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Bacterial Pyrogenic Exotoxins as Superantigens

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INTRODUCTION

In recent years, a great deal of new knowledge about a group of microbial proteins known as superantigens has been generated. These molecules have elicited tremendous interest because they interact with the immune system in a nonconventional manner and can potentially trigger diseases such as toxic shock, food poisoning, and autoimmunity. Realizing the immunological and biological effects of superantigens has helped to discern the mechanism of pathogenesis of a number of diseases linked to microbial infections and has offered new possibilities for the development of novel and effective therapeutic strategies. Knowledge gained from studying the interaction of superantigens with cells of the immune system has illuminated many aspects of immune regulation and signal transduction via the T-cell receptor (TCR) and major histocompatibility complex (MHC) class II molecules. In addition, scientists were quick to exploit certain features of superantigens in developing novel immunotherapeutic strategies for use in cancer therapy. As a result, superantigens have attracted scientists from diverse disciplines to investigate various aspects of these fascinating molecules. This amalgamation of expertise has contributed tremendously to our knowledge of the immune system and our understanding of the pathogenesis of many human diseases.

Superantigens can be produced by viruses and bacteria, including certain *Mycoplasma* species. Some are secreted toxins, whereas others are membrane associated. This review will focus on the properties of a group of superantigens that belong to the family of bacterial pyrogenic exotoxins and is intended to highlight their role in human diseases.

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SUPERANTIGENS: DEFINITION AND MECHANISM OF IMMUNE STIMULATION

Superantigens are bifunctional molecules that utilize at least two types of receptors expressed on different mononuclear cells of the immune system (35, 46, 100, 116, 121, 135, 142, 162, 220). The receptor for superantigens on T cells is the αβ heterodimeric TCR for antigen (280). MHC class II molecules expressed primarily on B cells, monocytes, and dendritic cells (Fig. 1) also serve as superantigen receptors (71, 72, 174, 224). Recent studies have suggested that other surface molecules including integrins may also be involved in binding superantigens (11, 32). The binding of superantigens to the TCR and/or to class II molecules triggers intracellular biochemical signals that program a number of events leading to cell activation, differentiation, proliferation, and the release of inflammatory cytokines (36, 177). A unique feature of superantigens is that, unlike conventional antigens, they do not require processing by the antigen-presenting cells (APC) and they can interact with a large number of T cells that share particular sequences within the variable region of the β chain of the TCR, known as Vβ elements (96, 162).

Normally, conventional antigens are processed into small peptides within the lysosomal compartments of the APC (13, 87, 245, 269). These peptides are targeted to special vesicles where they form complexes with MHC class II molecules. The MHC-peptide complexes are transported to the cell surface to be sampled by many T cells, each expressing a unique αβ TCR that is specific for a particular MHC-antigen complex. The α and β chains of TCR consist of constant and variable regions, and the specificity of TCR to an antigen is determined by the five variable regions of the TCR: Vβ, Dβ, Jβ, Vα, and Jα (53, 143, 161). The ability of the T-cell repertoire to recognize a wide array of MHC-peptide combinations is attributed to the presence of many different germ line Vβ and Vα gene segments that can be shuffled together with the appropriate Dβ, Jβ, and Jα genes and rearranged to form the variable units of

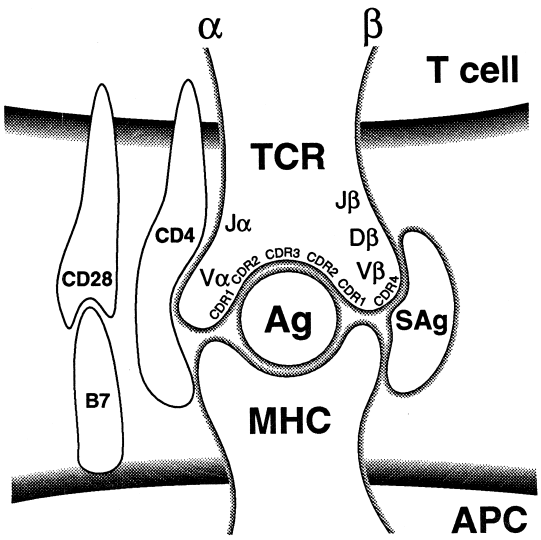

FIG. 1. Bridging of T cells and APC: a schematic model of superantigen (SAg) interaction with TCR and class II molecules.

TABLE 1. Summary of the major differences among antigen, superantigen, and mitogen

Feature	Antigen	Superantigen	Mitogen
% of responding cells	0.0001–0.000001	5–20	80–90
Accessory cell requirement	+	+	+
Dependence on MHC class II expression	+	+	−
MHC restriction in presentation	+	−	−
Requirement for complex processing	+	−	−
Restricted Vβ usage by responding cells	−/(+)	+	−
Role of Vα elements	+	−/(+)	−
CDR3 conservation among responding cells	+	−	−

the TCR (Vβ:Dβ:Jβ and Vα:Jα), which are then juxtapositioned next to the Cβ or Cα gene segments to form a contiguous unit that encodes the mature α or β polypeptide chains (Fig. 2). Together, the junctional regions between Vβ:Dβ, Dβ:Jβ, and Vα:Jα create the hypervariable CDR3 domain of the TCR that recognizes MHC-peptide complexes with a high degree of specificity (53).

By contrast to antigen, the interaction of superantigen with T cells is governed primarily by Vβ elements with little contribution from the other variable elements of the TCR (96, 112, 115). In humans, the Vβ elements are grouped into 25 major families on the basis of their sequence (69, 212, 265, 282). Each superantigen has a signature specificity for a set of Vβ families and can interact with all T cells expressing those Vβ elements regardless of the antigenic specificity of their TCR. Therefore, by comparison to antigens that may interact with one cell in every 10^4 or 10^6 T cells, superantigens are capable of interacting with as many as 5 to 20% of resting T cells (Table 1). This number varies depending on the number of Vβ families that recognize a given superantigen and on the frequency of T cells expressing those Vβ families in each individual's repertoire.

The interaction of superantigens with class II molecules is important for their ability to stimulate T cells, because accessory cells that do not express class II fail to provide costimulation for the superantigenic response, whereas they support nonspecific polyclonal mitogen-induced T-cell responses (33, 71, 174, 203, 261). The requirement for class II is also demonstrated by the ability of anti-class II antibodies to block superantigen-induced proliferation of T cells (174, 261). However, the roles of APC and class II molecules in antigen and superantigen presentation are quite different. Superantigens do not need to be processed by the APC, and furthermore, fragmentation usually results in loss of their activity because these fragments are no longer able to bridge the T cells and the APC (90). Recent studies have provided evidence that the superantigen staphylococcal enterotoxin B (SEB) can form a ternary complex with TCR and class II molecules that contain different peptides in their groove (117, 230). These results

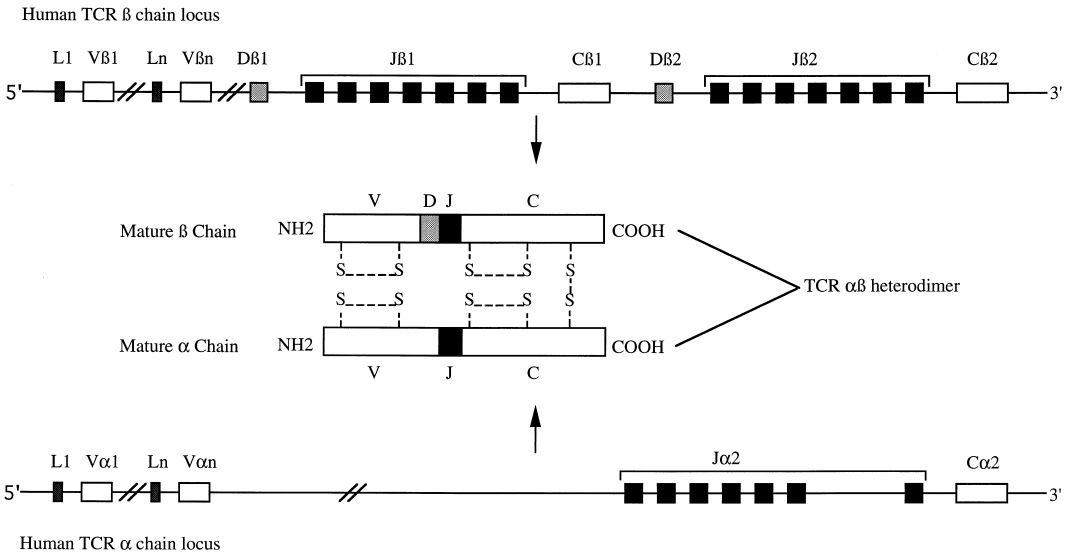

FIG. 2. Schematic representation of gene rearrangement and generation of the mature TCR αβ heterodimer.

confirmed earlier studies showing that the superantigens bind to MHC class II molecules at a site that is distinct from the conventional antigen binding groove (54, 127, 197) (Fig. 1). Furthermore, whereas processed antigen is recognized by the TCR in the context of only self MHC class II molecules, a phenomenon known as MHC restriction, the response of T cells to superantigen is MHC unrestricted and can occur in the presence of either self or foreign MHC class II molecules (Table 1).

It is clear from the above discussion that the role of class II molecules in superantigen presentation is nonconventional. In fact, we showed that TCR Vβ elements can interact directly with superantigens and that this interaction is independent of superantigen-class II complex (137, 139, 159, 160, 191). Further, we demonstrated that the requirement for APC in the superantigen response can be totally bypassed if the T cell is provided with the costimulatory signals that are normally delivered by the class II-expressing APC (137, 139, 159, 160, 191). Collectively, these data led us to propose that superantigens depend on class II expression, not because they can only be seen in the context of these molecules but because they utilize the class II molecules as signaling receptors through which they can induce the APC to express the costimulatory molecules required for T-cell activation (135). In support of this theory are studies showing that cells that express class II but are unable to provide appropriate costimulation are ineffective in supporting a superantigen response and can, instead, induce T-cell anergy (98, 190a). In addition, several recent studies provided direct evidence that the interaction of superantigen with class II molecules triggers biochemical reactions that initiate several cellular events, including the upregulation of cytokine gene expression (36, 76, 177, 239). These functional studies have recently been confirmed by the work of Seth et al. (230), who provided physical evidence for the existence of SEB-TCR binary complexes and showed that the formation of these complexes increases the binding to class II and stabilizes the ternary complex of TCR-superantigen-class II.

Studies addressing differential binding of superantigens to different TCR Vβ elements or different class II isotypes or allotypes are greatly needed to better understand the immunobiological effects of superantigens in vivo and decipher their role in disease pathogenesis. Individuals who have relatively higher frequencies of T cells expressing Vβ elements that can recognize a particular superantigen will be most likely to develop stronger responses to this superantigen than those individuals who have a lower frequency of these T cells in their repertoire. Similarly, individuals expressing distinct class II molecules with different binding affinities to superantigen may differ in their responses to a particular superantigen and consequently vary in their clinical symptoms following in vivo exposure to this superantigen.

PRACTICAL CONSIDERATIONS IN ASSIGNING SUPERANTIGENIC PROPERTIES

In order to demonstrate that a particular protein is a superantigen, three main criteria should be met: (i) a reproducible pattern of selective Vβ interaction; (ii) dependence of the response on APC that express either autologous or allogeneic class II molecules; and (iii) lack of requirement for complex processing by APC. To analyze for preferential Vβ expansion in response to superantigen, three methods are widely used (39, 86, 125, 140). The flow cytometric method utilizes human Vβ-specific mouse monoclonal antibodies; however, at present this method is of limited use because of the unavailability of antibodies to all human Vβ families. The second method is a PCR-based technique which pairs 5′ Vβ family-specific primers with a 3′ Cβ primer to amplify specific Vβ family cDNA (39, 86, 140). When performed properly, this method yields highly reproducible results and allows analysis of the entire Vβ repertoire. However, the best method for TCR repertoire analysis is the riboprobe method, which is an RNase protection assay (8a). It is recommended that, whenever possible, more than one method should be used to confirm the Vβ specificity of a particular superantigen.

The demonstration that certain Vβ elements selectively interact with a particular protein is not sufficient evidence for its superantigenicity because there are quite a few examples of conventional antigens that are also preferentially recognized by certain Vβ elements (25). Therefore, to provide evidence for superantigenic stimulation, it is important to determine that the response is independent of the other variable elements of the TCR and to demonstrate that the responsive T cells exhibit extensive junctional sequence diversity at the CDR3 region of their TCR. Finally, because certain superantigens can stimulate T cells in the picomole range, it is essential to confirm that the activity seen is indeed mediated by the protein of interest and not by a minor contaminant. Detailed methods to address these issues have been recently reviewed (140).

TABLE 2. Human Vβ specificities of pyrogenic exotoxins[a]

Pyrogenic exotoxin	Human Vβ specificity
Staphylococcal exotoxin	
SEA	1, 5, 6, 7, 9
SEB	3, 12, 14, 15, 17, 20
SEC1	3, 6, 12, 15
C2	12, 13.2, 14, 15, 17, 20
C3	3, 5, 12, 13.2
SED	5, 12
SEE	5.1, 6, 8, 18
TSST-1	2
EXF-T[b]	2
Streptococcal exotoxins	
SPeA	2, 12, 14, 15
SPeB	8
SPeC	1, 2, 5.1, 10
SPeF (MF)	2, 4, 8, 15, 19
SSA	1, 3, 5.2, 15

[a] Data were compiled from references 39, 96, 140, 172, 183, and 262.
[b] EXF-T, exfoliative toxin.

BACTERIAL PYROGENIC EXOTOXINS AS SUPERANTIGENS

A number of gram-negative and gram-positive bacteria have been shown to produce or suspected of producing superantigens. Among the best characterized superantigens are the family of pyrogenic exotoxins produced by *Staphylococcus aureus* and *Streptococcus pyogenes* (15, 64, 96, 119–121, 135, 142, 150, 162, 220). The known staphylococcal pyrogenic superantigens include the staphylococcal enterotoxins (SEs) A through E (SEA through SEE), toxic shock syndrome toxin-1 (TSST-1), and exfoliative toxin (96, 220). In *S. pyogenes*, also known as group A streptococci, the streptococcal pyrogenic exotoxins (SPe) represent a family of superantigens which includes SPeA, SPeB, SPeC, SPeF, and SSA (1, 172, 183, 262). Table 2 summarizes the human Vβ specificity for the known secreted pyrogenic superantigens of bacterial origin. Some of the properties of these superantigens and their roles in human diseases are discussed below.

The *Mycoplasma arthriditis* mitogen, which causes preferential expansion of human T cells that express Vβ17 elements, has been also extensively investigated (46, 47). Recent studies by Cole and his colleagues suggest that other *Mycoplasma* species may also produce superantigens. We expect that other bacterial species that produce superantigens will be found. Already we know of reports on superantigens produced by *Pseudomonas aeruginosa* (152), *Yersinia pseudotuberculosis* (2, 268), and *Clostridium perfringens* (26), as well as group B and group G streptococci (221).

STRUCTURAL FEATURES OF SECRETED PYROGENIC SUPERANTIGENS

Pyrogenic exotoxic superantigens share many biological features including the abilities to interact with large numbers of T cells, to elicit a strong inflammatory cytokine response, and to enhance susceptibility to endotoxin shock (reviewed in references 23, 135, 142, 220, and 250). It is not surprising, therefore, that many of these superantigens also share structural features. The majority of secreted pyrogenic superantigens are globular proteins that range from 20 to 30 kDa in size, and with few exceptions many have obvious sequence homology (162). If the staphylococcal superantigens are grouped according to the highest degree of similarity, SEA, SEE, and SED would fall into one group and SEB and SEC would fall into another. Considerable homology among superantigens from different bacterial species has also been reported. For example, SPeA and SSA are highly homologous with SEB at the protein level (210); in fact, SSA is more related to SEB and SEC (60% identity) than it is to SPeA (49% identity) or SPeC (22.4% identity) (210). By contrast, superantigens such as TSST-1, exfoliative toxin, and SPeB share little sequence homology with most other superantigens (162). However, although the overall structure of the pyrogenic exotoxic superantigens is different from that of other superantigens, including the mouse mammary tumor viral superantigens (17, 106, 207, 283), the *M. arthriditis* mitogen (47), and the streptococcal M proteins (263, 276), it appears that the pyrogenic superantigens share certain sequence motifs (264, 275). One example is the α-helical coiled-coil M proteins, which appear quite distinct from other superantigens but share a functional motif with SPeA, SEA, SEB, SEC, and SEE (275).

Despite common functional features and the presence of sequence homology among the pyrogenic superantigens, there does not appear to be any obvious primary structural feature that predicts superantigenicity. It is possible, however, that superantigens may share conformational features which allow them to interact with both the TCR and class II molecules.

FUNCTIONAL DOMAINS WITHIN THE PYROGENIC SUPERANTIGENS IMPORTANT FOR THEIR INTERACTION WITH MHC CLASS II MOLECULES AND TCR

Several groups have thoroughly investigated residues within superantigens, TCR, and class II molecules that are important for their physical and functional interaction (5, 10, 22, 23, 30, 41, 42, 65, 101, 107, 112, 113, 117, 126, 202, 205, 206, 213, 235, 254, 257, 275). Studies investigating functional domains of the staphylococcal enterotoxin (SE) superantigens have localized mitogenically important regions to the amino-terminal part of the molecule (30, 126, 203), while others have suggested the importance of residues at the carboxy-terminal half (24, 113). This apparent controversy was explained by the recently resolved three-dimensional crystal structure of SEB (117, 254) which helped identify functional domains involved in binding to these receptors. SEB has two different class II binding sites, and although the amino-terminal domain forms most of the contact with the class II molecule, several residues at the carboxy-terminal end of the molecule also contact the MHC (117). Recent studies suggest that this feature may be common for most bacterial superantigens (101, 117, 204).

Despite primary structural variations, common three-dimensional conformations may exist among superantigens, and these may confer the bifunctional property that allows these proteins to simultaneously interact with distinct receptors on different cells. Interestingly, recent studies revealed that TSST-1 and SEB, which are only 20 to 30% homologous in their primary sequence, have a similar overall three-dimensional structure that allows them to contact both the class II molecules and the TCR (5, 205). However, there are important and very interesting differences. For example, because TSST-1 has no cysteine residues, it is missing the disulfide loop that is shared among pyrogenic superantigens with emetic activity, which may explain why TSST-1 lacks such activity (84, 238). Differences in regions that interact with class II molecules and TCR were also found, confirming earlier studies that indicated that superantigens bind to different sites on these molecules (38, 222, 229). Although some important residues involved in class II binding are conserved among certain superantigens, individual superantigens may utilize other residues from different regions along the molecule to mediate such binding. These studies, which are discussed below, suggest the existence of different modes by which superantigens can interact with class II molecules.

In addition to studies elucidating functionally important residues and regions for superantigens, specific sites on the class II molecule that bind to different superantigens are being thoroughly investigated by a number of laboratories. From the available data, it is becoming more clear that (i) most superantigens have at least two class II binding sites (73, 117, 126, 254); (ii) superantigens interact with class II molecules at a site that is distinct from the antigen binding groove (27, 54, 97, 117, 127–129, 197, 230); (iii) related superantigens interact with different sites on the class II molecules, although some sites may overlap (38, 72, 173, 222); (iv) certain superantigens may interact with the same class II molecule at multiple sites, and it is likely that the superantigen cross-links class II molecules by binding to one site on one molecule and to the other site on a second molecule (38, 117, 229, 235); and (v) the α and β chains of class II molecules may contribute differently to the binding of related or distinct superantigens, and different residues within either chain of the class II molecule can be involved in the binding of different superantigens (27, 73, 97, 117, 128, 129, 197, 203). It appears, therefore, that superantigens differ in their mode of interaction with class II molecules. Furthermore, several studies have demonstrated the existence of isotypic and allotypic hierarchy in the binding and presentation of superantigens by class II molecules. In other words, although superantigens can be presented to T cells in an MHC-nonrestricted manner, certain alleles may present them more efficiently than others. The majority of staphylococcal superantigens interact better with DR than with DQ or DP molecules (95, 129, 173, 203, 223), whereas several streptococcal superantigens appear to have a preference for DQ (109, 183). As mentioned above, the differential binding of class II alleles to superantigens can have a significant effect on the in vivo effects of these molecules and may explain the wide array of clinical symptoms seen when different individuals are infected with the same superantigen-producing organism.

Although distinct superantigens may bind with different affinities to the various class II alleles, and the response may be modulated by this allelic polymorphism, the TCR Vβ specificity of a particular superantigen is usually not influenced by the isotypic or allotypic form of the class II molecules expressed on the APC. Studies by Gascoigne and Ames (77, 78) suggested that superantigen can bind to soluble TCR β chains only when complexed with class II molecules. These studies have led to the general belief that TCR recognition of superantigen occurs only when the molecule is complexed with class II molecules; however, it is likely that the interaction between superantigen and TCR may not have been of sufficient strength to be detected by the method of Gascoigne and Ames (77, 78) because recent reports have provided direct functional (98, 139, 191, 230) and physical (230) evidence for direct recognition of superantigen by TCR and for the existence of TCR-superantigen binary complexes in the absence of class II molecules. In the context of the latter studies, it is easier to understand why the Vβ specificity of a superantigen does not vary in the presence of distinct class II molecules. It should not be implied from these studies that class II molecules are not important for the superantigen response, because the ability of superantigen to bridge the T cell and APC is required for an efficient intercellular communication and for the induction of meaningful activation signals.

Several studies have indicated that although the binding of superantigens to TCR is primarily governed by Vβ elements (42, 101, 107, 113, 117, 200, 204, 206, 230, 234, 253, 275, 284), this binding can be modulated by other non-Vβ elements (12, 284). Studies of the interaction between superantigens and TCR Vβ elements have clearly established that the CDR4 domain of the TCR β chain is primarily involved in superantigen binding, and mutational studies have localized key residues within this region (42, 117, 206, 281). In addition, superantigen residues that engage Vβ have been identified for several superantigens (101, 107, 113, 171). Mutation and recombination studies have shown that, in the case of a number of the staphylococcal superantigens, residues that engage Vβ lie in a shallow pocket on the surface of the molecule and involve amino acids from the carboxy- and amino-terminal ends of the molecule (reviewed in references 142 and 215). Therefore, residues from both ends of the superantigen molecule are involved in both class II and TCR binding, and for most of the superantigens studied thus far, it appears that the amino-terminal end confers high-affinity binding to class II while residues at the carboxy terminus are responsible for the strong binding to TCR. However, the specificity of a superantigen for a particular Vβ element cannot be predicted from the primary structure. For example, SEA and SEE, which are >90% structurally related, have quite distinct patterns of human Vβ specificity (Table 2) and the same is true for SEC1, SEC2, and SEC3, which have only minor amino acid differences (39, 101). By contrast, TSST-1 and exfoliative toxin are structurally unrelated but share the same Vβ specificity. Furthermore, studies have shown that in certain cases a change of one amino acid can create or abolish Vβ specificities. Hudson et al. (107) used a panel of recombinant SEA-SEE hybrids and mapped the TCR binding domain to the carboxy-terminal region of SEA and SEE. Residues 206 and 207 were found to be particularly important for Vβ engagement inasmuch as exchanging these two residues was sufficient to convert the TCR Vβ specificity.

Additional studies on the structure-function relationship of different superantigens is greatly needed and will undoubtedly reveal valuable information concerning the mechanism by which these molecules mediate their biological activities.

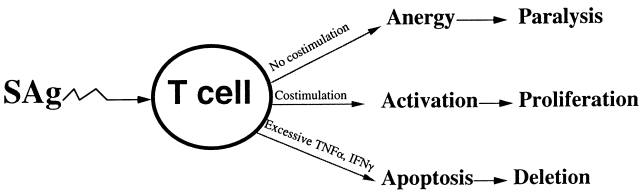

FIG. 3. Possible fate of T cells that encounter superantigen (SAg) in vivo.

POSSIBLE FATE OF T CELLS THAT ENCOUNTER SUPERANTIGEN IN VIVO

The interaction between superantigen and T cells does not always lead to activation, proliferation, and expansion of T cells that express the appropriate Vβ elements. The activation of T cells requires two signals: one is delivered by TCR engagement and the second is via the interaction of APC-associated costimulatory molecules with their respective ligands on the T cell (118, 149). Through their ability to bridge T cells and the APC, superantigens may bring costimulatory molecules such as B7 and intracellular adhesion molecule-1 (ICAM-1) in closer proximity to their respective ligands, CD28 and lymphocyte functional associated molecule-1 (LFA-1), allowing for better interaction and more efficient transduction of signals required to program the activation and proliferation of T cells (191). In the absence of relevant costimulatory signals, the engagement of the TCR by superantigen induces T-cell anergy (98, 190a, 211). Conversely, in the presence of elevated levels of a cytokine such as tumor necrosis factor alpha (TNF-α) or gamma interferon (IFN-γ), reengagement of the TCR by superantigen in preactivated T cells can lead to a process of programmed cell death (known as apoptosis) which can be followed by selective deletion of superantigen-specific T cells (130, 131, 166, 188, 277, 278) (Fig. 3).

Therefore, specific patterns of Vβ expansion or Vβ depletion serve as fingerprints for a particular superantigen and can be used to trace its production in vivo and determine its involvement in human diseases. During a severe infection, specific changes in the T-cell Vβ repertoire that reflect the in vitro Vβ specificity of a particular superantigen produced by the pathogen are considered evidence for the role of this superantigen in disease pathogenesis (1, 40, 110, 277).

PYROGENIC SUPERANTIGENS AS MEDIATORS OF HUMAN DISEASES

Perhaps the most fascinating aspect of superantigens is their potential involvement in a variety of human diseases, some of which are listed in Table 3. The pathogenesis of superantigen-associated diseases is believed to be mediated by aberrant immune responses elicited in response to these molecules. The ability of superantigens to interact with a large number of T cells and to induce the production of high levels of inflammatory lymphokines and monokines has led to their implication in the pathogenesis of food poisoning, toxic shock syndrome, sudden infant death syndrome, and a number of autoimmune diseases (119, 135, 142, 220, 232, 292). However, it is important to distinguish between diseases in which a direct association with a particular superantigen has been made and those in which the role of superantigens is highly suspected but not yet proven. Selected examples of acute and chronic diseases in which superantigens have been implicated are discussed below.

TABLE 3. Known and suspected association of superantigens with human disease

Disease	Superantigen[a]
Acute diseases	
Food poisoning	SEs
StaphTSS	
Menstrual	TSST-1
Nonmenstrual	SEB, SEC, TSST-1
StrepTSS	SPe's
Sudden infant death syndrome	SEs?, SPe's?
Autoimmune diseases	
Rheumatic fever, rheumatic heart disease	M proteins, SPe's?
Kawasaki disease	TSST-1?, SPe's?
Lyme disease	*Borrelia burgdorferi* SAg?
Rheumatoid arthritis	SAg?, MAM?
Multiple sclerosis	SAg?
Sjogren's syndrome	SAg?
Autoimmune thyroiditis	SAg?
AIDS	HIV SAg?
Silicone-induced autoimmunity	SAg?
Lymphoproliferative diseases	EBV SAg?

[a] A question mark indicates a highly suspected but not yet proven role of superantigens in disease. SAg, superantigen; MAM, *M. arthriditis* mitogen; HIV, human immunodeficiency virus; EBV, Epstein-Barr virus.

Food Poisoning

The staphylococcal pyrogenic exotoxins are known to be the most common cause of food poisoning associated with the ingestion of contaminated or spoiled food (14). By virtue of being protease resistant, these exotoxic superantigens are adapted to act enterically and may induce diarrhea and vomiting. However, it is not clear that the enterotoxic activity is directly related to the superantigenicity of these molecules (reviewed in references 119 and 142). Studies examining the Vβ repertoire of patients with food poisoning have not been performed, and it is doubtful that the ability of the SEs to mediate the manifestations of food poisoning is related to their ability to induce T-cell proliferation because modification of this function does not block the enterotoxic effect of these molecules (7, 209). The disease has been related to the release of histamine from gut-associated mast cells (216). It is possible that the SEs may mediate food poisoning by a direct interaction with gut-associated cells and indirectly by inducing the release of inflammatory mediators from T cells that can further exacerbate the symptoms. Interestingly, oral administration of SEs into laboratory animals does not induce the same enterotoxic effects seen in humans. It may be of interest to compare patterns of cytokine production in gut tissues of animals and humans following ingestion of SEs and to investigate whether there are differences that may reveal the mechanism by which these mediate the disease only in humans.

Superantigen-Mediated Toxic Shock Syndrome

The role of superantigens in human diseases is best defined in acute illnesses such as the staphylococcal toxic shock syndrome (staphTSS) and streptococcal toxic shock syndrome (strepTSS). StaphTSS is a severe multisystem disorder characterized by fever, rash, hypotension, and multiple organ failure (37, 52, 259, 260). The vast majority of menstrual staphTSS cases are associated with strains of *S. aureus* that produce the toxin TSST-1 (23, 150, 167, 219). This toxin has been shown to be a potent superantigen that preferentially interacts with human T cells expressing Vβ2 elements (39). Direct evidence for the role of TSST-1 in staphTSS was provided by the studies of Choi et al. (40), who demonstrated significant skewing in the expression of Vβ2-bearing T cells in blood of affected patients. Although SEB and SEC have been implicated in the majority of nonmenstrual cases of staphTSS (218), direct in vivo evidence for their involvement in the disease has not been investigated.

Superantigens are also believed to mediate strepTSS and severe invasive group A streptococcal infections. The incidence of these diseases has dramatically risen in recent years (9, 49, 55, 79, 102, 103, 114, 134, 164, 208, 226, 227, 244, 249). Although staphTSS and strepTSS share many symptoms, there are important differences. Unlike staphTSS, strepTSS is often associated with disseminated infections, severe pain, tissue invasion, and bacteremia (241). In its most severe form, strepTSS manifestations include shock, multiple organ failure, soft tissue destruction, capillary leakage, and necrotizing fasciitis, and these reactions can lead to debridement or death in 30% of the cases (241, 285). The devastating manifestations of strepTSS, which involve several organs and soft tissues, and the amazing speed by which this illness can progress in the affected host were in part responsible for the recent descriptions of the so-called flesh-eating bacteria. However, this is not a new disease; rather, it represents the resurgence of severe invasive group A streptococcal infections.

Pyrogenic exotoxins produced by particular strains of *S. pyogenes* have long been suspected as the most likely mediators of the pathogenesis of strepTSS (23, 43, 89, 178, 180, 185, 244, 277, 288). TSS-like illnesses have also been associated with group B and G streptococci, and preliminary reports indicate that these strains may also produce superantigens (221). In group A streptococci there are at least five different SPes that belong to the superantigen family; these include SPeA, SPeB, SPeC, SPeF (MF), and SSA (1, 172, 183, 210, 262, 289). In early studies, SPeA was found to be associated with the majority of the strepTSS cases in the United States (43, 102, 178, 244, 256), whereas SPeB- and SPeC-producing strains were the most prevalent isolates from strepTSS cases studied in Europe and Canada (55, 103, 182). Recent studies from our laboratory suggest that novel superantigens may also be associated with strepTSS (277). Direct proof for the role of superantigens in strepTSS came from studies that demonstrated specific depletion of Vβ1, Vβ5.1, and Vβ12 in the blood of the majority of patients with strepTSS and severe invasive group A streptococcal infections (277). Inasmuch as this in vivo pattern of Vβ specificity did not correlate with the in vitro pattern of any of the previously characterized streptococcal superantigens (Table 2) (262, 276), the data suggest that a novel superantigen(s) may be involved in these new outbreaks of strepTSS. Indeed, several strains of *S. pyogenes* that were isolated from the most recent cases of patients with strepTSS were found to lack the genes for SPeA, SPeC, and SSA (277), and one such strain expresses a novel superantigen-like activity that is being investigated in our laboratory.

It is generally believed that the pathogenesis of staphTSS and strepTSS is related to potent immune responses elicited by pyrogenic superantigens. Although evidence for T-cell involvement has been established in both staphTSS and strepTSS, superantigen-mediated toxic shock syndrome is probably not related to an effect on T-cell proliferation; rather, it appears to be related to the ability of these molecules to induce the production of T-cell-derived cytokines and to cause the release of excessive amounts of inflammatory cytokines. Cytokines orchestrate intercellular interactions and regulate immune responses; however, excessive production of certain cytokines can be detrimental to the host. Superantigens are potent in-

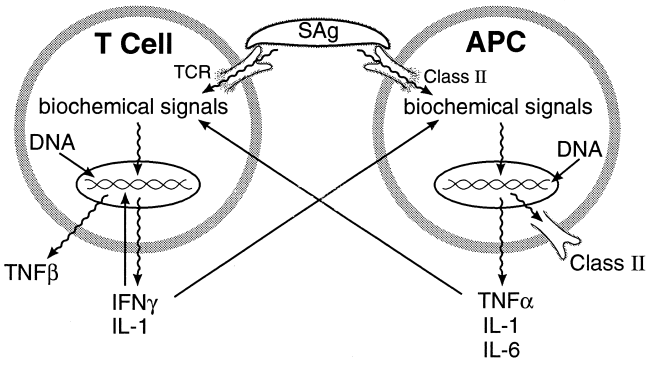

FIG. 4. Interplay between T-cell- and APC-derived cytokines and induction of inflammatory cytokine cascade by superantigen (SAg).

ducers of inflammatory cytokines such as IFN-γ, interleukin-1 (IL-1), IL-6, and TNF (6, 8, 68, 80, 83, 85, 93, 94, 108, 122, 138, 168, 184, 198, 199, 243). Several studies have confirmed that the induction of monokines requires the participation of T cells or T-cell-derived cytokines, namely, IFN-γ (80, 138), which may explain why the ability of superantigens to cause toxic shock requires the presence of T cells and is affected by drugs that interfere with cytokine production (169). Figure 4 depicts the synergistic interaction between T-cell- and APC-derived cytokines in the superantigen response. Note that the known ability of IFN-γ to upregulate class II expression (82, 258) increases the number of superantigen receptors on these cells and further augments their ability to induce inflammatory cytokines.

The importance of synergistic interaction between T-cell- and APC-derived cytokines in the superantigen response is also demonstrated in vivo. Miethke et al. (169, 170) showed that mice treated with cyclosporine A, a drug known to block T-cell activation and lymphokine production, were completely protected against the lethal shock induced by SEB administration. Furthermore, these investigators showed that SEB does not induce lethal shock in severe combined immunodeficiency mice and that reconstitution of these mice with T cells renders them susceptible to superantigen-induced shock (169, 170). Interestingly, these mice were quite susceptible to endotoxic shock. Inasmuch as endotoxin does not interact with T cells, these experiments support a central role of T cells in superantigen-mediated but not endotoxin-mediated shock. These data argue strongly for the importance of T cells in superantigen-mediated shock.

Although cytokines play an important role in gram-positive and gram-negative sepsis, several studies have confirmed the existence of common and divergent pathogenic pathways in superantigen- and endotoxin-mediated shock. The cytokine profiles induced in response to superantigen and endotoxin are also quite different (8, 184). For example, the T-cell-derived cytokines IFN-γ and TNF-β are produced in response to superantigen but not endotoxin (8, 184). These cytokines may be useful in distinguishing gram-positive from gram-negative shock. Understanding the differences in cytokine production in different types of sepsis may help us better understand the roles of the various cytokines in disease pathogenesis and aid in the design of anticytokine therapy.

The central role of cytokines as mediators of septic shock has also been illustrated by numerous in vivo experiments performed in humans and other animals. These experiments have shown a clear correlation between elevated cytokine production and physiological changes characteristic of septic shock (16, 199, 251, 266). TNF-α, which is released in response to both endotoxin and superantigens, is believed to be a major mediator of the pathophysiological manifestations of septic shock (16, 266). This cytokine has a wide range of biological activities. For example, it can produce a thrombogenic state by downregulating thrombomodulin, by inhibiting the production of plasminogen activators, and by increasing plasminogen activator inhibitors (153). TNF-α also has direct effects on a variety of cell types (147) and mediates tissue injury through the activation of inflammatory cells and the upregulation of adhesion molecules. Exposure of endothelial cells to cytokines such as TNF-α can cause a profound increase in adherence of neutrophils, eosinophils, lymphocytes, and monocytes, thereby interrupting normal blood flow and leading to vascular ischemia, thrombosis, and disseminated intravascular coagulopathy (243). Upon adherence, these leukocytes become activated and release oxygen-free radicals, phospholipase A_2, prostaglandin E_2, and proteases and cause activation of complement (C5a). Together, these events contribute to endothelial cell damage (267). The released inflammatory mediators enhance the influx of neutrophils and cause the extravasation of blood leukocytes into surrounding tissues, thereby causing organ damage. In addition, the production of oxygen radicals and nitric oxide by activated leukocytes contributes to the ability of TNF-α to cause direct cytotoxicity in endothelial cells and to induce vasodilation and shock (67). Together these events cause loss of vascular tone and massive leakage of fluid from the intravascular to the interstitial space and hypotension. Multiple organ failure and increased capillary permeability are also major manifestations of toxic shock (242).

In addition to its direct effects, TNF-α also induces the release of other cytokines such as IL-1, IFN-γ, and TNF-β that mediate similar proinflammatory effects (31, 34, 56, 271). The effects of IL-1 and IFN-γ are also related to their ability to potentiate TNF-α activity. IL-1 is known to induce fever, acute-phase protein synthesis, and neutrophilia, and at high doses it can induce hypotension and shock (194). IL-1 has also been shown to induce neutrophil degranulation and superoxide production. The latter can induce lipid peroxidation and can alter endothelial cell membranes. IL-1 overproduction promotes adherence of leukocytes and stimulates endothelial cell production of prostaglandins and platelet-activating factor (57). Furthermore, IL-1 procoagulant activity increases the production of plasminogen activator inhibitor, thus promoting a decrease in blood flow and a further increase in the accumulation of leukocytes and platelets (57). Like TNF-α, IFN-γ and IL-1 activate the synthesis of nitric oxide, which is believed to contribute importantly to toxic shock (175). Thus, IFN-γ and IL-1 synergize with TNF-α in mediating the pathophysiologic manifestations of toxic shock. In addition, TNF-β probably plays an important role in superantigen-mediated shock. The kinetics of TNF-β release show that it lags behind TNF-α. Inasmuch as TNF-α and TNF-β share many biological activities, their temporal release may be an important mechanism in the pathogenesis of gram-positive toxic shock.

Because cytokines interact as a complex network, the temporal release of certain cytokines can have a great influence on the overall response. We have shown that in the presence of elevated IFN-γ, the superantigen-induced increase in IL-1, TNF-α, and IL-6 levels is sustained for a longer period of time (138). In addition, the production of TNF-β was found to be regulated by the levels of IFN-γ (138). Thus, the amount of IFN-γ released, which varies for different superantigens, can influence the outcome of infection by potentiating the levels and kinetics of release of other inflammatory cytokines. Furthermore, endogenous levels of certain cytokines may have a

profound effect on the outcome of an infection. For example, if a viral infection precedes and overlaps a bacterial infection, high levels of IFN-γ produced in the first assault may further augment and prolong the release of inflammatory cytokines in the second infection, thereby causing a more severe form of the disease. In fact, clinical studies have shown that individuals infected with varicella-zoster virus followed by group A streptococci experience a much more complicated clinical course than do those with either infection alone (179). Reports of fatal cases of strepTSS in infants who had chickenpox and then became infected with group A streptococci underscore the importance of studying the mechanism of superantigen-mediated toxic shock and trying to understand the influence of environmental factors such as viral infections, stress, and hormonal changes in these diseases (50, 81, 99).

The magnitude of the inflammatory cytokine response and consequently the extent of the systemic manifestations and severity of toxic shock are also influenced by the properties of the putative superantigen, as well as by the production of other virulence components by the bacteria. For example, streptolysin O, which is produced by all strains of *S. pyogenes*, synergizes with SPeA, which is only produced by certain strains, to augment the release of IL-1 and TNF-α (85). Thus, the biological effects of superantigens may be potentiated by other bacterial components, and together they can mediate severe disease.

Host factors appear to play an important role in the pathogenesis of superantigen-mediated toxic shock. For example, in strepTSS the same organism can be isolated from different individuals (siblings, contacts, etc.) who exhibit starkly distinct symptoms ranging from being completely asymptomatic or having a mild sore throat to suffering from a severe and complicated disease associated with multiple organ failure, hypotension, and shock. Therefore, there must be a strong host component in this disease. Inasmuch as cytokines play a pivotal role in mediating the pathogenesis of strepTSS, it is reasonable to assume that host genetic factors that regulate cytokine responses to superantigens will be important in determining disease severity and clinical outcome. Therefore, factors that influence the interaction with superantigens, including the host TCR repertoire, the type of MHC class II alleles expressed, and the ability to upregulate cytokine gene expression, can all modulate susceptibility to severe and complicated infections.

In addition to their ability to directly induce cytokine production, superantigens can contribute to the pathogenesis of toxic shock by other mechanisms. For example, toxic shock-associated vascular leakage can be caused by a direct cytotoxic effect of superantigens on endothelial cells (151, 195) as well as by an indirect mechanism involving cytokines and nitric oxide, as previously discussed (67). Superantigens can also greatly enhance host susceptibility to endotoxic shock either by synergizing with endotoxin to further augment the release of inflammatory cytokines or by associating with lipopolysaccharide to form lytic complexes that are lethal to immune cells (154).

It is clear from the above discussion that the pathophysiologic manifestations elicited by the pyrogenic superantigens will be influenced by the context of the infection as it relates to the type of pathogen, the nature of other virulence factors produced, and the existence of coincidental predisposing environmental factors such as an overlapping viral infection and that the interaction between these variables will be greatly influenced by host genetic factors. We know very little about host factors in these diseases and in-depth research is greatly needed in this area. Both host and bacterial factors must be taken into consideration in the design of anticytokine therapies for the effective treatment of septic shock. Administration of such therapies in the wrong host or at the wrong time may exacerbate rather than eradicate disease and may have adverse effects, with increased morbidity and mortality.

Superantigens and Autoimmunity

An infectious etiology has been either proven or suspected in a number of autoimmune diseases (reviewed in reference 136). It is believed that infection with certain organisms, particularly those that produce superantigens, can trigger autoimmunity in the susceptible host (186, 228). Several mutually nonexclusive mechanisms for postinfection autoimmunity have been proposed (reviewed in reference 136). These include the effect of mimicry epitopes shared between the host and pathogen and the ability of pathogen components to elicit inflammatory reactions that can cause abnormal processing and presentation of sequestered self-antigens through the upregulation of chaperones, heat shock proteins, costimulatory molecules, cell adhesion molecules, and MHC molecules or by altering cytokine regulatory networks. Several recent studies have suggested that superantigens may be involved in triggering or exacerbating autoimmune reactions (3, 4, 28, 48, 64, 74, 75, 111, 135, 136, 142, 162, 196, 217, 225). The proposed role of superantigens in autoimmunity involves their effect on T-cell proliferation and their ability to induce inflammatory cytokines and alter the cytokine regulatory network.

Studies have shown that autoreactive T cells exist in the blood of healthy individuals (44, 45, 291). Normally, these cells are either anergized or present in very low numbers, but they can potentially induce autoimmunity if activated beyond certain thresholds (280). The ability of superantigens to activate T cells solely on the basis of their Vβ type and regardless of the specificity of the TCR to antigen may cause the expansion of naturally occurring autoreactive T-cell clones, leading to a break in self-tolerance and triggering autoimmunity (3, 35, 64, 75, 135, 136, 142, 155, 292). In addition, as discussed above, the interaction of superantigens with MHC class II molecules can activate B cells and macrophages to secrete excessive amounts of inflammatory cytokines, release nitric oxide, express adhesion molecules, upregulate the expression of costimulatory molecules, and enhance tissue damage. Some of the inflammatory cytokines elicited by superantigen, including TNF-α and IFN-γ, can further augment these effects by increasing leukocyte adhesion and upregulating MHC expression. These reactions may lead to abnormal presentation of self-proteins and the activation of autoreactive T cells. In addition, the ability of superantigen to activate cells that express class II molecules on their surface has led to the suggestion that this may lead to polyclonal activation of B cells and the generation of autoantibodies (74).

Several autoimmune disorders, including rheumatic heart disease (276), rheumatoid arthritis (196, 237), multiple sclerosis (141, 192, 193, 240, 286, 287), and Graves disease (51), have been recently linked to superantigens. Scientists seeking proof for the role of superantigens in these diseases have examined the Vβ repertoire of T cells stimulated with candidate autoantigens and found evidence that the responding T cells are restricted in their Vβ gene usage (141, 165, 287). In addition, restricted TCR Vβ gene usage has been found in affected tissues in rheumatoid arthritis (104, 196, 237), multiple sclerosis (29, 141, 189, 192, 193, 214, 240, 286), Sjogren's syndrome (252), autoimmune thyroiditis (51), and psoriasis (157, 158). Skewed patterns of the Vβ repertoire have also been reported in patients with Kawasaki disease (155). However, despite compelling indirect evidence that superantigens are involved in autoimmunity, a direct link between a particular superantigen

and autoimmunity has only been made in a few cases. For example, the rheumatogenic streptococcal M-protein superantigens are believed to play a major role in the pathogenesis of rheumatic fever and rheumatic heart disease (18, 19, 246–248, 261, 276). Recent data from our laboratory suggest that T cells stimulated with rheumatogenic serotypes of M protein can proliferate in response to myocardial antigens, whereas unprimed T cells are unable to recognize these antigens. Therefore, superantigens can also be viewed as adjuvants enhancing the ability of T cells to respond to other microbial proteins that may mimic host antigens.

Any evaluation of the role of superantigens in autoimmunity should take into account the fact that these molecules differ in their potency of inducing T-cell proliferation and eliciting the production of inflammatory cytokines and that they may have starkly different in vivo effects (188). The in vivo administration of potent pyrogenic superantigens such SEB and SEA has been shown to cause deletion of superantigen-specific T cells (105, 110, 130, 131, 166, 211, 272, 273, 277). This effect, however, depends on the dose and persistence of the superantigen in the host and is likely to be affected by the magnitude of the cytokine response mounted by the infection. We hypothesize that the less potent superantigens, which can induce in vivo T-cell proliferation but not deletion, would be more likely to cause autoimmunity. Indeed, the streptococcal M proteins and the *M. arthriditis* mitogen superantigen, which in comparison to the pyrogenic exotoxins are considered milder superantigens, have been associated with autoimmunity in humans and rodents (48, 74, 75, 135, 136). In addition, TSST-1, which does not cause in vivo T-cell deletion (188) and results in expansion of specific Vβ-bearing T cells, has also been proposed to play a role in Kawasaki disease (156). TSST-1 has also been shown to exacerbate streptococcal cell wall-induced arthritis in rats (225). Similarly, under certain conditions even the very potent superantigens can also induce or exacerbate autoimmunity, particularly if they are produced at a low level in the host (28, 217). Supporting this view are several recent reports implicating streptococcal pyrogenic exotoxins in guttate psoriasis (157, 158).

Given the various mechanisms by which superantigens can arouse the immune system, it is reasonable to assume that they must play a role in autoimmunity, if not by directly breaking the tolerance of autoreactive T cells, then possibly by evoking conditions that allow recognition of autoantigens or exacerbation of an ongoing autoimmune inflammatory response. However, it is very restrictive to expect specific diseases to be linked to a particular superantigen. I propose that different superantigens that can initiate the same effect in the susceptible host would be equally capable of causing disease under the right conditions. Thus, the finding of different patterns of TCR Vβ restricted usage by T cells in autoimmune affected sites does not rule out a role for superantigen in disease; instead, it suggests the existence of common pathways of pathogenesis induced by superantigens that have similar effects. Clearly, more research is required to decipher the mechanisms by which superantigens are associated with specific autoimmune diseases. This fascinating area of investigation may uncover valuable information regarding the etiology of these diseases and offer novel and effective therapies.

Other Human Diseases That May Be Linked to Bacterial Pyrogenic Superantigens

Because of their multiple biological activities, superantigens have been implicated in a variety of other human diseases including AIDS (110, 148, 279), a number of lymphoproliferative diseases (reviewed in reference 142), and even silicone-induced autoimmunity (146). In addition, pyrogenic superantigens are suspected to play a role in sudden infant death syndrome (20, 176). Gram-positive infections, including streptococcal and staphylococcal infections, have been implicated in the pathogenesis of sudden infant death syndrome. Several groups have hypothesized that pyrogenic exotoxins produced by certain strains of *S. pyogenes* and *S. aureus* may induce immunological reactions that contribute to some cot deaths (20, 176). Cytokines released in response to these pyrogenic exotoxins can alter infant sleep patterns and induce deep sleep, resulting in failure to breath properly and causing death. Direct proof of these attractive hypotheses can be derived only from direct examination of blood and tissue samples obtained from these infants to determine whether there is any evidence of superantigen involvement.

THERAPEUTIC STRATEGIES IN SUPERANTIGEN-ASSOCIATED DISEASES

In most cases of staphTSS and strepTSS, early diagnosis leads to successful treatment with appropriate antibiotics. However, antibiotics can be totally ineffective once the acute manifestations are triggered, because these events are primarily mediated by the host immune response to the superantigens produced by the bacteria (243). In the advanced stages of the disease, therapies directed towards blocking the flared immune response may be more effective in ameliorating disease than those directed at the pathogen. However, the design of such therapeutic strategies requires adequate knowledge of host-bacterium interactions and a better understanding of the mechanism of pathogenesis of toxic shock.

It is logical to propose that anticytokine therapies would be quite effective for clinical intervention in superantigen-mediated shock. Given the central role of TNF-α in septic shock, it is possible that blocking its synthesis with drugs such as pentoxifylline or thalidomide or by the administration of soluble receptors or neutralizing antibodies that interfere with its ability to mediate its activity may halt disease progression and ameliorate the systemic manifestations of toxic shock (reviewed in references 243 and 251). Although TNF-α is pivotal in gram-negative and gram-positive shock, it is clear that the patterns of cytokines produced are different. Therefore, it is incorrect to assume that strategies used in the treatment of endotoxic shock can be extrapolated to the treatment of superantigen-associated shock. In addition, as mentioned above, effective therapeutic approaches must take into consideration individual variations in the response to superantigens or endotoxin. Failure to do so may have contributed to the fact that several cytokine-directed clinical trials have been unsuccessful and have been associated with severe adverse effects in some cases.

Blocking other mediators of shock such as nitric oxide may also have some benefit. In 1990, researchers at M. D. Anderson Cancer Center reversed septic shock in dogs by using analogs of L-arginine, a precursor of nitric oxide (133). Physicians in England administered methyl-Arg to patients with shock and reversed their symptoms (201). This approach may be useful alone or in combination with other anticytokine regimens.

In cases of severe group A streptococcal infections and strepTSS, the absence of neutralizing antibodies against superantigens has been correlated with severe forms of strepTSS (185). These studies suggest that perhaps a vaccine can be developed for use in outbreaks of these diseases. However, it is not always known which superantigen is more relevant to disease pathogenesis and therefore which vaccine would be more

effective. In addition, in most cases (as discussed above) minute amounts of superantigens can mediate their effects by synergizing with other virulence factors that also contribute to the disease process, and thus it may be equally important to neutralize their activity.

Another interesting recent approach involves the use of intravenous (i.v.) immunoglobulins for treatment of gram-positive toxic shock (255). The mode of action of i.v. immunoglobulins is not entirely clear, but there are several possible mechanisms. These i.v. immunoglobulin preparations have been shown to contain toxin-neutralizing antibodies and anti-cytokine antibodies (233, 255). Skansen-Saphir et al. (233) recently demonstrated the immunomodulatory potential of i.v. immunoglobulin on superantigen-induced T-cell activation and lymphokine production. Also, these i.v. immunoglobulin preparations contain soluble HLA molecules (21), and I would like to propose that these molecules may competitively inhibit the binding of superantigen to class II-positive APC, thereby interfering with their ability to induce the production of excessive amounts of inflammatory cytokines that are the major mediators of the pathophysiological manifestations of septic shock. This possibility needs to be investigated. To date, the use of i.v. immunoglobulins seems to be one of the most promising approaches for treatment of superantigen-associated shock, but more studies are needed to elucidate the mechanism and determine its efficacy when it is administered at different phases of the disease.

Although, as previously discussed, we have only indirect evidence that superantigens are involved in human autoimmune diseases, it is possible to speculate on therapeutic approaches that may halt the progression of these diseases. If a particular subset of Vβ-bearing T cells is suspected to play a role in the disease, then a logical approach would be to specifically target those cells by either physically or functionally eliminating them with anti-Vβ-specific antibodies or anti-Vβ-specific cytotoxic T cells (190, 270, 290, 291). Studies in experimental animal models indicate that these approaches may be valuable (190, 270, 290).

PYROGENIC SUPERANTIGENS AS CURES FOR HUMAN DISEASES

In 1990, Dohlsten et al. (62) made the interesting observation that the inclusion of the superantigen SEA in the T-cell cytotoxicity assay altered its target specificity. These investigators later went on to determine that superantigens can activate and direct T cells to eradicate class II-expressing cells (59, 91). The phenomenon was named superantigen-dependent cellular cytotoxicity (SDCC). T cells that express αβ TCR and certain subsets of γδ TCR cells are the sole mediators of SDCC (66). Consistent with the fact that superantigens can stimulate CD4 and CD8 cells, both T-cell subsets were found to mediate SDCC. By contrast, NK cells are unable to mediate SDCC, presumably because they lack the receptor for superantigen (145). The target structure for the SDCC phenomenon was determined to be the class II molecules, because antibodies that interfered with the binding of superantigen to class II also blocked SDCC (61, 70) and because class II-transfected fibroblasts but not untransfected cells were susceptible to T-cell lysis (124) (Fig. 5). The SDCC is remarkable because it can be induced by picomolar quantities of SEs, lysis occurs within minutes, and it can be maintained for several days (62, 91, 145). The activity is greatly enhanced when adhesion molecules such as ICAM-1 are upregulated on target cells (60, 274). SDCC was demonstrated in vivo following administration of SEA into rats or mice (88, 92). The preferential killing of cells

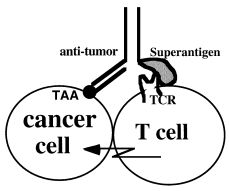

FIG. 5. Superantigen-directed, T-lymphocyte-mediated killing of tumor cells.

that have upregulated class II and adhesion molecules on their surface can cause complete destruction of potential APC, thereby downregulating immune reactions, including those that are directed against the pathogen.

Together, the above findings led some to propose that SDCC may be a mechanism by which certain pathogens can avert the immune system (59, 124, 132, 142, 163) (see below). However, scientists were quick to exploit this feature to the advantage of their species (58, 59, 123, 181, 187, 231). It was reasoned that the ability of superantigens to direct T-cell killing can be utilized as a therapeutic strategy in the treatment of autoimmunity and in the eradication of class II-expressing tumors. Recent evidence indicates the successful use of superantigens in treating experimental autoimmunity (132, 236) and in killing tumor cells in vivo (58, 59, 123, 181, 187, 231).

Inasmuch as SDCC is limited to class II-expressing cells, it can only be useful in killing class II-positive tumors. The use of superantigen in treatment of cancer has been further extended by the discovery that the target cell specificity can be redirected by conjugating the superantigen to a suitable monoclonal antibody with specificity to a particular tumor antigen (123). Chemical conjugates of SEA and two different colon carcinoma-reactive monoclonal antibodies, C215 and C242, were found to mediate T-cell-dependent destruction of colon carcinoma cells lacking MHC class II molecules (58, 123, 144, 274). These monoclonal antibody-superantigen conjugates retained their ability to induce SDCC and were competent in eradicating tumors in vivo (58, 92, 123, 144). Thus, the superantigen conjugate can stimulate T cells and in the meantime direct it to the tumor to mediate tumor-specific lysis. In addition, the ability of these conjugates to act like regular superantigens in inducing the production of cytokines further contributes to tumor cell lysis (63). This novel approach, widely known as superantigen-directed T-cell killing, may prove to be one of the most exciting new developments in cancer immunotherapy. The success of this approach has been shown in animal models, and recent data in humans are very encouraging (63).

WHY DO BACTERIA PRODUCE SUPERANTIGENS?

Certainly bacteria that produce superantigens did not evolve so that we can cure cancer or autoimmunity, although many microorganisms provide us with antibiotics that can eradicate many infectious diseases. At first glance, it may seem that the production of superantigen is quite detrimental to the organism because these molecules are potent inducers of immune responses. However, it is these potent immune responses that may, under certain conditions, act as bait, enabling the pathogen to take over the host. It has been proposed that superantigens allow the organism to avert the immune system by at least three mechanisms. First, the ability to induce SDCC would eliminate cells that can present microbial antigens and provide adequate costimulation for T-cell activation. SDCC is enhanced by inflammatory cytokines and the upregulation of adhesion molecules. Elimination of class II-expressing cells by

SDCC may render T cells anergic and incapable of responding to the pathogen. Second, the ability of superantigen to cause overproduction of inflammatory cytokines may allow them to induce specific apoptosis in T cells that have the appropriate Vβ elements for that superantigen. The third hypothesis is that the generation of a nonspecific immune response by the superantigen diverts attention from what would have been a specific response to the pathogen. These related hypotheses may not be far-fetched because the induction of SDCC, T-cell anergy, and the deletion of superantigen-specific T cells have all been shown to occur in vivo, and exposure to superantigen-producing bacteria has been associated with an immunosuppressive state. Superantigens may therefore render the host immunocompromised in preparation for a takeover by the organism, as is manifested in some cases of superantigen-associated toxic shock.

It should be emphasized that the effects of superantigen will vary considerably depending on the host and the interplay between individual immune systems and the pathogen. Thus, I caution the reader to avoid making generalized conclusions or to overestimate the role of these molecules, because not all superantigens behave the same and a particular superantigen may produce starkly diverse effects in different individuals. Carefully designed studies that simultaneously examine both host and pathogen will help us elucidate the significance of superantigens for the pathogen and the mechanism by which these molecules trigger disease.

CONCLUDING REMARKS

Superantigens are a fascinating group of molecules that have captured the attention of scientists from many different fields. Understanding their mode of action and structure-function relation will help reveal the underlying mechanisms in a number of diseases that have remained a mystery for years. It is important to realize that superantigens differ in their in vitro and in vivo effects on the immune system and that their biological activity may depend to a great extent on the host and environmental factors (e.g., coincidental viral infection, stress, or hormonal changes) that may potentiate its interaction with the host. Studying different superantigens has taught us a great deal about complex pathways of immune activation and regulation and provided important information that was not possible to retrieve with conventional antigens. It is anticipated that future studies will continue to take advantage of these fascinating molecules and will exploit them for therapeutic benefits.

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