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MINIREVIEW

Microbial "Superantigens"

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INTRODUCTION

Bacterial products, including bacterial exotoxins, can exert their immunomodulatory effects on various lymphoid cell populations (6; M. L. Misfeldt, Clin. Microbiol. Newsl. 9:21–24, 1988). These bacterial products, which modulate the host defense system, may play an important role in the overall pathogenesis of the organism. Numerous bacterial exoproteins have been shown to elicit nonspecific activation of lymphocytes derived from various mammalian species (6). Some of these bacterial exoproteins, at very low concentrations, have been shown to induce T-lymphocyte proliferation (6, 20). Since these bacterial exoproteins stimulate a large percentage of T cells, they have been considered T-cell mitogens rather than antigens. Yet, like antigens, these bacterial exoproteins require antigen-presenting cells bearing major histocompatibility complex (MHC) class II molecules to stimulate T cells (20).

The most prevalent antigen receptor on T lymphocytes is a heterodimer composed of α and β chains, referred to as the T-cell receptor (TCR). The ligand for this TCR is an antigen-derived peptide bound to or associated with the MHC protein. The specificity of the TCR for antigen-MHC is determined by the amino acid residues coded for by each of the genetic elements which make up the variable portions of the α and β chains (4). These variable elements include V_α, J_α, V_β, D_β, and J_β. Recently, several research groups identified mouse self antigens which, in combination with specific products of the mouse MHC, can form ligands that stimulate virtually all T lymphocytes that express particular V_β elements, with little regard for the contribution of the other variable elements (1–3, 27, 28, 30, 32). The term "superantigen" has been suggested for self antigens, such as the minor-lymphocyte-stimulating (Mls) gene products, and bacterial T-cell mitogens which at concentrations several magnitudes lower than those of conventional T-cell mitogens, phytohemagglutinin and concanavalin A, stimulate a large percentage of T cells to proliferate (40). One bacterial T-cell mitogen, staphylococcal enterotoxin B (SEB), has been extensively studied and shown to function as a superantigen (28, 40). Furthermore, a number of recent studies have revealed that several bacterial exoproducts which act as T-cell mitogens may be classified as superantigens based on certain common properties (11, 20).

GENERAL PROPERTIES OF BACTERIAL SUPERANTIGENS

The term superantigen has been suggested for proteins which can stimulate T cells bearing a particular V_β element of the TCR, regardless of the contribution of the other variable elements (40). The term superantigen was used originally to describe self antigens (Mls locus gene products) which function as T-cell stimulatory determinants. However, a number of bacterial exoproducts recently have been proposed to function as superantigens (11, 13–15, 17, 19, 20, 28, 34, 38, 40, 41). Bacterial exoproducts which have been considered superantigens are listed in Table 1. All of these bacterial exoproducts share several properties which provide the basis by which these molecules fulfill the general requirements for consideration as a superantigen. Superantigens resemble T-cell mitogens by stimulating a large proportion of T cells. However, these proteins share a property associated with antigens, as they require MHC class II-bearing antigen-presenting cells to stimulate T cells (20, 28, 41). Furthermore, the stimulation of T cells by superantigens can be blocked by the addition of antibodies to MHC class II molecules during culturing (39, 41). Since superantigens stimulate T cells that bear a particular V_β element of the TCR, antibodies to the appropriate V_β element can also inhibit the proliferation of T cells (20, 41). Finally, superantigens are capable of stimulating T cells that bear a particular V_β element regardless of other cell surface proteins. Thus, superantigens can stimulate both $CD4^+$ and $CD8^+$ cells (20, 41).

INTERACTION OF SUPERANTIGENS WITH MHC CLASS II MOLECULES

Bacterial exoproducts which function as T-cell mitogens require the participation of accessory cells (AC) which express MHC class II molecules (9, 11, 12, 14, 15, 18, 19, 21–23, 25, 26, 31, 34, 35, 37–39, 41). The capacity of different cell types to function as AC correlates with their expression of MHC class II molecules (22). Experiments by Mollick et al. showed that staphylococcal enterotoxin A (SEA) could bind to MHC class II molecules on Raji cells, a human B-cell line, but not to RJ2.2.5 cells, class II-negative mutants of Raji cells (35). In addition, these investigators showed that SEA could bind to HLA-DR1-transfected fibroblasts but not to untransfected fibroblasts (35). Uchiyama et al. observed that the binding of staphylococcal toxic shock syndrome toxin 1 (TSST-1) to HLA class II molecules on AC was required for T-cell activation. Furthermore, these investigators observed that TSST-1 could directly bind to murine MHC class II molecules (38). The importance of MHC class II molecules in superantigen stimulation of T cells is further supported by the observations that antibodies to MHC class II molecules block the proliferation of T lymphocytes induced by superantigens (39, 41). Thus, these results indicate that murine MHC class II molecules or human HLA class II molecules on AC may serve as binding sites for the superantigens.

This requirement for MHC class II molecules is not due to the immunological recognition of the processed superantigen in association with MHC class II molecules (19, 35, 38).

TABLE 1. Bacterial exotoxins or exoproducts known to function as superantigens

Toxin or product	Reference(s) or source
SEA	11, 12, 18, 21, 22, 26–29
SEB	11, 14, 21, 26–29, 39–41
Staphylococcal enterotoxin C1	11, 28, 29, 41
Staphylococcal enterotoxin C2	11, 14, 29
Staphylococcal enterotoxin C3	11, 29
Staphylococcal enterotoxin D	11, 29
Staphylococcal enterotoxin E	11, 14, 29
TSST-1	11, 14, 29, 37, 38
Staphylococcal exfoliative toxin	11, 14, 29
Streptococcal pyrogenic exotoxin A	17, 19
MAS	7–9, 15, 31, 33
PE	34

Experiments with paraformaldehyde-treated AC indicated that cellular processing of the superantigen was unnecessary. AC treated with paraformaldehyde were as effective in supporting T-cell activation by SEA and TSST-1 as were untreated AC (12, 21, 38). Thus, these data suggest that it is the intact toxin and not peptide derivatives of the toxin which is presented by AC, leading to T-cell stimulation. However, there have also been isolated reports which suggest that certain superantigens may require processing by AC to activate T cells. Bauer et al. (8) showed that the superantigen *Mycoplasma arthritidis* supernatant (MAS) requires processing by AC for T-cell stimulation. Agents which inhibit lysosomal function, such as chloroquine and ammonium chloride (NH_4Cl), or competitively inhibit proteases, such as leupeptin, were shown by these investigators to inhibit in a dose-dependent manner the proliferation of T lymphocytes induced by MAS. Thus, these investigators suggested that intracellular processing of the mitogen MAS must occur for AC to effectively present MAS to T cells, leading to their activation. Our laboratory has observed that *Pseudomonas aeruginosa* exotoxin A (PE) also requires processing by AC to induce T-cell activation. Treatment of AC with paraformaldehyde prior to the addition of PE eliminated the ability of PE to activate murine T lymphocytes (P. K. Legaard and M. L. Misfeldt, submitted for publication). However, AC which were allowed to process PE prior to paraformaldehyde fixation were fully capable of presenting processed PE to T lymphocytes, resulting in their proliferation (Legaard and Misfeldt, submitted).

Superantigens not only differ in their requirements for processing by AC but may also differ in the role of the cytokine(s) produced by AC in the induction of T-lymphocyte proliferation. Bauer et al. reported that the addition of human recombinant interleukin-1α (IL-1α) reconstituted the mitogenic effect of MAS for human T lymphocytes cultured with UV-irradiated AC (7). Therefore, IL-1 appeared to be involved in MAS-induced T-cell proliferation. IL-1 has also been reported to be involved in PE-induced T-lymphocyte proliferation (34). Our laboratory has observed that PE induced the production of IL-1 from adherent murine peritoneal macrophages, resulting in murine thymocyte proliferation (34). In addition, our laboratory has reported that antibody to IL-1α abrogated the murine thymocyte proliferation induced by PE, suggesting that murine thymocyte proliferation induced by PE is dependent on IL-1 (34). Thus, these results suggest that certain microbial superantigens require different AC functions.

The different functions of AC in the induction of T-lymphocyte proliferation by superantigens may be attributed to the differences in the superantigens themselves. The staphylococcal superantigens SEA, SEB, staphylococcal enterotoxin C, staphylococcal pyrogenic exotoxin A, and TSST-1, which have been cloned and sequenced, show significant DNA and amino acid homologies (10, 16). Fraser has shown that SEB directly competes with SEA for the same binding site on HLA-DR; this site is distinct from the peptide groove on MHC class II proteins (23). The structure of the superantigen MAS has not yet been elucidated, and its binding site on MHC class II proteins has not yet been determined. In contrast, PE has been cloned and sequenced (24). Furthermore, the structure of PE has been determined by X-ray crystallography (5). PE is an ADP-ribosyl transferase with a molecular mass of 66,000 daltons. PE has been shown to be internalized by receptor-mediated endocytosis, which may facilitate the processing of the molecule to generate a peptide fragment which could function as a superantigen (36; Legaard and Misfeldt, submitted). Therefore, future studies are needed to elucidate the regions and/or peptide fragments which function as the superantigen. It will also be important to determine whether all superantigens interact at the same time or at totally different sites on MHC class II molecules.

DEPENDENCE OF CLONAL EXPANSION ON THE V_β ELEMENT UTILIZED

In contrast to T-cell mitogens, e.g., the plant lectins concanavalin A and phytohemagglutinin, which have the ability to stimulate all T cells, bacterial superantigens stimulate only T cells which bear particular V_β elements within their antigen-specific αβ TCRs. In an initial study, White et al. reported that SEB stimulated murine T cells bearing predominantly the $V_\beta3$, $V_\beta8.1$, $V_\beta8.2$, and $V_\beta8.3$ elements in the αβ TCR (40). By using monoclonal antibodies specific for a particular V_β element or V_β family, these investigators were able to show that SEB stimulated the clonal expansion of particular V_β-bearing T cells. Furthermore, these same investigators constructed T-cell hybridomas which were selected for SEB responsiveness and showed that all of these hybridomas utilized either $V_\beta3$ or one of the $V_\beta8$ family elements in their αβ TCRs. These investigators also reported that SEB administered to mice at birth and every other day thereafter caused the disappearance of nearly all $V_\beta3^+$ and $V_\beta8^+$ cells in the treated mice, demonstrating that the tolerance to SEB was caused by clonal deletion of SEB-reactive T cells (40).

Numerous reports have indicated that other microbial superantigens may stimulate both murine and human T cells (11–15, 19–22, 26–29, 33, 38–41). As was initially observed for murine T cells, human T cells were also stimulated to

TABLE 2. Superantigens and known TCR ligand specificities

Superantigen	Murine V_β chain	Human V_β chain	Reference(s)
SEA	1, 3, 11	ND[a]	11
SEB	3, 7, 8.1, 8.2, 8.3, 11	12, 14, 15, 17	11, 14, 29
Staphylococcal enterotoxin C1	3, 7, 8.2, 8.3, 11	12	11, 29
Staphylococcal enterotoxin C2	3, 8.2, 8.3, 11	12, 14, 15, 17	11, 14, 29
Staphylococcal enterotoxin C3	3, 8.2, 11	12	11, 29
Staphylococcal enterotoxin D	3, 7, 8.1, 8.2, 8.3, 11	12	11, 29
Staphylococcal enterotoxin E	11	6.1, 6.2, 6.3, 8, 18	11, 14, 29
TSST-1	3, 4, 15	2	11, 14, 29
Staphylococcal exfoliative toxin	1, 3, 8.2, 10, 11, 15	2	11, 14, 29
Streptococcal pyrogenic exotoxin A	ND	ND	
MAS	6, 8.1, 8.2, 8.3	ND	15
PE	3, 5.1	ND	
Mls[a]	6, 8.1	ND	3, 32
Mls[c]	3	ND	3

[a] ND, Not determined.

proliferate by the superantigens, and the stimulation was shown to be limited to T cells bearing V_β elements (Table 2). The known murine and human T-cell V_β specificities are summarized in Table 2. Superantigens only stimulate T cells bearing particular V_β elements and are distinguished from each other by which V_β T cells they stimulate. Some superantigens may stimulate T cells bearing particular V_β elements that have not yet been reported. However, as V_β-specific reagents become more readily available and as new technologies such as polymerase chain reactions are utilized, we will be able to define exactly which V_β T cells are stimulated by a particular microbial superantigen (11, 14).

Bacterial superantigens stimulate a large percentage of T cells expressing particular V_β genes. However, even though this T-cell stimulation requires AC expressing MHC class II molecules, it is not restricted to $CD4^+$ cells. Staphylococcal enterotoxins have been observed to stimulate both $CD4^+$ T cells and $CD8^+$ T cells. Fleischer and Schrezenmeier reported that both human $CD4^+$ T-cell clones and human $CD8^+$ T-cell clones were stimulated to proliferate by SEA when MHC class II-bearing AC were present (21). Matthes et al. reported similar findings in their studies of the bacterial superantigen MAS which, in the presence of AC expressing MHC class II molecules, induced the proliferation of both human $CD4^+$ and human $CD8^+$ T-cell clones (33). Recent studies have reported that murine $CD4^+$ and $CD8^+$ T cells respond to the superantigens SEA, SEB, and MAS (26, 41). Thus, these results indicate that microbial superantigens stimulate T cells, in correlation with the expression of certain V_β gene segments (Table 2).

γδ-EXPRESSING T CELLS MAY ALSO BE CLONALLY EXPANDED

Although the majority of studies examining bacterial superantigens have focused on T cells expressing αβ TCR, some preliminary studies have been done with T cells lacking αβ TCR. Fleischer and Schrezenmeier (21) reported that an $\alpha\beta^-$ TCR^+ T-cell clone could respond to SEA in an MHC class II-dependent manner. In addition, Matthes et al. reported that human $CD3^+$, $CD4^-$, $CD8^-$, and γ^+ TCR T-cell clones responded to MAS (33). Although these represent very preliminary experiments, they suggest that T cells which express the alternative form of the TCR, γδ TCR, may respond to certain microbial superantigens. With the future development of specific γ and/or δ reagents, we should be able to enhance our understanding of γδ T cells, their role in the immune response, and their responsiveness to microbial superantigens.

ASSOCIATION OF SUPERANTIGENS WITH PATHOGENESIS

Bacterial exoproducts have been shown to function as biological response modifiers which can affect host immune defense mechanisms. These products can exert their activity by stimulating particular lymphoid cell populations. As detailed in this review, bacterial exoproducts can lead to the activation of T lymphocytes. This process requires the involvement of MHC class II-expressing AC and in certain situations may also involve cytokine production by AC. The role of AC is to present the antigen to T lymphocytes, resulting in their activation, as indicated by an increase in cytosolic calcium and second-messenger production (10, 17). Subsequently, T lymphocytes can express the appropriate receptors for growth factors, such as the interleukin-2 receptor, and produce lymphokines, including interleukin-2, interleukin-4, gamma interferon, and others, all of which have the capacity to affect the immune response in either a positive or a negative manner.

The immune modulation of T lymphocytes by microbial superantigens described in this review may represent one mechanism by which bacteria are able to influence the host immune response. The stimulation of T lymphocytes, which would lead to the production of large amounts of lymphokines, including interleukin-2, may render the host environment more conducive to bacterial growth. Another possibility is that these superantigens may activate certain populations of T lymphocytes to react against host tissues, leading to an autoimmune condition. Finally, in several mammalian species the T-cell repertoire may have been selected to recognize and respond to these microbial superantigens. With further study, we should gain a better understanding of the role of these superantigens in bacterial pathogenesis.

CONCLUSIONS

In summary, bacterial exoproducts can stimulate T lymphocytes bearing particular V_β elements within the TCR. The stimulation requires the presence of MHC class II-bearing AC. However, these microbial superantigens may require different AC functions. For staphylococcal toxins

such as SEA, SEB, and TSST-1, the role of AC may be to present the molecule to the appropriate T lymphocyte. In contrast, for MAS and PE, it appears that AC may be required to process the bacterial superantigen and present the antigen-derived peptide to the responding T cells. Furthermore, AC may also produce cytokines which are required for T-lymphocyte stimulation. Therefore, it would appear that a multitude of bacterial products can function as superantigens. We hope that further study of these powerful bacterially derived T-cell mitogens will help increase our understanding of the role of these bacterial superantigens in disease pathogenesis and enable researchers to develop better therapeutic approaches for bacterial disease intervention.

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