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Interaction of toxin-1 and T lymphocytes in toxic shock syndrome

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1. ABSTRACT

Toxic shock syndrome (TSS) is a potentially fatal illness caused by infection with the bacterium *Staphylococcus aureus*. TSS toxin-1 (TSST-1) contains a T-cell epitope with specificity for human V-beta-2. Binding of TSST-1 to the human major histocompatibility complex and T cell receptors activates T cells and triggers the secretion of high amounts of inflammatory cytokines, leading to TSS and potentially death. During this process, $CD4^+$ T cells are inhibited by TSST-1, while regulatory T cells are increased. This suggests a protective immune response by the body in TSS. Thus, TSST-1 can trigger both, an inflammatory response that attacks the body and a protective response. In this review, we discuss the interaction between TSST-1 and T lymphocytes in TSS.

2. INTRODUCTION

Toxic shock syndrome (TSS), a potentially fatal illness caused by infection with the bacteria, including *Staphylococcus aureus* (1), was first reported in 1978 by James K Todd, who described the staphylococcal illness in three boys and four girls aged 8–17 years (2). Patients with TSS can recover in 2–3 weeks under proper treatment, but can also die within hours. In TSS, *Staphylococcus aureus* produces a superantigenic toxin, toxic shock syndrome toxin-1 (TSST-1), which is responsible for 50% of non-menstrual and 100% of all menstrual TSS cases and also plays a role in immune evasion, allowing further invasion of *Staphylococcus aureus* (3,4). Moreover, TSST-1 allows the nonspecific binding of class II major histocompatibility complex (MHC II) to T cell receptors (TCRs), resulting in

the activation of polyclonal T lymphocytes, especially human T cells that express V-beta-2, which may represent 5-30% of all host T cells (5). During the development of TSS, the cross-linking of V-beta-specific regions of the alpha-beta TCR to MHC II molecules on antigen presenting cells (APC) is required to stimulate T cells (5). TSST-1 therefore plays a key role in TSS through its effect on T cells. In addition to its role in TSS, TSST-1 is associated with an increased number of T cells in nasal polyps (6). In a recent study, T cells activated by TSST-1 were shown to destroy colorectal tumor cells, particularly under hypoxic conditions (7). This finding suggests that T cells may adopt certain characteristics during their interaction with TSST-1, which may be promising in immunotherapy not only in TSS but also in tumors. In the present review, we focus on the interaction between TSST-1 and T cells in TSS, and we provide novel insights into the immunotherapy of TSS.

3. TOXIC SHOCK SYNDROME TOXIN-1 IN THE T CELL-RELATED IMMUNE RESPONSE OF TSS

Although the key role of T cells in TSST-1-induced TSS is well accepted, the involvement of the superantigen TSST-1 in the T cell-related immune response of TSS is poorly understood. TSST-1 is a 22-kDa single-chain polypeptide of 194 amino acid residues that belongs to the family of staphylococcal enterotoxin superantigens (8). TSST-1 residues essential for its mitogenic activity, such as Tyr 115, Glu 132, His 135, Gln 136, Ile 140, His 141 and Tyr 144, were identified by site-directed mutagenesis (9–16). As superantigen-MHC II binding is a prerequisite for subsequent mitogenic activity, MHC-binding sites on TSST-1 have been identified that are located within residues 39–78 and 155–194 (17). Thus, residues 115–144 of TSST-1 may be related to T-cell epitopes on TSST-1, which was supported by the three-dimensional structure of TSST-1, resolved by X-ray crystallographic analysis (18). Ramesh *et al.* (19) reported that the synthetic peptides derived from superantigens can serve as classical antigens to activate T cells. Bonventre *et al.* (20) found a mutation at histidine residue 135 of TSST-1 that yields an immunogenic protein with minimal toxicity. Furthermore, Hu *et al.* (21) localized the T-cell epitope of TSST-1 to a region between residues 125 and 158. These authors also examined the V-beta specificity of T cells activated by T34 and T58 and found that T34 and T58 possessed two of four TSST-1-targeted V-beta specificities in humans and mice, human V-beta-2 and murine V-beta-15 (21). These findings confirmed that TSST-1 contains a T-cell epitope with specificity for human V-beta-2, and suggest that TSST-1 can specifically activate T cells in TSS. However, because of the lack of an effective approach, the analysis of T cell epitopes is still limited.

High mobility group box-1 (HMGB-1) is an important chromatin protein secreted by activated monocytes that interacts with nucleosomes, transcription factors and histones and has been identified as a key late mediator of endotoxic shock (22). Although the translocation and secretion of HMGB-1 mediated by TSST-1 is dependent on the presence of both activated T cells and monocytes, nuclear HMGB-1 is released from TSST-1-induced T cells (23). This finding provided insight into the interaction between TSST-1 and T cells and the basis for investigating the potential of targeting HMGB-1 for TSST-1-induced TSS therapy.

T-cells activated by TSST-1 secrete IFN-gamma, which mediates the TSST-1-induced hypersensitivity to LPS, resulting in inflammation in TSS (24). During the acute phase of menstrual TSS, T cells are persistently reactive to TSST-1 (25). This may partly explain the association of TSST-1 production with expansion of TSST-1-reactive T cells and a rapid worsening of symptoms in TSS. In addition to IFN-gamma, staphylococcal enterotoxin A, which is produced simultaneously with TSST-1 by *Staphylococcus aureus*, has a collaborative effect with TSST-1 in T cell activation and TNF secretion (26).

4. TSST-1 BINDING SITE IN T CELL RECEPTORS

TSST-1 was shown to induce T cell activation in both animal models and patients with TSS (27-29). In this process, T cell activation by staphylococcal TSST-1 is dependent on TCR recognition of the intact toxin molecule bound to a nonpolymorphic region of the Ia molecule (30). Furthermore, Dennig and colleagues (31) demonstrated that although costimulation for TSST-1-induced T cell proliferation is provided by human leukocyte antigen (HLA) class II negative accessory B cells, TSST-1 directly binds TCR, and TSST-1-induced T cell proliferation is involved in the BB1/CD28 pathway (31). This differs from typical T cell recognition, in which an antigen is taken up by an APC, processed, expressed on the cell surface in complex with MHC II in a groove formed by the alpha and beta chains of class MHC II, and recognized by an antigen-specific T cell receptor.

A study investigating the binding sites of MHC II and TCR showed that the MHC II binding site is located in the hydrophobic region of the NH_2-terminal domain, and the TCR binding site is primarily in the major central groove of the COOH-terminal domain (32). This study characterized TSST-1 binding to TCR and MHC molecules at the molecular level and showed that MHC class II-associated peptides that do not promote TSST-1 presentation can be converted into "promoting" peptides by the progressive truncation of C-terminal residues. Furthermore, A different study confirmed that the length of the MHC II-bound peptide is crucial in the presentation of TSST-1 by splenic APC and that different subpopulations of APCs are equally peptide dependent in TSST-1 presentation (33). This finding suggested that the MHC II binding site affects the binding of T cells.

In addition to the MHC II receptor, TCR is critical for T cell activation induced by TSST-1. Cullen *et al.* (34) showed that a functional site defined by a TSST-1 mutation at histidine 135 affects toxin interactions with TCR instead of MHC II, suggesting a key role for TCR in the interaction between TSST-1 and T cells in TSS. A recombinant human TCR V-beta-2 fusion protein (V-beta-2 sol) produced in *Escherichia coli* was shown to have

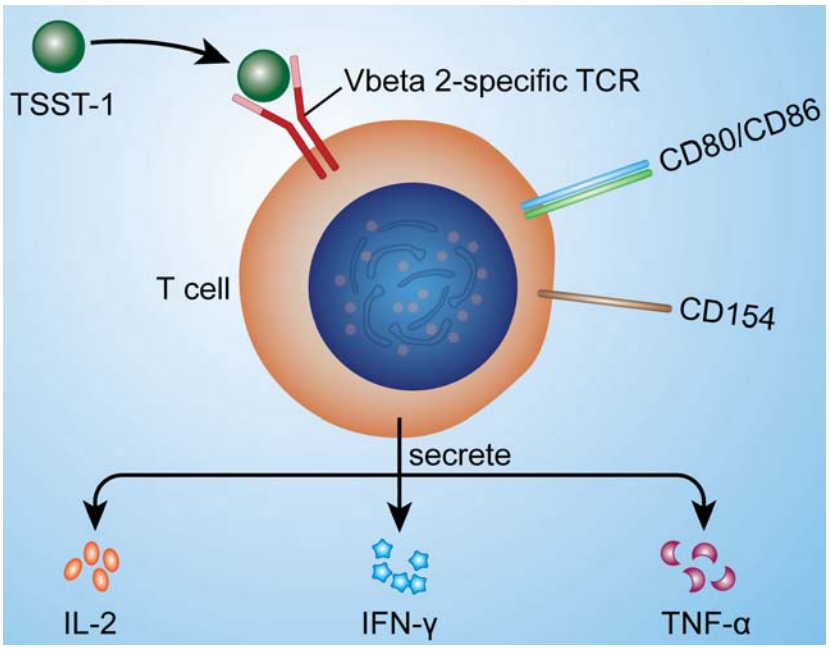

Figure 1. TSST-1 activates T cells in TSS. TSST-1 stimulates T cell activation via V-beta-2 specific T cell receptor activation along with CD80/CD86 and CD154 costimulation in TSS, which promotes inflammation by controlling the secretion of TSST-1-induced cytokines.

specificity in binding to TSST-1 *in vivo* (35). An *in vitro* study demonstrated that in response to TSST-1 stimulation, TCR V-gamma-2 is expressed in purified bovine WC1+ gamma delta T cells, as well as TCR V-gamma-1, and these WC1+ gamma delta T cells can be driven to proliferate by TSST-1 (36). In human peripheral blood mononuclear cells subjected to TSST-1 stimulation, early V-beta-2 specific TCR activation is accompanied by CD80/CD86 and CD154 costimulation, which may determine TSST-1-induced proinflammatory cytokine responses including IL-2, IFN-gamma and TNF-alpha (37). In summary, TSST-1 stimulates T cell activation via V-beta-2 specific TCR activation along with CD80/CD86 and CD154 costimulation in TSS, which promotes inflammation by controlling the secretion of TSST-1-induced cytokines (Figure 1). During this process, in which the T cell immune response is stimulated and activated following local or even systemic inflammation, inflammatory cytokines circulate in the body with blood, and TCR V-gamma-2 plays a key role. In a follow-up study, a panel of high affinity TCRs for TSST-1 was generated to investigate the molecular details of the interaction between TSST-1 and human V-beta-2.1 TCR, and the findings showed that the energetic importance of a single human V-beta-2.1 wild-type residue may determine the restriction of TSST-1 specificity to only this human V-beta region (38).

Since V-beta-2 TCR activation is specific in early TSS, an anti-human V-beta-2 monoclonal antibody can be used to detect human T-cells that react with TSST-1 (39). Considering the importance of the V-beta-2 TCR in TSST-1-induced TSS, T cells marked with V-beta-2 specific TCR were used to achieve an early and definitive diagnosis of TSS in two cases, which showed that the use of these T cells is a promising approach for the rapid and definitive diagnosis of TSS (40). Later, Wenisch *et al.* (41) confirmed the diagnostic value of V-beta-2-positive T-cells in a case report that included three patients. These authors also reported that the diagnosis of TSS based on the detection of V-beta-2 positive T-cells was significantly faster than the traditional standard of the Centers for Disease Control and Prevention (CDC), which could be attributed to a complicated clinical picture or the delay caused by waiting for the results of microbiologic investigations (41).

In addition to TCR mutations, antigen receptor mutations can also affect TSST-1-induced T cell activation. Although TSST-1 does not activate V-beta-8.2 T cells, a fas antigen receptor mutation was found to be associated with TSST-1-induced lethal shock in V-beta-8.2 TCR transgenic mice (42). Thus, the role of antigens should be considered in the T cell response in TSS. In addition, factors other than neutralizing antibodies and the frequency of V-beta-2 T lymphocytes can also determine immunological responsiveness to TSST-1. The differential responsiveness of lymphocytes to TSST-1 may form the basis of interindividual variations in susceptibility to menstrual TSS (43). In summary, TCRs are crucial in the TSST-1-induced T cell response in TSS, and MHC II may play a role in the TCR effect. Antigen and interindividual variations are involved in this complex process.

5. T CELL SUBSET IN TSST-1-INDUCED TSS

In TSS, TSST-1 binds to human MHC and TCR molecules, promoting T cell activation and the production of high amounts of inflammatory cytokines, finally leading

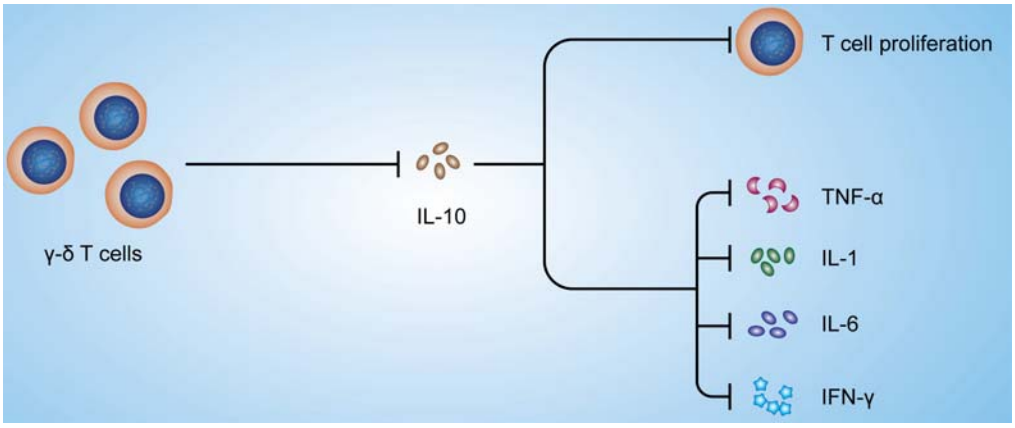

Figure 2. IL-10 inhibits T cell proliferation and the production of inflammatory cytokines induced by TSST-1 in TSS. IL-10 inhibits T cell proliferation and the production of inflammatory cytokines induced by TSST-1 in TSS, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6 and interferon (IFN)-gamma. This process is negatively modulated by peripheral gamma delta T cells.

to TSS and potentially death. Therefore, TSST-1 stimulates T cell proliferation in TSS. Even in neonatal TSS, the adult-type T cell responds to TSST-1 (44). Lymphopenia and impaired cellular immunity were found in TSS patients, although at a lower incidence than in patients with septic shock (45), suggesting the involvement of T cell immune responses in TSST-1 induced TSS. Recent studies have provided information on the specific T cell subset associated with the development of TSS. CD4+ T cells, which can orchestrate immune responses against a wide variety of pathogenic microorganisms and regulate/suppress immune responses both to control autoimmunity and to adjust the magnitude and persistence of responses (46), may be inhibited by TSST-1 (47). CD4+ T cells are important mediators of immunologic memory, and when their numbers are diminished or their functions are lost, the individual becomes susceptible to a wide range of infectious disorders. Inhibition of CD4+ T cells by TSST-1 results in immunological dysfunction in TSS patients.

During and after the acute phase of TSS, there is no reduction in peripheral T cells. By contrast, upregulation of the T cell activity marker HLA-DR was reported in a TSS patient during the acute phase and its levels declined significantly after the acute phase (27). The TSST-1 peptide binds to the HLA-DR, a MHC class II cell surface receptor, and the complex is presented to many TCRs on T-helper cells. These findings indicate the activation and proliferation of T cells in TSS. However, another T cell activity marker, CD25, is not altered in TSS (27). This is different from streptococcal TSS, in which the CD25 T cell subset and HLA-DR are increased, as well as the gamma delta T cell subset (48). An important difference in T cells between staphylococcal TSS and streptococcal TSS is the expression of CD25. Although CD25 is an activation marker for T cells, the different T cell subtypes have different effects on the expression level of CD25. Dauwalder *et al.* (49) showed that TSS patients had increased amounts of circulating regulatory T cells (Tregs), which are CD25+ T cells. Since Tregs are vital for preventing autoimmunity and immune-mediated inflammation, an increase in circulating Tregs may be reflective of a protective immune response to TSST-1. Furthermore, these authors did not observe decreased lymphopenia or HLA-DR expression, which is consistent with Arvand's findings (27). Therefore, Tregs were identified as effectors in TSST-1 associated TSS, suggesting a key role of Tregs in TSS pathogenesis and immunotherapy.

Tregs are poised to sense IL-10, and the IL-10 receptor IL-10R on Treg cells plays a pivotal role in their function (50). IL-10, a cytokine with pleiotropic effects in immunoregulation and inflammation, was able to inhibit the production of inflammatory cytokines induced by TSST-1 in TSS, such as TNF-alpha, interleukin (IL)-1, IL-6 and interferon (IFN)-gamma (51). Although the inhibitory effect of IL-10 on T cell proliferation was not as strong as its effect on inflammatory cytokines, it could inhibit TSST-1 induced T cell proliferation by more than 10% (51). Kalyan *et al.* (52) reported a decreased level of IL-10 and increased levels of IFN-gamma, TNF-alpha and IL-2 induced by TSST-1. They further demonstrated that depletion of gamma delta T cells completely abrogated this effect. This finding suggests that peripheral gamma delta T cells can markedly modulate IL-10 dependent anti-inflammatory responses and TSST-1 associated proinflammatory responses (Figure 2). These findings indicate that IL-10 may be involved in the immune response of Tregs and gamma delta T cells, and suggest the possible importance of IL-10 for immunotherapy against TSST-1-induced TSS.

6. CONCLUSIONS

In this review, we summarized the current knowledge on the interaction between TSST-1 and T lymphocytes in TSS. TSST-1 contains a T-cell epitope with specificity for human V-beta-2. Binding of TSST-1 to human MHC and TCR molecules results in the activation of T cells and the secretion of high amounts of

inflammatory cytokines, finally leads to TSS and death. During this process, $CD4^+$ T cells are inhibited by TSST-1, while Tregs are upregulated. This suggests a protective immune response by the body in TSS. Thus, TSST-1 can lead to both an inflammatory response that results in destruction and a protective response. Therefore, the underlying mechanism of TSST-1 induced TSS may involve an imbalance between the destructive and protective responses of the body. Immunotherapy against TSST-1-induced TSS may be a promising approach in the future, especially considering the rise in antibiotic resistance and the fact that *Staphylococcus aureus* is becoming one of the major resistant pathogens.

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Abbreviations: TSS: Toxic shock syndrome; TSST-1: TSS toxin-1; MHC II: class II major histocompatibility complex; TCRs: T cell receptors; APC: antigen presenting cells; HMGB-1: High mobility group box-1; HLA : human leukocyte antigen; CDC: Centers for Disease Control and Prevention; Tregs: regulatory T cells; IL-1: interleukin-1; IFN-gamma: interferon-gamma

Key Words: Toxic shock syndrome; TSS toxin-1; antigen presenting cells; IFN-gamma, Review

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