate receptor on neighboring cells. This implies that this cytokine may play a regulatory role within the immunological synapse, even at a concentration that is undetectable in culture supernatants. The primary exposure to sAgs also appears to consistently prime for more enhanced IL-10 production and evoke a memory-like response during secondary sAg stimulation [16, 63, 67, 75].

IL-10 augments cell survival, probably by an, as yet, undetermined, Bcl-2-independent pathway [118]. IL-10 has also been shown to activate cell cycle inhibitors [119], and directly inhibit T cell proliferation [120] by inducing cell cycle arrest in the G_0/G_1 phase [121]. IL-10 also inhibits IFN-gamma, TNF-alpha and TNF-beta production by T cells [122], and TNF-alpha production by APCs [58, 123]. Moreover, IL-10 has several inhibitory effects on APC function, including down-regulation of both MHC class II [124], ICAM-1 [125], and CD80/86 (B7.1/B7.2) expression [126, 127]. IL-10 also inhibits the synthesis of IL-12 by APC,

a critical factor for the induction of pro-inflammatory and cytolytic T cell responses [128].

The pivotal role of IL-10 in inhibiting the production of pro-inflammatory cytokines and decreasing the severity of toxic shock has been demonstrated in several key studies. Firstly, Bean *et al.* [30] showed that IL-10 treatment, either before or up to 30 min following SEB challenge, protected mice in a dose-dependent manner, in the D-galactosamine-sensitized mouse model of lethal toxic shock. Secondly, neutralization of endogenous IL-10 with monoclonal antibodies increased SEB-induced lethality, even in the absence of D-galactosamine sensitization [41]. The cytokine profile in these mice showed elevated levels of both IL-2 and IFN-gamma, indicating a strong Th1 effector response. The lethal effect induced by IL-10 neutralization was abrogated if these mice concurrently received neutralizing antibodies to IFN-gamma, again underscoring the important role of IFN-gamma in mediating toxic shock, and the counteracting role of IL-10 in the suppression of IFN-gamma [41]. In a third study, similar results were obtained with IL-10 knock-out mice in which SEB induced lethal shock even in the absence of D-galactosamine sensitization [42]. Again, the absence of endogenous IL-10 in these knock-out mice correlated with markedly increased levels of several pro-inflammatory cytokines, including IL-2, IFN-gamma, TNF-alpha, IL-1beta, and IL-12, following challenge with SEB.

***Transforming growth factor*-beta *(TGF*-beta)**

TGF-beta is another potent regulatory cytokine which inhibits IL-2 expression [129] and cell cycle progression [130]. The involvement of TGF-beta in peripheral tolerance following chronic antigen stimulation has been shown in a number of animal models [131]. Furthermore, TGF-beta has been shown to suppress Th1-mediated autoimmunity in a number of model systems including colitis [96], non-obese diabetes [132], transplant rejection [114], and multiple sclerosis [112], as well as Th2-mediated autoimmunity [97].

Although a number of studies have explored the role of exogenous TGF-beta in modulating the effector functions of $CD4^+$ and $CD8^+$ T cells [133-135], the induction of TGF-beta following primary stimulation with sAgs remains to be elucidated. However, Miller *et al.* [63] found that $CD4^+$ splenocytes obtained from mice, which had received repeated injections of SEA, entered into a tolerant state in which little IL-2, IL-4 or IFN-gamma were produced upon

rechallenge with a pigeon cytochrome C peptide. Instead, these cells produced high levels of TGF-beta as well as IL-10 [63]. Furthermore, these $CD4^+$ cells actively suppressed IL-2 production by naïve splenocytes when stimulated with the peptide. This suppressive activity of SEA-treated T helper cells was only partially reversed with antibodies directed against TGF-beta and IL-10, suggesting that additional, as yet unidentified, molecules may participate in inducing this profound state sAg-mediated anergy or tolerance [63].

HETEROGENEITY OF, AND INTERACTIONS BETWEEN, POLARIZED Th SUBSETS FOLLOWING sAg STIMULATION

Based on the current knowledge summarized above, it is clear that the initial outcome of primary sAg stimulation is a polarized Th1 response. Whether the eventual outcome of sAg stimulation will shift to a Th2-dominated response may be determined early after sAg exposure, and depends on the net balance between IL-12/IFN-gamma secretion that favors a Th1 response [84] and IL-6/IL-4 which favors a Th2 response [33, 56]. However, following repeated sAg exposure, both Th1 and Th2 responses are suppressed [16]. While Th1 and Th2 subsets are capable of cross regulation *via* IFN-gamma and IL-4 respectively, decreased production of both these polarizing cytokines are seen after repeated sAg exposure [16, 63]. This suppression is probably due to the emergence and predominance of a regulatory Th response accompanied by the secretion of IL-10 with or without TGF-beta [16, 63]. While the production of IL-10 could support a classical Th2 phenotype, the consistent observation that both IL-4 mRNA [76] and IL-4 production [16, 63, 67] are markedly inhibited following repeated sAg treatment suggests that a novel regulatory T helper subset such as Tr1 cells may be activated. The observation that sAg-activated T cells can also induce the secretion of TGF-beta [63] further supports this contention, since this regulatory cytokine has been shown to inhibit IL-4 production, and both Th1- and Th2- mediated immune responses [97, 133].

The mechanism for activation of immunoregulatory Tr1 cells following repeated sAg stimulation is incompletely understood at present. Since IL-10 provokes negative-feedback inhibition of an overwhelming Th1 immune response, one might expect a pro-inflammatory cytokine such as IFN-gamma to up-regulate IL-10 production. However, the link between IFN-gamma and IL-10 production in the induction of anergy seems to be indirect at best. Neutralization of IFN-gamma, while inhibiting clonal deletion and apoptosis of reactive lymphocytes, has little

effect on preventing sAg-induced anergy or IL-2 non-responsiveness [136]. The source of this indirect link between excessive IFN-gamma production and subsequent induction of IL-10 may be provided by IL-12, an essential IFN-gamma-inducing cytokine which also up-regulates IL-10 in human $CD4^+$ T cells [87, 88]. This unexpected ability of IL-12 may explain the curious protective effect of IL-12 when administered prior to sAg exposure, as was observed by Takahashi *et al.* [37]. Rather than priming for a Th1 response, administration of exogenous IL-12 in this instance may have primed for a greater Tr1-dependent IL-10 response which counteracted the lethal effects of sAg-induced Th1 activation.

Based on this review of T helper cell responses following sAg activation, we believe that the induction of this T regulatory (Tr1) helper subset, resulting in the sustained release of the inhibitory cytokines IL-10 and TGF-beta plays a pivotal role in reversing the deleterious Th1 hyperimmune response to sAgs [16, 63]. The kinetics of Tr1 subset proliferation and the rapidity and magnitude of IL-10 or TGF-beta induction may be the critical determinant of the ultimate survival of the host. A schematic representation of the postulated polarization and interactions between the Th1, Th2 and Tr1 T cell subsets following staphylococcal sAg stimulation is depicted in Figure 1.

CONCLUSION

While many studies support the relevance of proinflammatory cytokines (such as TNF-alpha and IFN-gamma) as prognostic indicators in the clinical outcome of staphylococcal toxic shock, relatively little investigation has been devoted to the systemic release of anti-inflammatory or regulatory cytokines, particularly IL-10 and TGF-beta. In particular, there is currently no information regarding any relationship between IL-10 levels and survival among patients with staphylococcal TSS, or whether Tr1 cells are induced following an initial exposure to sAgs in the murine model system. It is clear that an understanding of the interactions among different pro-inflammatory and anti-inflammatory cytokines following sAg activation becomes increasingly important. Further investigation into the mechanism and role of regulatory T helper subsets in toxic shock is clearly warranted. By improving our knowledge of the optimal conditions for the induction of anti-inflammatory and regulatory Tr1 responses following sAg activation, it may be possible to design novel immunotherapeutic strategies aimed at restoring immuno-homeostasis following toxic shock. In addition, the study of regulatory T cell development following sAg exposure may lead to new

approaches for the immunomodulation of other Th1- and Th2-mediated diseases such as multiple sclerosis, rheumatoid arthritis, transplantation rejection, graft *versus* host disease, and other autoimmune conditions.

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Figures

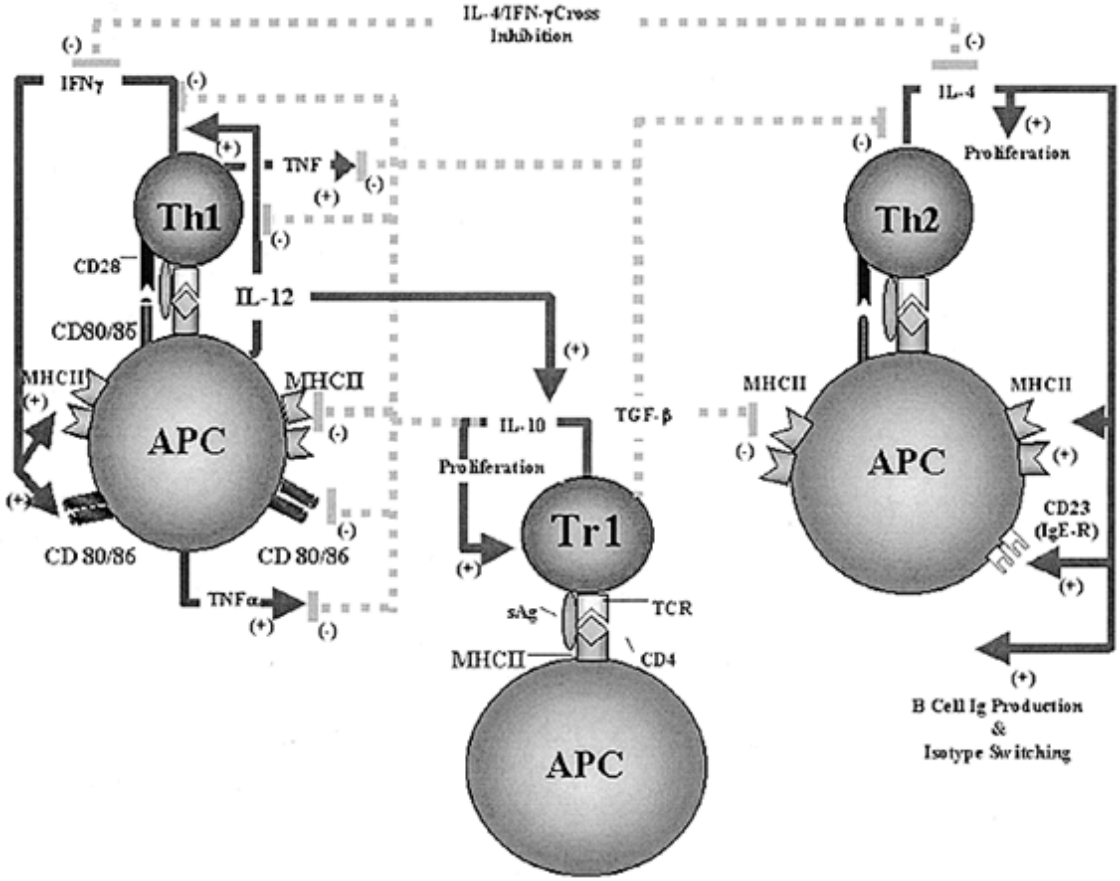

IL-4/IFN-γCross Inhibition
IFNγ
TNF
Th1
CD28
IL-12
CD80/86
MHCII
APC
CD 80/86
TNFα
IL-10
Proliferation
Tr1
sAg
TCR
CD4
IL-4
Proliferation
Th2
TGF-β
CD23 (IgE-R)
B Cell Ig Production & Isotype Switching

Figure 1

Schematic representation of the proposed interactions between polarized Th1, Th2 and Tr1 subsets of helper T cells following staphylococcal superantigen (sAg) stimulation.

Induction of the Tr1 subset accompanied by the sustained secretion of the regulatory cytokine IL-10 (with or without TGF-beta) is believed to play a pivotal role in the down-regulation of Th1 hyperimmune responses and eventual immuno-homeostasis and recovery from toxic shock. IL-10 serves to down-regulate (-) APC function by suppressing both the expression of MHC class II (MHCII) and co-stimulatory molecules CD80/86 (B7.1/7.2), and the secretion of IFN-gamma, TNF-alpha, TNF-beta and IL-12. Th1 cells are also directly suppressed through the inhibition of IFN-gamma and TNF-beta production by TGF-beta, which also down-regulates the Th2 response of T cell proliferation and IL-4 secretion.

Table 1
Cytokines involved in the polarization of Th1, Th2, and Tr1 subsets of helper T cells following staphylococcal superantigen (sAg) stimulation

	Th1	Th2	Tr1
T cell-derived cytokines	IL-2 IFN-gamma TNF-alpha TNF-beta	IL-2 IL-4 IL-6 IL-10	IL-10* TGF-beta
APC-derived cytokines	TNF-alpha IL-1beta IL-8 IL-12 IL-18	IL-6	Currently unknown

* While APCs (macrophages in particular) are capable of IL-10 production following sAg treatment, the major source of IL-10 induced by sAg is in fact T cell-derived.

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