



Review

Superantigens and Their Role in Autoimmune Disorders

JOEL SCHIFFENBAUER

Department of Medicine, University of Florida College of Medicine, PO Box 100221, Gainesville, FL 32610-0221, USA

Abstract. The ability of superantigens to activate large numbers of T cells suggests that they may play a role in the course of autoimmune disorders. Data from several animal models of autoimmune disorders including experimental allergic encephalomyelitis and collagen induced arthritis supports this hypothesis. Administration of bacterial superantigens can induce an exacerbation of the autoimmune process in these models, or induce disease *de novo* in the appropriately immunized animal. Studies of several human disorders including rheumatoid arthritis, Kawasaki disease, insulin-dependent diabetes, and psoriasis lend credence to the concept that bacterial superantigens may play a role in the pathogenesis of these diseases. Nevertheless, in some cases, depending on the timing of administration and the model, superantigens may lead to an amelioration of the autoimmune process. Based on these results it seems logical to conclude that superantigens can have a significant impact on the course of the immune and autoimmune mediated disorders.

Key words: superantigen; staphylococcal enterotoxin; autoimmune; experimental allergic, encephalomyelitis.

Autoimmune disorders are the result of a complex interplay between environmental and genetic factors. Evidence to support the contribution of each can be found in a number of studies. For example studies of systemic lupus erythematosus show a 30–50% concordance of involvement of identical twins³. Although some genetic factors which contribute to a number of autoimmune disorders such as major histocompatibility complex (MHC) genes have been identified², others will certainly be discovered in the near future. However, environmental agents contributing to autoimmune processes have been difficult to identify. Clearly, specific drugs can induce a number of different autoimmune problems. These are usually easily identified. For example, drugs such as hydralazine or procainamide are known to cause a lupus-like illness in certain predisposed individuals⁵⁹.

It has been more difficult to document the contribution of infectious agents to the development of autoimmune processes. The contribution of hepatitis C to

cryoglobulinemia or hepatitis B to the development of polyarteritis nodosa, a systemic vasculitis, has been demonstrated^{4, 11, 57}. However, the potential contribution of infectious agents to other autoimmune disorders is not well understood and the exact mechanisms by which these agents may lead to a breakdown in tolerance has not been worked out. Several theories have been suggested to explain the possible contribution of infectious agents to autoimmunity¹⁰. First, an individual may not possess the appropriate MHC class II molecule to allow immune recognition of antigens expressed by the infectious agent, leading to a chronic infectious state and progressive destruction of any affected organ. Alternatively, if the immune system can recognize the infectious agent as foreign but cannot clear the infection, then a chronic infection may lead to organ damage. In this regard, an infection may initiate the immune response which through molecular mimicry leads to an immune response against a self antigen.

More recently attention has focused on the ability of bacteria and viruses to contribute to the autoimmune process through their ability to produce proteins termed "superantigens". The term "superantigen" was first used by MARRACK and KAPPLER³² to describe the ability of these agents to activate large number of T cells in a V β restricted manner. Although superantigens may be the products of either viruses or bacteria, this discussion will focus on bacterial superantigens. This is not to say that viral superantigens cannot be involved in autoimmune disorders. However, most of the work examining the relationship of superantigens to autoimmunity involves the study of bacterial superantigens.

Superantigens differ in several important ways from conventional antigens²⁶: 1) superantigens elicit strong primary responses; 2) the V β chain is sufficient for recognition of a superantigen. This allows for upwards of 20–30% of T cells to be activated by a single superantigen; 3) although MHC class II molecules are required for presentation of superantigens to T cells, the T cell response is not class II restricted in the sense that superantigens can bind to several different class II molecules; and 4) superantigens do not have to be processed in order to be recognized by the T cell.

Considerable evidence demonstrates the ability of superantigens to profoundly influence the immune system by activating T cells, B cells, and macrophages with the subsequent release of inflammatory cytokines. Indeed because of these profound effects on the immune system, superantigens may influence the development of autoimmune disorders through a number of different mechanisms. For example, superantigens may activate autoreactive T cells. This may occur *de novo* in an individual without previous evidence of autoimmunity. Alternatively, superantigens may lead to a recrudescence of disease in an individual with a pre-existing autoimmune disorder who already possesses autoreactive T cells. Once activated these T cells may continue to proliferate in the presence of autoantigens leading to a chronic autoimmune disorder. Repeated exposure to the superantigen may lead to significant clinical relapses of the autoimmune disorder. In a related mechanism, an individual may be exposed to an infectious agent that contains both an antigen that acts as a molecular mimic as well as a superantigen that can further activate the autoreactive T cell. In this scenario neither the peptide nor the superantigen alone are sufficient to induce an autoimmune process. However, the combination may lead to the initial activation of autoreactive T cells with subsequent amplification by the superantigen. Therefore in the above scenarios, super-

antigens can either initiate or reactivate an autoimmune disorder. Indeed, we have demonstrated (see below) that superantigens can reactivate autoimmune experimental allergic encephalomyelitis (EAE) when administered to an animal that has recovered from an acute episode of clinical illness⁴⁴. However, one confounding problem with this scenario is that besides activating T cells, superantigens have the ability to delete T cells or induce anergy in these cells¹⁷. In spite of this we were able to administer superantigens to mice on multiple occasions and reactivate EAE each time⁴⁴. In summary, from a clinical standpoint it seems likely that in the appropriately predisposed individual superantigens can activate autoreactive T cells leading to their expansion with subsequent release of cytokines and development of autoimmunity. Therefore, superantigens could initiate autoimmune disorders *de novo*, or they could lead to a worsening of the autoimmune process in an individual who already has active disease.

A second mechanism by which superantigens may induce disease is by the activation of autoreactive B cells with secretion of autoantibodies leading to an immune complex disorder. This process could occur through the activation of T cells leading to cognate T-B cell interactions with release of cytokines and activation of the B cell¹⁰. Alternatively, superantigens may activate B cells through the interaction with MHC class II molecules^{36, 55}. This mechanism could also lead to the activation of macrophages (see below), and in either case lead to the enhanced presentation of autoantigens. As a consequence of B cell activation autoantibody production may lead to immune complex formation, complement deposition, and subsequent tissue damage.

Third, superantigens may activate antigen presenting cells that leads to the processing of autoantigens and the presentation of peptides potentially derived from cryptic epitopes, to autoreactive T cells with the subsequent release of multiple inflammatory mediators by both the T cell and the activated macrophage. Indeed, superantigens have been demonstrated to induce the release of IL-12 by macrophages which plays a key role in the development of Th1 responses⁴⁸. Furthermore, IL-12 has been demonstrated to be essential for the generation of autoreactive Th1 cells that induce EAE, and administration of IL-12 to Lewis rats that have recovered from an episode of EAE was found to lead to a clinical relapse^{21, 49}. Other microbial products such as lipopolysaccharide (LPS) or bacterial DNA can convert quiescent myelin basic protein (MBP) specific T cells into effector cells capable of transferring disease⁴⁶. Of course the possibilities discussed above are not mutually exclusive, and it is likely that superanti-

gens induce a cascade of processes that ultimately results in the development of autoimmunity.

The previous discussion can serve as a basis for understanding the potential role of superantigens in the pathogenesis of autoimmune disorders. The discussion that follows will present available data relating the role of superantigens in autoimmune of processes in both humans and animal models of autoimmune disorders. As will be seen, the role for superantigens in various animal models of autoimmunity is clear. However, the role of superantigens in the pathogenesis of human disorders is for the most part circumstantial.

While there is no evidence that superantigens play a role in the development of multiple sclerosis (MS) in humans, there is considerable data supporting the potential role of bacterial superantigens in the exacerbation of EAE in mice. Our group examined the effects of administration of staphylococcal enterotoxin B (SEB) to PL/J mice that had recovered from a clinical episode of EAE⁴⁴. SEB was able to induce a clinical relapse in these mice and we initially postulated that this was likely to be due to the ability of SEB to activate V β 8⁺ T cells which are known to play a role in the development of EAE in these mice. To our surprise, another superantigen SEA was also able to induce a clinical relapse in these mice even though SEA does not activate V β 8⁺ T cells. We then postulated that non-V β 8⁺ T cells must be present in the central nervous system (CNS) lesions in these mice, and that activation of any resident T cells could lead to the production of inflammatory cytokines in an antigen non-specific manner with resultant demyelination. In retrospect, clinical relapse could also be secondary to activation of class II positive microglia or macrophages with release of IL-12 and activation of autoreactive T cells. Interestingly, we also showed that superantigens were capable of inducing disease in mice immunized with major basic protein (MBP) but who never developed clinical evidence of EAE in the first place. Again, we suggested one of two possibilities: 1) either that these mice had subclinical lesions in their CNS and that resident T cells were activated with superantigen, or 2) that immunization with MBP led to the development of autoreactive T cells, although a threshold for disease induction was not met. Administration of superantigen then led to the sufficient expansion of a subset of autoreactive cells to produce clinical EAE. More recently we demonstrated that the course of EAE could be accelerated by pretreating mice with SEB before immunization with MBP⁵⁰. Mice pretreated with SEB did not initially develop EAE. However if mice were then treated with SEA, they developed EAE after only about

3 days (instead of the usual 12–14 days). In a related study DAS et al.⁹ demonstrated that (PL/J $\times$ SJL) F1 mice pre-treated with SEB and immunized with proteolipid protein (PLP) peptide 43–64, had an increased severity of EAE and developed a chronic illness.

Therefore, based on our animal studies we believe that superantigens are capable of activating autoreactive T cells and contributing to the development of autoimmune disorders such as MS. In this regard, one possibility to consider is that individuals with an established autoimmune illness such as MS but who are otherwise in remission may be induced to develop an acute clinical flare after a clinical or subclinical infection with the appropriate superantigen containing organism. Alternatively, patients with active disease may have a worsening of their disease after an infection. In either case, the physician would recognize this as a flare of the autoimmune process, but may not recognize the inciting event, that is the infection. In this regard, we found that reactivation of EAE in mice often followed administration of superantigen by several days and often up to a week. Based on this it certainly seems possible that infections with superantigen producing bacteria could precede a flare of MS by some period of time and not be recognized by the clinician.

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by an inflammatory arthritis. Mononuclear cells composed of CD4⁺ lymphocytes and plasma cells initially accumulate around blood vessels although it also appears that macrophages are involved in the disease process^{20, 56, 57}. To examine the potential contribution of superantigens to the development of RA two groups studied the T cell receptor (TCR) V β usage in patients with RA. PALIARD et al.³⁸ reported that RA patients examined had a lower percentage of V β 14 positive T cells in the periphery than in synovial fluid. An examination of junctional sequences of the V β 14 TCR's revealed that one or a few clones of T cell dominated the V β 14 population in synovial fluid. Taken together, this data suggests that a superantigen specific for V β 14⁺ T cells was able to activate these T cells and that a subset of V β 14⁺ T cells crossreacts with a joint antigen. These activated autoreactive T cells would eventually migrate to the joint and produce a local inflammatory process. This proposed mechanism would account both for the relative absence of V β 14⁺ T cells in the periphery, since superantigens are known to lead to the deletion of T cells after activation, as well as to the increase in oligoclonal V β 14⁺ T cells in the joints.

In a second paper, HOWELL et al.¹⁵ also examined V β usage in RA patients. However, this group analyzed

IL-2 receptor positive T cells with the idea that autoreactive T cells in the joints would be activated spontaneously. Three gene families were found in a majority of the synovial samples analyzed. Given that in many instances the V β repertoires were dominated by a single rearrangement and given the sequence similarity between these V β 's, the authors postulated that superantigens could account for these findings.

In a somewhat different approach, HE et al.¹³ demonstrated that superantigens could stimulate B cells to produce rheumatoid factors. SED but not SEC or anti-CD3 was able to preferentially stimulate the production of rheumatoid factors. Several *in vitro* studies demonstrated the ability of superantigens to activate synovio-cytes, induce the expression of various chemokines and act as potential antigen presenting cells secondary to the induction of class II molecules^{33, 35, 37}.

A number of animal studies support the concept that superantigens may be involved in the development of autoimmune arthritis. COLE et al.⁶ demonstrated the ability of the superantigen mycoplasma arthritidis mitogen (MAM) to cause a recurrence of arthritis using the collagen induced arthritis (CIA) model of RA. In a similar manner to studies in EAE, mice that had recovered from CIA were given a dose of MAM and developed an exacerbation of their arthritis. Again in a fashion analogous to the EAE work, mice given a suboptimal immunization of collagen developed clinical arthritis to the EAE work, mice given a suboptimal immunization of collagen developed clinical arthritis when challenged with MAM. In the bacterial cell wall arthritis model, the superantigen toxic shock syndrome toxin (TSST-1) was able to induce a recurrence of arthritis characterized by prolonged inflammation, pannus formation, and marginal erosions⁴⁵. Finally, V β 8 transgenic mice carrying the *lpr* gene developed histological evidence of villus formation with erosions and destruction of cartilage and bone after intra-articular administration of SEB³⁴.

In summary, it can be concluded from these studies that superantigens can exacerbate disease in animal models. However, the evidence for the relationship of superantigens and RA or MS for that matter, is much more tenuous. For RA circumstantial evidence from V β usage suggests that superantigens may play a role in either the initiation or exacerbation of disease. Unfortunately there are no studies directly linking the presence of a superantigen producing bacteria and RA. Without this evidence the hypothesis that superantigens contribute to the pathogenesis of RA remains unsupported, although intriguing.

One of the more interesting stories relating super-

antigens to autoimmune disease is that of Kawasaki disease (KD). Kawasaki disease is an acute febrile illness characterized by persistent fevers associated with conjunctival injection, redness of the palms or soles, redness of the lips and oral mucosa, edema of the hands, cervical adenopathy, and a skin rash. A pancarditis may develop acutely and coronary aneurysms may lead to sudden death. Although the cause is unknown, the epidemiology suggests an infectious etiology. KD is associated with elevated serum levels of inflammatory cytokines including IL-1 and 6, TNF- α and IFN- γ . Activated T cells as well as macrophages may be found in the lesions of KD patients^{22, 28}. Interestingly, intravenous immunoglobulin (IVIG) has been used as a treatment for toxic shock syndrome (TSS) and KD. TAKEI et al.⁵³ was able to demonstrate that preparations of IVIG were able to inhibit activation of T cells by superantigens *in vitro*²³.

Several studies have examined the potential contribution of superantigens to the development of KD. ABE et al.¹ examined V β expression in patients with acute or convalescent KD. Using quantitative PCR, analyses revealed significantly elevated levels of circulating V β 2⁺ T cells compared to control populations during the acute phase, while there was observed a reduction during the convalescent phase. This was confirmed with an anti-V β 2 antibody by the same group and also confirmed in an independent study⁸. Sequencing of V β 2 TCR revealed extensive junctional diversity suggesting activation of these cells by a superantigen. By comparison, TSS which is known to be caused by a superantigen and which is manifest by fever and rash with desquamation, also shows a selective expansion of V β 2⁺ T cells during the acute phase⁵. Taken together, the above results strongly suggest that superantigen activation of the immune system leads to the development of KD in some individuals.

To further examine the relationship between superantigens and KD, LEUNG et al.²⁷ attempted to identify whether patients with KD harbored superantigen producing bacteria. This group was able to isolate *Staphylococcus aureus* producing TSST from 11/16 KD patients but only 1/15 controls. Of significance is that TSST can activate V β 2⁺ T cells. In addition, LEUNG et al.²⁴ identified a selective expansion of V β 2⁺ T cells in the myocardium of a patient who died of acute KD. Both CD4 and CD8⁺ T cells showed extensive junctional diversity.

Although the above studies are quite compelling for the association of superantigens and KD, there are 2 studies that could not document the contribution of superantigens to KD arguing against the hypothesis that

superantigen mediates KD^{39, 43}. However, there were several differences between the various studies including different populations studied, different methods for collecting blood samples, different timing of collection of samples (acute vs convalescent), whether T cells were activated *in vitro* before analysis, and finally use of PCR vs flow cytometry to analyze V β 2⁺ T cell populations. In spite of these potential problems the similarities between KD and TSS makes the concept of superantigen induced KD very appealing.

There is data to suggest that several other autoimmune disorders including insulin dependent diabetes mellitus (IDDM), Wegener's granulomatosis, and psoriasis may be influenced by exposure to superantigens. A brief discussion of these will follow here. First, IDDM is characterized by autoimmune T cell mediated destruction of the beta islets of the pancreas although no specific V β 's have been associated with the disease. However, CONRAD et al⁷ examined the islet infiltrating T cells from two IDDM patients and identified a selective expansion of V β 7⁺ T cells which exhibited extensive junctional diversity and were associated with unselected V α chains. These data suggest that superantigens may play a role in the development of IDDM in humans.

Our group (SCHIFFENBAUER and ATKINSON, unpublished data) attempted to influence the course of diabetes in the NOD mouse by administering superantigens to mice at either 4 or 10 weeks of age, at a time when insulinitis is either just beginning (4 weeks) or is well established (10 weeks). However, we were unable to induce either a more severe disease or a more rapid onset of disease (see below).

Wegener's granulomatosis is a systemic disorder characterized by a necrotizing granulomatous vasculitis of the respiratory tract and kidneys. An infectious cause has long been considered but not proven, although some reports suggest that antibiotics such as sulfamethoxazole-trimethoprim may be beneficial in early or mild disease. STEGEMAN et al.⁷² prospectively examined whether chronic nasal carriage of *S. aureus* was a risk factor for relapses of Wegener's. They followed a group of 57 patients with Wegener's for 1–3.5 years and found that chronic nasal carriage of *S. aureus* was an independent risk factor for relapses. However, they did not identify whether the *S. aureus* were producing superantigens nor did they look at V β usage in peripheral or lesional T cells. This work is certainly provocative, in the sense that it suggests that although superantigens may not initiate disease they may lead to relapses of immune mediated disorders. This concept is reminiscent of our finding of relapses of EAE with SEB

administration. Besides Wegener's granulomatosis, lung complications occur in several other autoimmune disorders including SLE and polymyositis. One group demonstrated that intratracheal administration of SEB to autoimmune MRL-lpr/lpr mice and normal AKR mice resulted in the development of interstitial pneumonia manifested by mononuclear infiltration of alveolar septal walls along with an increase in pulmonary interstitial collagen⁴⁷.

The last disorder for discussion is that of psoriasis. Psoriasis is a skin disorder characterized by increased proliferation of epidermal cells associated with an inflammatory component comprised of neutrophils, T cells, macrophages and keratinocytes expressing MHC class II molecules. There are several findings that suggest that infections may play a role in the development of this disorder. First, about 50% of patients carry *S. aureus* on their skin³¹. Second, patients with a form of psoriasis called guttate psoriasis, often have flares of disease associated with streptococcal infections^{14, 25, 58}. These patients may improve with antibiotics⁴¹. Third, intradermal injection of streptococcal antigens may induce psoriatic lesions⁴⁰. Taken together, these data suggest that bacterial infections may play a role in psoriasis and one mechanism suggested was through the production of superantigens by the appropriate strain of bacteria.

To further examine this question, LEUNG et al.²⁹ examined the V β usage of T cells found in psoriatic plaques and compared it to the superantigen produced by the cultured bacteria from the same patient. In both cases the V β expansion found in skin biopsies correlated with the superantigen elaborated by the bacteria. In contrast the peripheral blood did not demonstrate any expansion of the same B β subsets.

In a second paper, V β usage was examined in patients with guttate or chronic plaque psoriasis³⁰. Using flow cytometry investigators were able to identify an overrepresentation of V β 2 and V β 5⁺ T cells in the lesions. However, no attempt was made to examine the potential production of superantigens by bacteria isolated from these patients. Taken together, the data suggest that superantigens may activate T cells that lead to the development of psoriasis. This may involve superantigen activation of T cells resident in plaques leading to the persistence of lesions. Alternatively, superantigens may initiate psoriasis by activating autoreactive T cells that cross-react with skin antigens.

Although, the above discussion has focused on the ability of superantigens to initiate or exacerbate autoimmune processes because of their ability to activate large numbers of T cells, there is an additional com-

plexity to this story. Superantigens also have the ability to delete or anergize T cells. Based on this characteristic one would predict that superantigens could potentially prevent autoimmune disorders. Indeed, a number of animal studies have demonstrated that superantigens can be used to prevent or treat autoimmune disorders. For example, our group showed that SEB administered prior to immunization with MBP could protect mice from developing EAE⁵¹. It appeared that the mechanism of protection was the induction of anergy and/or deletion of V β 8⁺ T cells. KALMAN et al.¹⁶ also found a reduction in EAE after treatment with SEB, and similar results were obtained by treating Lewis rats with SEE⁴².

KAWAMURA et al.¹⁸ treated NOD mice with either SEA or SEC at 4, or at 4 and 10 weeks of age and by 32 weeks of age there was a significant reduction in the incidence of diabetes with treatment. As mentioned earlier, we also examined the effects of superantigens on the course of diabetes in the NOD mouse. However, we administered SEB at either 4 or 10 weeks of age. We initially hypothesized that superantigen administered to NOD mice after the onset of insulinitis would lead to an acceleration of the disease because of the activation of T cells in the islets. Surprisingly, we found that SEB administered at 10 weeks of age actually delayed the onset of overt diabetes, although by 20 weeks of age all groups of mice, treated or untreated, had developed diabetes to a similar extent. Therefore, unlike EAE where SEB was able to induce a clinical relapse, SEB not only did not exacerbate diabetes, but seemed to delay the onset of clinical disease even when given after the onset of insulinitis.

KIM et al.¹⁹ treated MRL-lpr/lpr mice, which develop a lupus like disorder, with SEB starting at 6 weeks of age. They were able to demonstrate reduced autoantibodies, proteinuria, and lymph node hyperplasia in treated mice, although no mention of an alteration in mortality was made. GONZALO et al.¹² demonstrated that a single injection of SEB was accompanied by a significant reduction in autoantibodies, arthritis, and nephritis.

Together these studies suggest that the effects of superantigens on autoimmunity will differ depending on the model studied as well as the timing of administration and on which superantigen is used. Based on the ability of superantigens to favorably alter the course of spontaneous autoimmune processes in the NOD and MRL mouse models, superantigens may yet have a place in the treatment of these and other disorders in humans.

We have presented evidence that superantigens possess the ability to initiate or exacerbate autoimmune

disorders. In most instances of human disease the evidence that superantigens have an impact on the autoimmune process is circumstantial. With the exception of KD where there appears to be good evidence that superantigens are involved in the pathogenesis of the disorder, there is no firm evidence to support the direct role of superantigen in the development of autoimmunity in humans. On the other hand, evidence from animal models clearly demonstrates the potential that superantigens have for exacerbating an autoimmune process. Based on this data, it certainly seems reasonable to conclude that superantigens will play some role in human disorders. We believe it is most likely that superantigens are capable of leading to an exacerbation of a pre-existing illness and not necessarily of initiating an autoimmune disorder *de novo*. If this is indeed proven to be the case, then therapies aimed at eliminating these bacterial agents or neutralizing the products of these bacteria will likely have a significant impact on the course and treatment of autoimmune disorders in humans.

References

1. ABE J., KOTZIN B. L., JUJO K., MELISH M. E., GLODE M. P., KOHSAKA T. and LEUNG D. Y. M. (1992): Selective expansion of T cells expressing T cell receptor variable region V β 2 and V β 8 in Kawasaki disease. *Proc. Natl. Acad. Sci. USA*, **89**, 4066–4070.
2. ARNETT F. C. and SHULMAN L. E. (1976): Studies in familial systemic lupus erythematosus. *Medicine*, **55**, 313–320.
3. BLOCK S. R., WINFIELD J. B., LOCKISHIN M. D., D'ANGELO W. A. and CHRISTIAN C. L. (1975): Studies of twins with systemic lupus erythematosus. *Am. J. Med.*, **59**, 533–551.
4. CACOUB P., FABIANI F. L., MUSSET L., PERRIN M., FRANGEUL L., LEGER J. M., HURAUX J. M., PIETTE, J. C. and GODEAU P. (1994): Mixed cryoglobulinemia and hepatitis C virus. *Am. J. Med.*, **96**, 124–131.
5. CHOI Y., LAFFERTY J. A., CLEMETS J. R., TODD J. K., GELFAND E. W., KAPPLER J., MARRACK P. and KOTZIN B. L. (1990): Selective expansion of T cells expressing V β 2 in toxic shock syndrome. *J. Exp. Med.*, **172**, 981–984.
6. COLE B. C. and GRIFFITHS M. M. (1993): Triggering and exacerbation of autoimmune arthritis by the mycoplasma arthritis superantigen MAM. *Arthritis Rheum.*, **36**, 994–1002.
7. CONRAD B., WELDMANN E., TRUCCO G., RUDERT W. A., BEHBOO R., RICORDI C., RODRIGUEZ-RILO H., FINEGOLD D. and TRUCCO M. (1994): Evidence for superantigen involvement in insulin-dependent diabetes mellitus aetiology. *Nature*, **371**, 351–355.
8. CURTIS N., ZHENG R., LAMB J. R. and LEVIN M. (1995): Evidence for a superantigen mediated process Kawasaki disease. *Arch. Dis. Child.*, **72**, 308–311.
9. DAS M., COHEN A., ZAMVIL S. S., OFFNER H. and KUCHROO V. K. (1996): Prior exposure to superantigen can inhibit or exacerbate autoimmune encephalomyelitis: T cell repertoire engaged by the autoantigen determines clinical outcome. *J. Neuroimmunol.*, **71**, 3–10.

10. FRIEDMAN S. M., POSNETT D. N., TUMANG J. R., COLE B. C. and CROW M. K. (1991): A potential role for microbial superantigen in pathogenesis of systemic autoimmune disease. *Arthritis Rheum.*, **34**, 468–480.
11. GÖCKE D. J., MORGAN C., LOCKSHIN M., HSU K., BOMBARDIERI S. and CRISTIAN C. L. (1970): Association between polyarthritis and Australia antigen. *Lancet*, **5**, 1149–1152.
12. GONZALO J., TARAZONA R., SCHUURMAN H., UYTDEHAAG F., WICK G., MARTINEZ C. and KROEMER G. (1994): A single injection of *Staphylococcus aureus* enterotoxin reduces autoimmunity in MRL/lpr mice. *Clin. Immunol. Immunopathol.*, **71**, 176–182.
13. HE X., GORONZY J. and WEYAND C. (1991): Selective induction of rheumatoid factors by superantigens and human helper T cells. *J. Clin. Invest.*, **89**, 673–680.
14. HENDERSON C. A. and HIGHET A. S. (1988): Acute psoriasis associated with Lancefield group C and group G cutaneous streptococcal infections. *Br. J. Dermatol.*, **118**, 559–562.
15. HOWELL M. D., DIVELEY J. P., LUNDEEN K. A., ESTY A., WINTERS S. T., CARLO D. J. and BROSTOFF S. W. (1991): Limited T-cell receptor β -chain heterogeneity among interleukin 2 receptor-positive synovial T cells suggests a role for superantigen in rheumatoid arthritis. *Proc. Natl. Acad. Sci. USA*, **88**, 10921–10925.
16. KALMAN B., LUBLIN F. D., LATTIME E., JOSEPH J. and KNOBLER R. L. (1993): Effects of staphylococcal enterotoxin B on T cell receptor V β utilization and clinical manifestations of experimental allergic encephalomyelitis. *J. Neuroimmunol.*, **45**, 83–88.
17. KAWABE Y. and OCHI A. (1990): Selective anergy of V β 8⁺, CD4⁺ T cell in staphylococcal enterotoxin B-primed mice. *J. Exp. Med.*, **2**, 1065–1070.
18. KAWAMURA T., NAGATA M., UTSUGI T. and YOON J. W. (1993): Prevention of autoimmune type I diabetes by CD4⁺ suppressor T cells in superantigen-treated non-obese diabetic mice. *J. Immunol.*, **151**, 4362–4370.
19. KIM C., SIMINOVITCH K. A. and OCHI A. (1991): Reduction of lupus nephritis in MRL/lpr mice by a bacterial superantigen treatment. *J. Exp. Med.*, **174**, 1431–1437.
20. KINGSLEY G. and PANAYI G. S. (1997): Joint destruction in rheumatoid arthritis: biological bases. *Clin. Exp. Rheumatol.*, **15** (suppl. 17), S3–14.
21. LEONARD J. P., WALDBURGER K. E., SCHAUB R. G., SMITH T., HEWSON A. K., CUZNER M. L. and GOLDMAN S. J. (1997): Regulation of the inflammatory response in animal models of multiple sclerosis in interleukin 12. *Crit. Rev. Immunol.*, **17**, 545–553.
22. LEUNG D. Y. M. (1990): Immunologic aspects of Kawasaki syndrome. *J. Rheumatol.*, **24**, 15–18.
23. LEUNG D. Y. M., BURNS J. C., NEWBURGER J. W. and GEHA R. S. (1987): Reversal of lymphocyte activation *in vitro* in the Kawasaki syndrome by intravenous gammaglobulin. *J. Clin. Invest.*, **79**, 468–472.
24. LEUNG D. Y. M., GIORNO R. C., KAZEMI L. V., FLYNN P. A. and BUSSE J. B. (1995): Evidence for superantigen involvement in cardiovascular injury due to Kawasaki syndrome. *J. Immunol.*, **155**, 5018–5021.
25. LEUNG D. Y. M., HARBECK R., BINA P., REISER R. F., YANG E., NORRIS D. A., HANIFIN J. M. and SAMPSON H. A. (1993): Presence of IgE antibodies of staphylococcal exotoxin on the skin of patients with atopic dermatitis. *J. Clin. Invest.*, **92**, 1374–1380.
26. LEUNG D. Y. M., HUBERT B. T. and SCHLIEVERT P. M. (1997): Historical perspective of superantigens and their biological activities. In: *Superantigens*. Marcel Dekker, New York, 1–13.
27. LEUNG D. Y. M., MEISSNER H. C., FULTON D. R., MURRAY D. L., KOTZIN B. L. and SCHLIEVERT P. M. (1993): Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet*, **342**, 1385–1388.
28. LEUNG D. Y. M., SIEGEL L., GRADY S., KRENSKY A., MEADE R., REINHERZ E. L. and GEHA R. S. (1982): Immunoregulatory abnormalities in mucocutaneous lymph node syndrome. *Clin. Immunol. Immunopathol.*, **23**, 100–112.
29. LEUNG D. Y. M., WALSH P., GIORNO R. and NORRIS D. A. (1993): A potential role for superantigens in the pathogenesis of psoriasis. *J. Invest. Dermatol.*, **100**, 225–228.
30. LEWIS H. M., BARKER B. S., BOKTH S., POWLES A. V., GARIOCH J. J., VALDIMARSSON H. and FRY L. (1993): Restricted T-cell receptor V β gene usage in the skin of patients with guttate and chronic plaque psoriasis. *Br. J. Dermatol.*, **129**, 514–520.
31. MARPLES R. R., HEATON C. L. and KLIGMAN A. M. (1973): *Staphylococcus aureus* in psoriasis. *Arch. Dermatol.*, **107**, 568–570.
32. MARRACK P. and KAPPLER J. (1990): The staphylococcal enterotoxins and their relatives. *Science*, **248**, 705–711.
33. MEHINDATE K., AL-DACCAR R., SCHALL T. J. and MOURAD W. (1994): Induction of chemokine gene expression by major histocompatibility complex class II ligands in human fibroblast-like synoviocytes. *J. Biol. Chem.*, **269**, 32063–32069.
34. MOUNTZ J. D., ZHOU T., LONG R. E., BLUETHMANN H., KOOPMAN W. J. and EDWARDS C. K. (1994): T cell influence on superantigen-induced arthritis in MRL-lpr/lpr mice. *Arthritis Rheum.*, **37**, 113–124.
35. MOURAD W., MEHINDATE K., SCHALL T. J. and MC COLL S. R. (1992): Engagement of major histocompatibility complex class II molecules by superantigen induces inflammatory cytokine gene expression in human rheumatoid fibroblast-like synoviocytes. *J. Exp. Med.*, **175**, 613–616.
36. MOURAD W., SCHOLL P., DIAZ A., GEHA R. and CHATILA T. (1989): The staphylococcal toxic shock syndrome toxin 1 triggers B cell proliferation and differentiation via major histocompatibility complex-unrestricted cognate T/B cell interaction. *J. Exp. Med.*, **170**, 2011–2022.
37. ORIGUCHI T., EGUCHI K., KAWABE Y., MIZOKAMI A., IDA H. and NAGATAKI S. (1995): Synovial cells are potent antigen-presenting cells for superantigen, staphylococcal enterotoxin B (SEB). *Clin. Exp. Immunol.*, **99**, 345–351.
38. PALIARD X., WEST S. G., LAFFERTY J. A., CLEMENTS J. R., KAPPLER J. W., MARRACK P. and KOTZIN B. L. (1991): Evidence for the effect of a superantigen in rheumatoid arthritis. *Science*, **253**, 325–328.
39. PIETRA B. A., INOCENCIO J. D., GIANNINI E. H. and HIRSCH R. (1994): TCR V β family repertoire and T cell activation markers in Kawasaki disease. *J. Immunol.*, **153**, 1881–1888.
40. ROSENBERG E. W. and NOAH P. W. (1988): The Koebner phenomenon and the microbial basis of psoriasis. *J. Am. Acad. Dermatol.*, **18**, 151–158.
41. ROSENBERG E. W., NOAH P. W., ZANOLLI M. D., SKINNER R. B., BOND M. J. and CRUTCHER N. (1986): Use of rifampin with penicillin and erythromycin in the treatment of psoriasis. *J. Am. Acad. Dermatol.*, **14**, 761–764.
42. ROTT O., WEKERLE H. and FLEISCHER B. (1992): Protection from experimental allergic encephalomyelitis by application of a bacterial superantigen. *Int. Immunol.*, **4**, 347–353.

43. SAKAGUCHI M., KATO H., NISHIYORI A., SAGAWA K. and ITOH K. (1995): Characterization of CD4⁺ T helper cells in patients with Kawasaki disease (KD): preferential production of tumor necrosis factor- α (TNF- α) by V β 2- or V β 8-CD4⁺ T helper cells. *Clin. Exp. Immunol.*, **99**, 276–282.
44. SCHIEFFENBAUER J., JOHNSON H. M., BUTFILOSKI E. J., WEGGRZYN L. and SOOS J. M. (1993): Staphylococcal enterotoxin can reactive experimental allergic encephalomyelitis. *Proc. Natl. Acad. Sci. USA*, **90**, 8543–8546.
45. SCHWAB J. H., BROWN R. R., ANDERLE S. K. and SCHLIEVERT P. M. (1993): Superantigen can reactive bacterial cell wall-induced arthritis. *J. Immunol.*, **150**, 4151–4159.
46. SEGAL B. M., KLINMAN D. M. and SHEVACH E. M. (1997): Microbial products induce autoimmune disease by an IL-12-dependent pathway. *J. Immunol.*, **158**, 5087–5090.
47. SHINBORI T., MATSUKI M., SUGA M., KAKIMOTO K. and ANDO M. (1996): Pneumonia in autoimmune mice by intratracheal administration of superantigen staphylococcal enterotoxin B. *Cell. Immunol.*, **174**, 129–137.
48. SKENN M. J., MILLER M. A., SHINNICK T. M. and ZIEGLER H. K. (1996): Regulation of murine macrophages IL-2 production. Activation of macrophages *in vivo*, restimulation *in vitro*, and modulation by other cytokines. *J. Immunol.*, **156**, 1196–1206.
49. SMITH T., HEWSON A. K., KINGSLEY C. I., LEONARD J. P. and CUZNER M. L. (1997): Interleukin 12 induces relaps experimental allergic encephalomyelitis in the Lewis rats. *Am. J. Pathol.*, **150**, 1909–1917.
50. SOOS J. M., HOBEIKA A. C., BUTFILOSKI E. J., SCHIFFENBAUER J. and JOHNSON H. M. (1995): Accelerated induction of experimental allergic encephalomyelitis in PL/J mice by a non-V β 8-specific superantigen. *Proc. Natl. Acad. Sci. USA*, **92**, 6082–6086.
51. SOOS J. M., SCHIFFENBAUER J. and JOHNSON H. M. (1993): Treatment of PL/J mice with the superantigen, staphylococcal enterotoxin B, prevents development of experimental allergic encephalomyelitis. *J. Neuroimmunol.*, **43**, 39–44.
52. STEGEMAN C. A., TERVAERT J. W., SLUITER W. J., MANSON W. L., DE JONG P. E. and KALLENBERG C. G. M. (1994): Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann. Intern. Med.*, **120**, 12–17.
53. TAKEI S., ARORA Y. and WALKER S. M. (1993): Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigen. *J. Clin. Invest.*, **91**, 602–607.
54. TREPO C. G., ZUCKERMAN A. J., BIRD R. C. and PRINCE A. M. (1974): The role of circulating hepatitis B antigen/antibody immune complexes in the pathogenesis of vascular and hepatic manifestations in polyarteritis nodosa. *J. Clin. Pathol.*, **27**, 863–868.
55. TUMANG J. R., POSNETT D. N., COLE B. C., CROW M. K. and FRIEDMAN S. M. (1990): Helper T cell-dependent human B cell differentiation mediated by a mycoplasmal superantigen bridge. *J. Exp. Med.*, **171**, 2153–2158.
56. WEYAND C. M. and GORONZY J. J. (1994): Functional domains on HLA-DR molecules: implication for the linkage of HLA-DR genes to different autoimmune disease. *Clin. Immunol. Immunopathol.*, **70**, 91–98.
57. WEYAND C. M., HICOK K. C., CONN D. L. and GORONZY J. J. (1992): The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Ann. Int. Med.*, **117**, 801–806.
58. WHYTE H. J., BALGHMAN R. D. and HANOVER N. H. (1964): Acute guttate psoriasis and streptococcal infection. *Arch. Dermatol.*, **89**, 350–356.
59. WOOSLEY R. L., DRAYER D. E., REIDENBERG M. M., NIES A. S., CARR K. and OATES J. A. (1978): Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N. Engl. J. Med.*, **298**, 1157–1159.

Received in June 1998

Accepted in August 1998