Chapter 17

STAPHYLOCOCCAL ENTEROTOXIN B AND RELATED TOXINS PRODUCED BY *STAPHYLOCOCCUS AUREUS* AND *STREPTOCOCCUS PYOGENES*

KAMAL U. SAIKH, PhD*; ROBERT G. ULRICH, PhD†; and TERESA KRAKAUER, PhD‡

*Microbiologist, Department of Immunology, US Army Medical Research Institute of Infectious Diseases, 1425 Porter Street, Fort Detrick, Maryland 21702
†Microbiologist, Department of Immunology, US Army Medical Research Institute of Infectious Diseases, 1425 Porter Street, Fort Detrick, Maryland 21702
‡Microbiologist, Department of Immunology, US Army Medical Research Institute of Infectious Diseases, 1425 Porter Street, Fort Detrick, Maryland 21702

INTRODUCTION

Staphylococcus aureus and *Streptococcus pyogenes* are ubiquitous, gram-positive cocci that play an important role in numerous human illnesses such as food poisoning, pharyngitis, toxic shock, autoimmune diseases, and skin and soft tissue infections. These common bacteria readily colonize humans via numerous virulence factors that facilitate their survival and dissemination. Among these factors, staphylococcal enterotoxins (SEs), toxic shock syndrome toxin-1 (TSST-1), and streptococcal pyrogenic exotoxins (SPEs) share a common three-dimensional protein fold characteristic of these bacterial exotoxins called "superantigens" due to their potency in activating cells of the immune system.[1,2] Picomolar concentrations of these bacterial superantigens activate specific Vβ-bearing T cells by binding to and cross-linking the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APC) and the T-cell receptor (TCR). Activated T cells proliferate and, together with APC, produce proinflammatory mediators that, in elevated quantities, can induce fever, hypotension, and lethal shock. Most strains of *S aureus* and *S pyogenes* examined harbor genes for superantigens and are likely to produce at least one of these toxins. Strains that lack the ability to produce superantigens are usually attenuated in virulence. The staphylococcal enterotoxins are most frequently associated with food poisoning, yet not all superantigens are enterotoxins. Life-threatening toxic shock syndrome (TSS) may result from exposure to any of the superantigens through a nonenteric route. High dose, microgram-level exposures to staphylococcal enterotoxin B (SEB) will result in fatalities, and inhalation exposure to nanogram or lower levels may be severely incapacitating as well as fatal.[3] In addition, the severe perturbation of the immune system caused by superantigen exposure may lower the infectious or lethal dose of replicating agents, such as influenza virus.[4]

SEB is a prototype enterotoxin and potential biological threat agent produced by many isolates of *S aureus*. During the 1960s, SEB was studied extensively as a biological incapacitant in the US offensive program. Recent studies on countermeasures and diagnostics have focused on SEB because of its effectiveness as a biological weapon, especially by inhalation. However, SEB represents many related biologically active superantigens that are readily isolated and manipulated by recombinant DNA (deoxyribonucleic acid) techniques. Moreover, the coadministration of SEB or related toxins with replicating pathogens or pathogen-associated molecules can lower the lethal dose of toxin by thousands fold. Pathogen-associated molecules such as endotoxins bind to toll-like receptors (TLRs) present on many cell types and activate similar intracellular signaling pathways as SEB, accounting for the synergy between these molecules and SEB in inducing pathophysiological effects.[5]

CHARACTERIZATION OF TOXINS

Genes encoding superantigens of *S aureus* and *S pyogenes* arise from a common ancestral gene. Most of the streptococcal superantigens are encoded by mobile genetic elements. SPE-A, SPE-C, SEA, and SEE are all phage-borne, while SED is plasmid-encoded. A chromosomal cluster of SE and SE-like genes are present in strains of *S aureus*.[6] Transcriptional control of TSST-1, SEB, SEC, and SED is mediated through the accessory gene regulator (agr) locus,[7] whereas SEA expression appears to be independent of agr. Strains that are agr-negative generally produce less toxin; however, there are also considerable differences in production levels among agr-positive isolates. These toxins are synthesized during the late logarithmic to stationary phases of growth, and production of many SEs is dependent on glucose concentration and environmental pH. The great diversity of superantigens and the highly mobile nature of their genetic elements suggest an accelerated rate of evolution. Staphylococcal and streptococcal strains that colonize domestic animals are potential genetic reservoirs for new toxin genes,[8] and the transfer of these sequences may contribute to hybrid polypeptides.

The bacterial superantigens are 19- to 30-kD single-chain proteins with two major domains, containing β-sheet and α-helix structures, separated by a shallow groove.[1,9] Based on amino acid sequences and structural homology, superantigens can be compiled into five different groups.[10] TSST-1 is the most distantly related and lacks a "disulfide loop" commonly found in SEs, whereas SEs with emetic properties such as SEA, SEB, SEC, SED, and SEE all possess this loop structure. Despite significant sequence divergence, with similarities as low as 14%, overall protein folds are similar among staphylococcal and streptococcal superantigens. Cross-reactivities of polyclonal and monoclonal antibodies to SEs, TSST-1, and SPEs indicate common epitopes among these superantigens.[11] The toxin genes have evolved by strong selective pressures to maintain receptor-binding surfaces by preserving three-dimensional protein structure. The contact surfaces with MHC class II molecules involve variations of conserved structural elements,[12,13] which include a ubiquitous hydrophobic surface loop, a polar-binding pocket present in most superantigens,

and one or more zinc-binding sites found in some toxins. Comparison of antibody recognition among superantigens[11] suggests that antigenic variation is maximized while three-dimensional structures, and hence receptor-binding surfaces, are conserved. From a practical standpoint, this observation indicates that a large panel of antibody probes will be required for proper sample identification.

Molecular details of the receptor interaction and biological actions of bacterial superantigens are well established. Superantigens target cells that mediate innate and adaptive immunity, resulting in an intense activation and subsequent pathology associated with aberrant host-immune responses. In contrast to "conventional" antigens, bacterial superantigens bind on the outside of the peptide-binding groove of MHC class II molecules and exert their biological effects without being "processed." Most superantigens share a common mode for binding MHC class II molecules, with additional stabilizing interactions that are unique to each toxin.[14] A second, zinc-dependent molecular binding mode for some superantigens increases T cell signaling and may impart greater toxicities in some cases. In normal T-cell responses to peptide antigens, the CD4 molecule stabilizes interactions between TCR and MHC class II molecules on APC (Figure 17-1). Superantigens also cross-link TCR and MHC class II molecules, mimicking the CD4 molecule,[15] and hence stimulate large numbers of T cells. Recognition of a superantigen by TCR is dependent on the variable region of the β chain (Vβ) of the TCR. Each toxin binds to a distinct repertoire of TCR Vβ, thus revealing the unique Vβ specificities of an individual superantigen.[16] An intense and rapid release of cytokines, such as interferon-γ, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα) is responsible for the systemic effects of the toxins.[17–19] Although SEB has enterotoxic effects, the interaction of toxin with specific cells and receptors of the gastrointestinal tract is less well-defined. A specific region in SEB is involved in transcytosis of toxin.[20] Other studies suggest various binding regions of SEB to epithelial cell membrane proteins.[21,22] The release of histamine and cysteinyl leukotriene from mast cells likely accounts for the emetic effects of staphylococcal enterotoxins.[23]

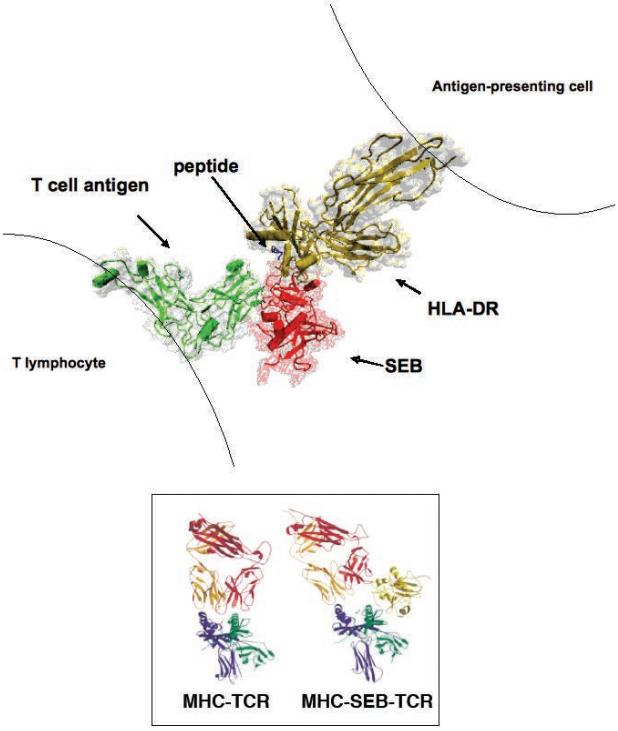

Figure 17-1. Molecular model of receptor binding. Staphylococcal enterotoxins and other bacterial superantigens target the multireceptor communication between T cells and antigen-presenting cells that is fundamental to initiating pathogen-specific immune clearance. The superantigen inserts itself between the antigen receptor of T cells and the major histocompatibility complex class II molecule displaying peptides from potential pathogens. Toxin exposure results in hyperactivation of the immune system, and the pathology is mediated by tumor necrosis factor-α, interferon-γ, and other cytokines.
HLA-DR: Human Leukocyte Antigen DR; SEB: staphylococcal enterotoxin B; TCR: T-cell receptor

HOST RESPONSE AND ANIMAL MODELS

Individuals may respond differently to superantigen exposure as a result of MHC polymorphisms, age, and many physiological factors. Each toxin exhibits varying affinities toward the HLA-DR, HLA-DQ, and HLA-DP isotypes and distinct alleles of class II MHC molecules, as observed by differences in T-cell responses in vitro. Generally, SE and TSST-1 bind HLA-DR better than HLA-DP or -DQ, whereas SPEA preferentially binds HLA-DQ better than HLA-DR. Primates, including humans, are most sensitive to superantigens when compared to other mammals.[24] Lethal or incapacitating doses of toxin may be lowered by coexposure to endotoxin from gram-negative bacteria[17] or hepatotoxins,[25] or by infection with replicating agents.[4]

At the cellular level, the interaction of superantigens with receptors on APC and T cells leads to intracellular signaling.[26] As with conventional antigens, costimulatory receptors are also required for cell activation by superantigens. The best-characterized costimulatory receptors are CD80/CD86 on APC and CD28 on T cells.[27–29]

The expression of intercellular adhesion molecule-1 (ICAM-1) on APC promotes stable cell conjugate with T cells and provides costimulatory activation signals.[27] The interactions of LFA-1 (lymphocyte function-associated antigen)/ICAM-1 and CD28/CD80 have both been implicated in SEA (staphylococcal enterotoxin A)-mediated T-cell activation.[30] High concentrations of SEB elicit induction of phosphatidylinositol and the activation of protein kinase C (PKC) and protein tyrosine kinase (PTK) pathways,[31,32] similar to mitogenic activation of T cells. PKC and PTK activation affect many intracellular signaling pathways, ultimately activating the transcription factors NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), NF-AT (nuclear factor of activated T cells), and AP-1 (activator protein 1), resulting in the expression of proinflammatory cytokines, chemokines, and adhesion molecules.[33–35] Both IL-1 and TNFα can directly activate the transcription factor NF-κB in many cell types, including epithelial cells and endothelial cells, perpetuating the inflammatory response. Another mediator, IFNγ (interferon gamma), produced by activated T cells and natural killer cells, synergizes with TNFα and IL-1 to enhance immune reactions and promote tissue injury. PTKs and T-cell cytokines also activate phosphoinositide 3 kinase (PI3K), affecting many intracellular processes and pathways, ultimately activating the mammalian target of rapamycin (mTOR).[36] SEB and other superantigens also directly induce chemotactic mediators, interleukin-8, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α, and macrophage inflammatory protein-1β, which can selectively chemoattract and activate leukocytes.[37–39] Thus, cellular activation by SEB and other superantigens leads to severe inflammation, hypotension, and shock. Additional mediators contributing to SEB-induced shock include prostanoids, leukotrienes, and tissue factor from monocytes; superoxide and proteolytic enzymes from neutrophils; and chemokines from epithelial and endothelial cells. Activation of coagulation via tissue factor leads to disseminated intravascular coagulation, tissue injury, and multiorgan failure. SE-induced TSS thus presents a spectrum and progression of clinical symptoms, including fever, tachycardia, hypotension, multiorgan failure, disseminated intravascular coagulation, and shock.[40,41]

In humans and nonhuman primates (NHP), SEs induce an emetic response and toxic shock when ingested.[42,43] Typically, the SEB-intoxicated NHPs developed anorexia, vomiting, and diarrhea within 6 to 24 hours postexposure, followed by depression, dyspnea, and shock 24 to 72 hours later.[43,44] Specific cells and receptors in the intestinal tract have not been identified for emesis, but some studies suggest the interaction of a dodecapeptide binding region of superantigen with epithelial cells.[21,22] Pulmonary edema and lung lesions with infiltrated leukocytes and macrophages appeared in NHP exposed to SEB.[44]

Although the SE studies in NHP are considered a "gold standard" for in vivo investigations, many rodent models have been developed as alternatives to study the toxic shock and acute lung injury aspects of superantigens.[4,17,25,37,39,45] The lower cost associated with maintaining mice, the availability of immunological reagents, and certain similarities to NHP models are obvious advantages for their use in the development of therapeutics and vaccines.

Mice are naturally less susceptible to SEs, TSST-1, and SPEs because of the lower toxin affinity to murine MHC class II molecules.[17] Potentiating agents, such as D-galactosamine,[25] actinomycin D,[46] lipopolysaccharide (LPS),[17] and viruses[4] have often been used to amplify the toxic effects of superantigens so that lower, practical amounts of toxins can be used for in-vivo studies. Many vaccine studies with SEB have been accomplished with an LPS-potentiated mouse model, as a natural synergy exists between these bacterial exotoxins and LPS.[17,47] Results of these studies show a correlation between increased serum levels of IL-1, IL-2, TNFα, and IFNγ with bacterial superantigen-induced shock. Pulmonary lesions with severe interstitial and alveolar edema, as well as perivascular leukocytic infiltrates in mouse models were similar to those in NHP exposed to SEB.[45,46] Transgenic mice with inserted human HLA class II molecules have also been developed to study SEB-induced shock.[48–50] In some cases, high doses of SEB and D-galactosamine were still required to induce toxic shock with transgenics.[48,50] Nevertheless, there is a correlation of proinflammatory cytokine induction and pulmonary lesions in the various transgenic models of SEB-induced toxic shock. A "double-hit" low-dose SEB model was developed in C3H/HeJ mice, an LPS-resistant mouse strain, to simulate human SEB-induced toxic shock.[39] This model mimics human TSS closely as intranasal delivery of SEB triggers lung inflammation, systemic release of cytokines, and hypothermia that culminate in death at later time points similar to human toxic shock.[45] All of these murine models have various drawbacks but they are useful as tools for the development of therapeutics and vaccines.

CLINICAL DISEASE

The clinical documentation of TSS provides the most comprehensive source of information on the pathology of superantigen (eg, SEB) exposure. To meet strict criteria of the Centers for Disease Control and Prevention for TSS,[51] negative blood (except for *S aureus* or *S pyogenes*), throat, or cerebrospinal

fluid cultures, as well as negative serological tests for Rocky Mountain spotted fever, leptospirosis, and measles should be obtained. TSS disease symptoms are characterized by a rapid drop in blood pressure, elevated temperature, and multiple organ failure. The profound hypotension and desquamation of the palms and soles of the feet characteristic of TSS is not observed in exposure by inhalation, and respiratory involvement is rapid, unlike other forms of TSS. Furthermore, the fever prominent after aerosol exposure is generally not observed in cases of SEB ingestion.

An accidental laboratory inhalation exposure of nine laboratory workers to SEB best exemplifies the clinical disease as reported below. The following description illustrates a severely incapacitating illness of rapid onset (3–4 hours) and modest acute duration (3–4 days) upon exposure to SEB.[43] Details of the disease and signs and symptoms are described below.

Fever

Fever was prominent in all nine of those exposed. Eight of the individuals experienced at least one shaking chill that heralded the onset of illness. Using the morning peak level of SEB aerosol generation in the laboratory as the most likely time of exposure, onset of fever occurred from 8 to 20 hours post initial exposure, with a mean time of onset of 12.4 ± 3.9 (SD) hours. Duration of fever was from 12 to 76 hours after onset, with a mean duration of 50 ± 22.3 hours. Fever ranged as high as 106° acutely. Myalgias were often associated with the initial fever. Onset of myalgia was between 8 and 20 hours, with a mean onset of 13 ± 5 hours. Duration was from 4 to 44 hours, and the mean duration was 16 ± 15 hours.

Respiratory Symptoms

All nine patients were admitted to the hospital with a generally nonproductive cough. Onset was at 10.4 ± 5.4 hours, and duration was 92 ± 41 hours. Five had inspiratory rales with dyspnea. The three most seriously compromised patients had dyspnea, moist inspiratory and expiratory rales, and orthopnea that gradually cleared. One individual had profound dyspnea for the first 12 hours that moderated to exertional dyspnea and rales, which persisted for 10 days. Chest radiographs on admission showed densities compatible with "patches of pulmonary edema" and Kerley lines suggesting interstitial edema. During recovery, discoid atelectasis was noted. Moderate compromise of the respiratory system was often accompanied by radiographic evidence of peribronchial accentuation, or "cuffing." The mildly ill patients had normal radiographs. One of the three severely ill patients had severe pulmonary compromise and profound dyspnea and received only slight relief when treated with an aminophylline suppository. Moderately intense chest pain, of a substernal pleuritic type, occurred in seven individuals. Onset of chest pain was at 12 ± 6.5 hours and lasted for 4 to 84 hours, with a mean duration of 23 ± 27 hours.

Headache

Eight of the nine patients experienced headache with onset ranging from 4 to 36 hours, and the mean time of onset was at 13.3 ± 10 hours. Duration ranged from 8 to 60 hours, with a mean duration of 30.6 ± 19 hours. The headaches ranged from severe to mild, but were usually mild by the second day of hospitalization. Five individuals' headaches responded to Darvon (propoxyphene hydrochloride; Eli Lilly & Company, Indianapolis, IN) or codeine.

Nausea and Vomiting

Gastrointestinal symptoms occurred in more than half of the individuals, nausea and anorexia in six, and vomiting in four. The onset of nausea ranged from 8 to 24 hours, with a mean onset of 17 ± 6.3 hours. Duration ranged from 4 to 20 hours, with a mean of 9 ± 5.5 hours. The time to onset of anorexia ranged from 8 to 24 hours, with a mean onset of 18.5 ± 5.6 hours. Duration of anorexia ranged from 4 to 136 hours, and the mean duration was 44.5 ± 45 hours. Vomiting occurred in four patients, sometimes after prolonged paroxysms of coughing. The range of onset of vomiting was 8 to 20 hours, with a mean time to onset of 14 ± 5.1 hours. Duration was not prolonged and usually consisted of one episode. The patients were successfully treated with Compazine (prochlorperazine; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) and Benadryl (diphenhydramine hydrochloride; Pfizer Pharmaceuticals Company, New York, NY). Only one individual demonstrated hepatomegaly and bile in the urine, although another patient also demonstrated mildly elevated liver-function tests. No diarrhea was reported in any of the exposed individuals.

Other Signs and Symptoms

Cardiovascular

All patients who experienced chest pain had normal electrocardiograms. Throughout the illness, all patients were normotensive. Vomiting was of brief duration, and no one, including those vomiting, required

intravenous fluid administration. The patients' pulse rates, when elevated, paralleled temperature elevation.

Hematology

Leukocytosis was observed in most of the patients 12 to 24 hours after exposure to the toxin.

Ocular Effects

None of the patients experienced conjunctivitis, although one individual later stated he remembered that his eyes had "burned" during the believed time of exposure. This contrasts with reports of conjunctivitis resulting from separate accidental laboratory exposures.[52]

DETECTION AND DIAGNOSIS

The staphylococcal enterotoxins are moderately stable proteins; therefore, immunological evaluation should be possible in field or clinical samples. A variety of rapid and sensitive detection methods are available.[53,54] Immunoassays are very sensitive and can detect picogram quantities of toxins in environmental and serum samples. Plasma concentrations of superantigens were measured in septic patients of an intensive care unit using an enzyme-linked immunosorbent assay.[55] In one study, [56] the mean concentration of TSST-1 in human sera from TSS patients was reported to be 440 pg/mL. In contrast, anti-TSST-1 antibody titers are often low in TSS patients[57,58] and only recover during convalescence. Furthermore, most normal human serum samples contain detectable levels of antibody reacting with several different toxins, including SEB. Therefore, serum antibody titers are of little diagnostic value. If bacterial sepsis is suspected and cultures can be obtained, detecting minute quantities of potentially toxigenic strains is possible using polymerase chain reaction (PCR) amplification and toxin gene-specific oligonucleotide primers. The results from both PCR and immunoassays are rapid, allowing quantitative or qualitative measurements in less than 24 hours. Finally, as the best approach to early diagnosis on the battlefield, toxins may be identifiable in nasal swabs from individuals exposed to aerosols for at least 12 to 24 hours postexposure.

MEDICAL MANAGEMENT

No specific therapy has been identified or described.[3,41,43] Supportive therapy in the nine mild accidental exposure cases described earlier seemed to provide adequate care. Symptoms of fever, muscle aches, and arthralgias may respond to cool compresses, fluids, rest, and judicious use of acetaminophen or aspirin. For nausea, vomiting, and anorexia, symptomatic therapy should be considered.

Antihistamines (eg, diphenhydramine) and phenothiazine derivatives (eg, prochlorperazine) have been used parenterally or as suppositories. The success of these drugs in controlling nausea may have been augmented by the relatively short duration of nausea and vomiting induced by aerosolized SEB. Because of the brevity of vomiting episodes, fluid replacement was not considered or required in the series discussed. However, replacement may be necessary in the event of prolonged vomiting resulting in fluid and electrolyte depletion. Although diarrhea was not observed in human accidental exposure cases, deposition of toxin on foodstuffs could produce the syndrome, which should be treated symptomatically.

Initial symptomatic therapy with cough suppressants containing dextromethorphan or codeine should be routinely employed. Prolonged coughing unrelieved by codeine might benefit from a semisynthetic, centrally acting narcotic antitussive containing hydrocodone (dihydrocodeinone).

Pulmonary status should be monitored by pulse oximetry, and when respiratory status is compromised, prompt evacuation to a site with capacity for intensive respiratory care by mechanical ventilation should be considered.

Infusion of intravenous immunoglobulin has been successfully used[59,60] to treat episodes of Kawasaki's syndrome linked to SE and TSST-1. An anecdotal case of TSS with elevated TSST-1 and SEA levels, complicated by life-threatening multiorgan dysfunction, was successfully treated by early introduction of plasma exchanges.[61] Prior exposure to SEB by inhalation does not appear to protect against a subsequent episode; however, increased antibody titers to SEB are protective, and efforts to devise both passive and active immunotherapy show promise. Because of the rapidity of receptor binding by these toxins (apparent saturation less than 5 minutes), active immunity should be considered the best defense.

The treatment of toxic shock with *S aureus*-secreting superantigens such as SEB and TSST-1 is much more complex in a clinical setting. Both *S aureus* and *S pyogenes* produce multiple virulence factors that aid in bacterial survival and dissemination in the host.

Furthermore, the emergence of methicillin-resistant *S aureus* strains poses constraint in treatment options and clinical guidelines were revised and updated recently.[62] A recent study in a rabbit model of *S aureus* pneumonia suggests that vaccination against superantigens and secreted cytolysins provides protection against *S aureus*, whereas vaccination against bacterial cell-surface antigens increases disease severity.[63]

VACCINES

A formalin-treated SEB toxoid demonstrated some degree of efficacy in animal trials, but is not approved for human use. Vaccines produced by site-specific mutagenesis of the toxins, delivered by intramuscular or intradermal routes, have also shown promising results in animal and human trials. These recombinant subunit vaccines were produced by substitution of active receptor-binding amino acid side chains that reduced affinities and consequential T-cell activation[13,14,47,64] without altering the three-dimensional structure of the antigen. Though promising, these engineered vaccines are neither licensed nor available for human use.

DEVELOPMENT OF THERAPEUTICS

An understanding of the cellular receptors, signaling pathways used by staphylococcal superantigens, and the biological mediators induced has provided insights to selecting appropriate therapeutic targets. Potential targets to prevent the toxic effects of SEs include (*a*) blocking the interaction of SEs with the MHC, TCRs,[26] or other costimulatory molecules[27,28]; (*b*) inhibition of signal transduction pathways used by SEs[26]; (*c*) inhibition of cytokine and chemokine production[36]; and (*d*) inhibition of the downstream signaling pathways used by proinflammatory cytokines and chemokines.

Limited therapeutics for treating superantigen-induced toxic shock are currently available. Intravenous immunoglobulin was effective as a treatment in humans after the onset of toxic shock syndrome.[41,59] Antibody-based therapy targeting direct neutralization of SEB or other superantigens is most suitable during the early stages of exposure before cell activation and the release of proinflammatory cytokines.[64] Because some neutralizing antibodies cross-react among different superantigens,[11] a relatively small mixture of antibodies might be effective in treating exposures to a greater variety of superantigens. Vaccines of SEB and SEA with altered critical residues involved in binding class II MHC molecules were also used successfully to vaccinate mice and monkeys against SEB-induced disease.[47,65]

Most therapeutic strategies in animal models of SEB-induced shock have targeted proinflammatory mediators. Therapeutic regimens include corticosteroids and inhibitors of cytokines, caspases, or phosphodiesterases.[45,66,67] Several in vivo murine models have been used to study potential therapies that prevent superantigen-induced shock. Therapeutic agents, such as nitric oxide inhibitors, decrease SEA and SEB effects by inhibiting the production of IL-1, -2, -6, TNFα, and IFNγ in the LPS-potentiated model.[68] Blockade of the CD28 costimulatory receptor by its synthetic ligand, CTLA4-Ig, prevented TSST-1-induced proliferation of T cells and lethal TSS.[69] Decreased mortality rates accompanied by an attenuation in liver apoptosis and hemorrhagic necrosis were seen in mice given D-galactosamine plus SEB along with a cell-permeable cyclic peptide targeting NFκB.[70] Dexamethasone, a well-known FDA-approved immunosuppressant and NFκB inhibitor, prevented toxic shock in the LPS-potentiated mouse model and the "double-hit" SEB-induced shock model.[45,71] Rapamycin, another FDA-approved drug currently used to prevent kidney graft rejection, was efficacious even when given 24 hours after SEB in the "double-hit" SEB-induced shock model.[72] Recently, myeloid differentiation primary response protein (MyD88)–mediated proinflammatory signaling has been shown to be activated after SEB binding to MHC class II[73] and that MyD88$^{-/-}$ mice are resistant to SEB and SEA intoxication.[74,75] Administration of a synthetic small molecule mimetic (EM-163) to the conserved BB loop in the toll/IL-1 receptor (TIR) domain of MyD88, reduced multiple cytokines and protected mice from lethal shock in the LPS-sensitized model. [76,77]

SUMMARY

SEB is representative of a group of bacterial proteins that exert profound toxic effects upon the immune system. Many sensitive immunoassays have been developed for laboratory detection of most of the staphylococcal and streptococcal superantigen toxins, but the limit of field detection is unknown. Inhalation exposure to agents such as SEB may result in severe but temporary incapacitation, while high-dose exposures

will result in fatalities. Supportive symptomatic therapy is the only known method of treatment. Vaccines currently under development may afford protection to individuals but are not yet licensed for human use. Therapeutics tested in murine models may provide insights to future development in treating toxic shock.

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