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Interleukins 6 and 11 Protect Mice from Mortality in a Staphylococcal Enterotoxin-Induced Toxic Shock Model

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BALB/By mice given doses of D-galactosamine plus *Staphylococcus aureus* enterotoxin B die within 48 h of administration. The cause of death is a syndrome much like toxic shock syndrome in humans. We used this model to investigate the role of two cytokines, interleukin 6 and interleukin 11, which share the signal transducing subunit, gp130, of their respective receptors. We observed that pretreatment of mice with antibody to interleukin 6 increased mortality from 55% to nearly 90% ($P < 0.001$), while pretreatment with either cytokine reduced death. The protection was dose dependent; however, interleukin 6 was about 10-fold more potent than interleukin 11. These data indicate that endogenous interleukin 6 plays a protective role in attenuating acute inflammatory responses; furthermore, interleukin 6 and interleukin 11 can abrogate T-cell activation due to triggering by superantigen. A possible clinical role for these cytokines in the treatment of toxic shock merits further investigation.

Toxic shock syndrome (TSS) is a life-threatening condition caused by the host inflammatory response to bacterial toxins of *Staphylococcus aureus* and some *Streptococcus* species (18, 19, 21). TSS is defined by high fever, rash, desquamation, multiple organ system failure, and severe hypotension (31, 35). Morbidity remains high even with antibiotic therapy.

Currently it is believed that the bacterial toxins bind to class II major histocompatibility molecules on antigen-presenting cells (11). The bound exotoxins then activate all $CD4^+$ T cells expressing a particular Vβ gene (9); thus, many more T cells are activated in response to the toxin superantigen than in response to a normal antigen (20, 36). TSS has been associated with the use of tampons by menstruating women. Both absorbancy and chemical composition have been invoked as reasons for differences among tampons in the risk of causing TSS. In recent years, TSS has also been described as a complication of various surgeries (28, 29, 31), as well as a complication of streptococcal infections, often with a high mortality rate when associated with necrotizing fasciitis (19, 34, 37). Therefore, insight into additional treatments for TSS are warranted.

Like gram-negative endotoxins, staphylococcal and streptococcal toxins induce a panoply of cytokines. Whereas treatment of human mononuclear cells with endotoxin caused the appearance of interleukin 1α (IL-1α), IL-1β, tumor necrosis factor alpha (TNF-α), and IL-8 within 4 h after stimulation, treatment with staphylococcal enterotoxin B (SEB) resulted in the appearance of IL-1α, IL-1β, and IL-8 at 12 h following challenge. T-cell-derived TNF-α was found 12 to 48 h after stimulation (8). As in endotoxin shock, TNF-α was found to be a major pathophysiological cytokine in TSS (26). Since TSS cannot be induced in athymic or severe combined immunodeficient mice (20, 24), it is inferred that T-cell activation and T-cell-derived cytokines such as TNF-α are most important in induction.

Previously we had studied the pathophysiological role of cytokines in endotoxin shock. We observed that pretreatment with antibody to TNF-α protected against mortality, whereas pretreatment with antibody to IL-6 increased mortality (5). Further study showed that pretreatment with IL-6 protected against lethality in that model. We wished to extend these studies to see the effects of antibody to IL-6 and IL-6 itself in a toxic shock model. A cytokine using the same signal transduction receptor subunit as IL-6, IL-11, was also studied for its protective potential. We observed that antibody to IL-6 increased mortality and that pretreatment with either IL-6 or IL-11 protected significantly against death in toxic shock. These cytokines may have clinical applications and may also be used to identify other endogenous protective mechanisms which might lead to improved therapy.

MATERIALS AND METHODS

Reagents. Endotoxin-free Dulbecco's phosphate-buffered saline (DPBS) was purchased from GIBCO (Bethesda, Md.). This was used to dissolve antibodies, cytokines, D-galactosamine, and *S. aureus* SEB. Hamster monoclonal antibody to mouse TNF-α (TN3-19.12; hereafter called TN3) was purchased from Genzyme (32). Rat monoclonal antibody to mouse IL-6 (20F-3) was obtained from John Abrams, DNAX Research Institute of Cellular and Molecular Biology, Palo Alto, Calif. (33). It was prepared by Verax (Lebanon, N.H.) and ascertained to be endotoxin free, as previously reported (4). Human IL-6 was purchased from Biosource International (Camarillo, Calif.) and dissolved in DPBS. Human IL-11 was the kind gift of James Keith, Genetics Institute, Andover, Mass. It was dissolved in 1 mg of bovine serum albumin (BSA) per ml in DPBS. Hamster immunoglobulin G (HIgG) was obtained from Cappel (West Chester, Pa.).

S. aureus SEB was purchased from Toxin Technology, Sarasota, Fla. It was dissolved in DPBS and stored at −70°C in single-use aliquots. These were thawed as needed immediately prior to use.

D-Galactosamine was purchased from Sigma Chemicals (St. Louis, Mo.). It was dissolved immediately before use in DPBS.

Mice. Male BALB/By mice (6 to 8 weeks of age) were purchased from Taconic Laboratories (Germantown, N.Y.). They were housed for at least 2 weeks in our vivarium prior to the start of each experiment.

Toxic shock induction. The protocol used for toxic shock induction was adapted (23) and approved by the Schering-Plough Animal Care and Use Committee. From 10 to 20 mice for each treatment group were given 20 mg of D-galactosamine plus 25 μg of SEB intraperitoneally. Mortality was assessed 24 and 48 h later. These doses of D-galactosamine and SEB were previously determined to result in 100% mortality at 48 h (data not shown). No change in mortality was ever observed beyond 48 h in preliminary experiments; therefore, longer times of observation were not used. The averages of at least three independent experiments are shown in the figures.

Intraperitoneal administration of antibodies was performed 18 h before lethal challenge, while treatment with cytokines was done 1 h prior to challenge.

Statistical analysis. Statistical analysis (Fisher's PLSD test for one-way anal-

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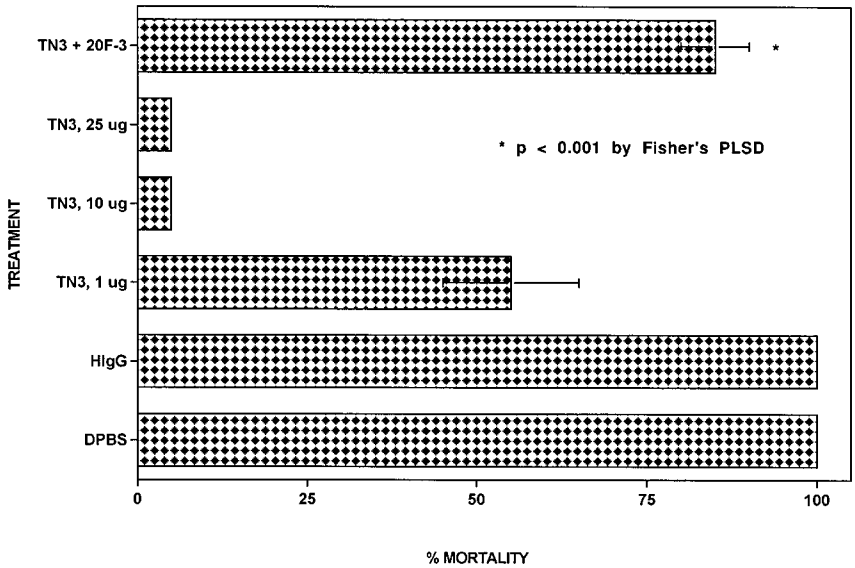

FIG. 1. Effects of pretreatment with antibodies to TNF-α and IL-6. Antibody to TNF-α protected, while antibody to IL-6 enhanced mortality. Twenty mice were used for each treatment group in each independent experiment. TN3 (anti-TNF), 20F-3 (anti-IL-6), or both were given 18 h prior to lethal challenge with D-galactosamine and SEB, as described in Materials and Methods. Mortality was assessed 48 h later.

ysis of variance) was performed with Statview software, version 4.0.1 (Abacus Concepts), on a MacIntosh IIsi computer.

RESULTS

Effects of pretreatment with antibodies to TNF-α and IL-6. It had been reported previously that pretreatment with antibody to TNF-α abrogated mortality to a lethal dose of SEB plus D-galactosamine (25). We therefore titrated the dose of anti-TNF-α TN3 antibody that we needed to prevent 50% mortality. HIgG was used as the control protein. Figure 1 shows that a dose of 1 μg of TN3 was sufficient to result in 55% ± 15% mortality. Higher doses of TN3 resulted in 95% protection from lethality. Treatment with HIgG did not affect mortality.

To see if concomitant treatment with antibody to IL-6 resulted in increased mortality (as previously demonstrated in a septic shock model [5]), we injected both antibodies intraperitoneally 18 h prior to lethal challenge. Figure 1 shows that pretreatment with 1 mg of 20F-3 (anti-mouse IL-6) plus 1 μg of TN3 raised the mortality level from 55% to 85% ($P < 0.001$ by Fisher's PLSD test). Pretreatment of mice with 1 mg of 20F-3 alone did not affect the mortality rate of 100% (data not shown), nor did treatment with HIgG, as observed in previous experiments.

Effect of pretreatment with IL-6. Since pretreatment with antibody to IL-6 enhanced mortality (Fig. 1), we decided to see if pretreatment with IL-6 abrogated mortality. We found that administration of as little as 100 ng of IL-6 1 h prior to lethal challenge decreased mortality by 50% (Fig. 2). Increasing the amount of IL-6 essentially eliminated mortality (average 98% survival when 300 and 600 ng were given [Fig. 2]).

Effect of pretreatment with IL-11. As previously mentioned, IL-11 shares the signal transducing subunit of its receptor with IL-6. Therefore, we were interested to see if another cytokine could mediate the same protective effect as IL-6 in this toxic shock model. The data from these experiments are shown in Fig. 3. While low doses (0.1 and 0.3 μg) of IL-11 had no significant effect on mortality, higher doses (1 and 10 μg) did improve survival (decreased mortality from 100% to 60%; $P <$ 0.05 by Fisher's PLSD test). BSA, which was included in the vehicle, did not affect mortality. Because of the limited supply of IL-11, doses higher than 10 μg per mouse were not tested; however, since increasing the dose of IL-11 from 1 to 10 μg did not improve survival, it seems unlikely that even higher doses of IL-11 would have improved survival further. Therefore, IL-11 was able to improve survival but at higher doses than were needed with IL-6 pretreatment.

DISCUSSION

The data in this paper demonstrate that IL-6 and IL-11 protected against mortality in a murine toxic shock model. In this model, mice were given the hepatotoxin D-galactosamine along with a low dose of SEB, which has been mentioned as a common cause of nonmenstrual TSS (14). As in a model of endotoxin shock, the administration of D-galactosamine lowered the lethal dose of SEB required for mice, which otherwise are much more resistant than humans to the effects of either endotoxin or SEB (23, 30). D-Galactosamine impairs liver function, thereby sensitizing mice and rats to the systemic effects of certain substances, such as lipopolysaccharide and SEB (23, 30). In our facility, the intraperitoneal injection of 20 mg of D-galactosamine plus 25 μg of SEB resulted in 100% mortality 48 h after challenge. Without D-galactosamine, 25 μg was not a lethal dose (data not shown).

Miethke et al. previously reported that TNF-α is a key mediator of lethality in this toxic shock model (26). We used the TN3 hamster monoclonal antibody to TNF-α (32) to abrogate about half the mortality in order to see what effect, if any, antibody to mouse IL-6 (20F-3) would have. Initially, we had observed that pretreatment with a neutralizing dose of 20F-3 conferred no protection (data not shown); thus, we wanted to see if 20F-3 synergized or antagonized protection by TN3. Previously we had observed that monoclonal isotype control antibody for 20F-3 had nonspecific protective effects in a septic shock model (5); therefore, we used HIgG in those experiments and here as well. We found that pretreatment with 20F-3 significantly enhanced mortality when given with the

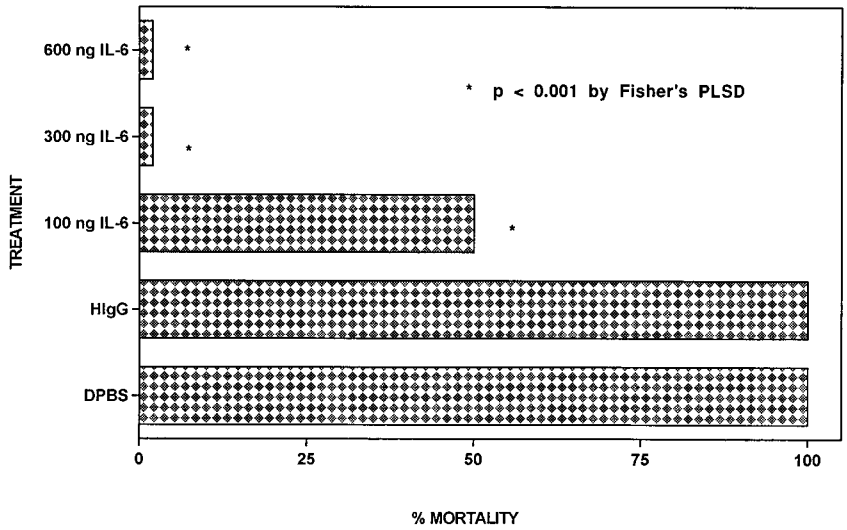

FIG. 2. Pretreatment with IL-6 protected against mortality. Intraperitoneal doses of IL-6 were given as described in Materials and Methods 1 h prior to lethal challenge with D-galactosamine and SEB. Fourteen mice were used in each treatment group in each independent experiment. Mortality was determined 48 h after lethal challenge.

partially protective dose of TN3 (Fig. 1; 85% versus 55% mortality, $P < 0.001$ by Fisher's PLSD). These results led us to hypothesize that pretreatment with IL-6 might abrogate mortality in this model.

IL-6 and IL-11 were observed to prevent death when given 1 h prior to lethal challenge (Fig. 2 and 3). The protection was dose dependent, although 10-fold more IL-11 than IL-6 was required for significant protection (at least 1 μg of IL-11 per mouse was required for 60% mortality, versus 100 ng of IL-6 for 50% mortality [Fig. 2 and 3]). At present, we have no absolute explanation for the discrepancy in the levels of protection observed with IL-6 and IL-11. One possibility is differences in affinities of the cytokines for their respective receptors. Even though IL-6 and IL-11 share the signaling peptide gp130, their ligand-binding subunits differ (39). The affinity of human IL-6 for the murine receptor is approximately 125 pM (about fivefold less than for the homologous binding) (10), while that of murine IL-11 for its homologous receptor is 300 to 800 pM (16). If the affinity of human IL-11 for the murine receptor is likewise approximately fivefold less than the affinity for the homologous receptor, then the difference in affinities of about 25-fold may account for the difference observed in protective doses.

A different cytokine, IL-10, was previously shown to confer

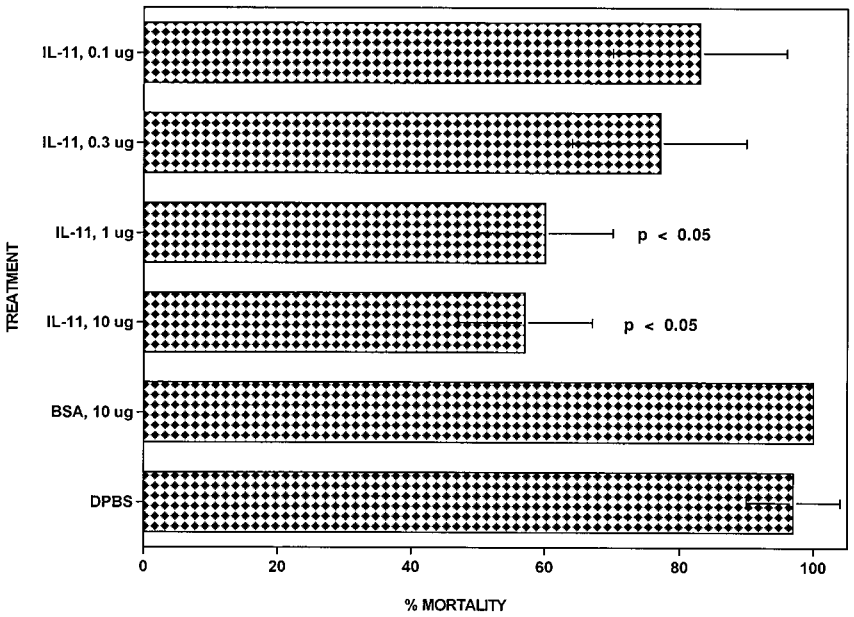

FIG. 3. Pretreatment with IL-11 protected against mortality. Intraperitoneal doses of IL-11 were given as described in Materials and Methods 1 h prior to lethal challenge with D-galactosamine and SEB. Ten mice per treatment group were used in each independent experiment. Mortality was determined 48 h after lethal challenge.

significant protection in this toxic shock model. This cytokine, which is known to inhibit the synthesis of both monocyte and T-cell cytokines (12, 15), was also shown to protect against lethality in a septic shock model (17). Presumably, IL-10 protects in both shock models by inhibiting the synthesis of the cytokine cascade. When 10 μg of IL-10 were given to each mouse, mortality was reduced from 75% to 35% at 48 h (7); in contrast, we observed that 300 ng of IL-6 reduced mortality from 100% to 2% (Fig. 2). Therefore, IL-6 was more potent than IL-10 in protecting against mortality in this toxic shock model.

Previously we had demonstrated that pretreatment with IL-6 could enhance the protective effect of anti-TNF-α antibody in a septic shock model (5). We wished to compare those results, in a monocyte-dependent model of acute inflammation and shock, to results in a T-cell-dependent model. In these two models, we observed that IL-6 protected against lethality. Moreover, the results presented here demonstrate that IL-6 given alone could reduce mortality by 98% when 300 ng per mouse was given (Fig. 2). These results contrast with what we previously observed in septic shock. In those experiments, IL-6 given alone did not confer protection; rather, IL-6 had to be administered in conjunction with a partially protective dose of TN3 to see enhanced survival of the mice (5). In the data presented here, we demonstrate the importance of endogenous IL-6 production in ameliorating severe acute inflammation, as evidenced by our observation that pretreatment with antibody to IL-6 enhanced the mortality of mice given a 50% protective dose of antibody to TNF-α (Fig. 1). These data confirm what we had originally observed in septic shock, whereupon pretreatment with antibody to IL-6 likewise enhanced the mortality of a partially protective dose of antibody to TNF-α (4).

The cytokines IL-6 and IL-11 are related in that they share the gp130 signal transduction subunit of their receptors, although they have different ligand-binding subunits (39). Because of this, IL-6 and IL-11 share many biological properties, including effects on thrombopoiesis (13) and induction of the acute-phase response (6). Our data indicate that they might share other anti-inflammatory effects which have been documented for IL-6, such as induction of corticosteroid synthesis (38), inhibition of T-cell activation in delayed-type hypersensitivity responses (27), and inhibition of IL-1 and TNF-α synthesis in vitro and in vivo (1, 2). Such effects have not yet been demonstrated for IL-11. Recently, investigators published that administration of antibody to IL-6 did not protect against mortality in either D-galactosamine-sensitized or unsensitized mice given a lethal dose of SEB (22). The authors did not look for enhancement of mortality by 20F-3 antibody treatment, nor did they assess the protective potential of IL-6 pretreatment.

At present, we have no data indicating the mechanism for the protection observed with either IL-6 or IL-11. While several possible anti-inflammatory mechanisms have been documented for IL-6 (reviewed in reference 3), similar studies have yet to be carried out for IL-11. It may even turn out that a hitherto unknown mechanism(s) is responsible for the effects seen in this toxic shock model. Because staphylococcal and streptococcal TSSs are severe and debilitating, and because of the threat of decreased sensitivity of the bacteria to antibiotics, it is important to identify new therapies to treat bacterial diseases and their complications. Insight into protective mechanisms induced by endogenous cytokines may provide new therapies for the future.

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REFERENCES

1. **Aderka, D., J. Le, and J. Vilcek.** 1989. IL-6 inhibits lipopolysaccharide-induced tumor necrosis factor production in cultured human monocytes, U937 cells, and in mice. J. Immunol. **143:**3517–3523.
2. **Aderka, D., Y. Maor, D. Novick, H. Engelmann, Y. Kahn, Y. Levo, D. Wallach, and M. Revel.** 1993. Interleukin-6 inhibits the proliferation of B-chronic lymphocytic leukemia cells that is induced by tumor necrosis factor-α. Blood **81:**2076–2084.
3. **Barton, B. E.** The biological effects of interleukin 6. Med. Res. Rev., in press.
4. **Barton, B. E.** 1993. Effect of interleukin-6 in septic shock. Drug News Perspectives **6:**641–646.
5. **Barton, B. E., and J. V. Jackson.** 1993. The protective role of IL-6 in a septic shock model. Infect. Immun. **61:**1496–1499.
6. **Baumann, H., and P. Schendel.** 1991. Interleukin-11 regulates the hepatic expression of the same plasma protein genes as interleukin-6. J. Biol. Chem. **266:**20424–20427.
7. **Bean, A. G. D., R. A. Freiberg, S. Andrade, S. Menon, and A. Zlotnik.** 1993. Interleukin-10 protects mice against staphylococcal enterotoxin B-induced lethal shock. Infect. Immun. **61:**4937–4939.
8. **Bjork, L., J. Andersson, M. Ceska, and U. Andersson.** 1992. Endotoxin and *Staphylococcus aureus* enterotoxin A induce different patterns of cytokines. Cytokine **4:**513–519.
9. **Choi, Y., J. A. Lafferty, J. R. Clements, J. K. Todd, E. W. Gelfand, J. Kappler, P. Marrack, and B. L. Kotzin.** 1990. Selective expansion of T cells expressing Vβ 2 in toxic shock syndrome. J. Exp. Med. **172:**981–984.
10. **Coulie, P. G., M. Stevens, and J. Van Snick.** 1989. High- and low-affinity receptors for murine interleukin 6: distinct distribution on B and T cells. Eur. J. Immunol. **19:**2107–2114.
11. **Dellabona, P., J. Peccoud, J. Kappler, P. Marrack, C. Benoit, and D. Mathis.** 1990. Superantigens interact with MHC class II molecules outside of the antigen groove. Cell **62:**1115–1121.
12. **de Waal Malefyt, R., J. Abrams, B. Bennett, C. G. Figdor, and J. E. de Vries.** 1991. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. J. Exp. Med. **174:** 1209–1220.
13. **Du, X. X., T. Neben, S. Goldman, and D. A. Williams.** 1993. Effects of recombinant human interleukin-11 on hematopoietic reconstitution in transplant mice: acceleration of recovery of peripheral blood neutrophils and platelets. Blood **81:**27–34.
14. **Fast, D. J., P. M. Schlievert, and R. D. Nelson.** 1989. Toxic shock syndrome-associated staphylococcal and streptococcal pyrogenic toxins are potent inducers of tumor necrosis factor production. Infect. Immun. **57:**291–294.
15. **Fiorentino, D. F., M. W. Bond, and T. R. Mosmann.** 1989. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J. Exp. Med. **170:**2081–2091.
16. **Hilton, D. J., A. A. Hilton, A. Raicevic, S. Rakar, M. Harrison-Smith, N. M. Gough, C. G. Begley, D. Metcalf, N. A. Nicola, and T. A. Willson.** 1994. Cloning of a murine IL-11 receptor alpha-chain: requirement for gp130 for high affinity binding and signal transduction. EMBO J. **13:**4765–4775.
17. **Howard, M., T. Muchamel, S. Andrade, and S. Menon.** 1993. Interleukin 10 protects mice from lethal endotoxemia. J. Exp. Med. **177:**1205–1208.
18. **Johnson, H. M., J. K. Russell, and C. H. Pontzer.** 1991. Staphylococcal enterotoxin microbial superantigens. FASEB J. **5:**2706–2712.
19. **Markowitz, M.** 1994. Changing epidemiology of group A streptococcal infections. Pediatr. Infect. Dis. J. **13:**557–560.
20. **Marrack, P., M. Blackman, E. Kushnir, and J. Kappler.** 1990. The toxicity of staphylococcal enterotoxin B in mice is mediated by T cells. J. Exp. Med. **171:**455–464.
21. **Marrack, P., and J. Kappler.** 1990. The staphylococcal enterotoxins and their relatives. Science **248:**705–711.
22. **Matthys, P., T. Mitera, H. Heremans, J. Van Damme, and A. Billiau.** 1995. Anti-gamma interferon and anti-interleukin-6 antibodies affect staphylococcal enterotoxin B-induced weight loss, hypoglycemia, and cytokine release in D-galactosamine-sensitized and unsensitized mice. Infect. Immun. **63:**1158–1164.
23. **Miethke, T., H. Gaus, C. Wahl, K. Heeg, and H. Wagner.** 1992. T-cell-dependent shock induced by a bacterial superantigen. Chem. Immunol. **55:**172–184.
24. **Miethke, T., D. Katja, C. Wahl, K. Heeg, and H. Wagner.** 1993. Pathogenesis of the toxic shock syndrome: T cell mediated lethal shock caused by the superantigen TSST-1. Eur. J. Immunol. **23:**1494–1500.
25. **Miethke, T., C. Wahl, K. Heeg, B. Echtenacher, P. H. Krammer, and H. Wagner.** 1991. T cell-mediated lethal shock triggered in mice by the superantigen staphylococcal enterotoxin B: critical role of tumor necrosis factor. J. Exp. Med. **175:**91–98.

26. **Miethke, T., C. Wahl, K. Heeg, B. Echtenacher, P. H. Krammer, and H. Wagner.** 1992. T cell-mediated lethal shock triggered in mice by the superantigen staphylococcal enterotoxin B: critical role of tumor necrosis factor. J. Exp. Med. **175:**91–98.
27. **Mihara, M., M. Ikuta, Y. Koishihara, and Y. Ohsugi.** 1991. Interleukin 6 inhibits delayed-type hypersensitivity and the development of adjuvant arthritis. Eur. J. Immunol. **21:**2327–2331.
28. **Miller, S. D.** 1993. Postoperative toxic shock syndrome after lumbar laminectomy in a male patient. Spine **19:**1182–1185.
29. **Nyirjesy, P., R. S. Jones, A. Chatwani, E. S. Zinner, and P. Axelrod.** 1994. Streptococcal toxic shock-like syndrome as an unusual complication of laparoscopic tubal ligation. J. Reprod. Med. **39:**649–651.
30. **Peavy, D. L., W. H. Adler, and R. T. Smith.** 1970. The mitogenic effects of endotoxin and staphylococcal enterotoxin B on mouse spleen cells and human peripheral lymphocytes. J. Immunol. **105:**1453.
31. **Rhee, C. A., R. J. Smith, and I. T. Jackson.** 1994. Toxic shock syndrome associated with suction-assisted lipectomy. Aesth. Plast. Surg. **18:**161–163.
32. **Sheehan, K. C. F., N. H. Ruddle, and R. D. Schreiber.** 1989. Generation and characterization of hamster monoclonal antibodies that neutralize murine tumor necrosis factors. J. Immunol. **142:**3884–3893.
33. **Starnes, H. F., Jr., M. K. Pearce, A. Tewari, J. H. Yim, J.-C. Zou, and J. S. Abrams.** 1990. Anti-IL-6 monoclonal antibodies protect against lethal *Escherichia coli* infection and lethal tumor necrosis factor-α challenge in mice. J. Immunol. **145:**4185–4191.
34. **Stevens, D. L.** 1994. Invasive group A streptococcal infections: the past, present and future. Pediatr. Infect. Dis. J. **13:**557–560.
35. **Todd, J., M. Fishaut, M. Kapral, and T. Welch.** 1978. Toxic-shock syndrome associated with phage-group-1 staphylococci. Lancet **ii:**1116.
36. **Uchiyama, T., X.-J. Yan, K. Imanishi, and J. Yagi.** 1994. Bacterial superantigens—mechanism of T cell activation by the superantigens and their role in the pathogenesis of infectious diseases. Microbiol. Immunol. **38:**245–256.
37. **Wolf, J. E., and L. G. Rabinowitz.** 1995. Streptococcal toxic shock-like syndrome. Arch. Dermatol. **131:**73–77.
38. **Woloski, B. M. R. N. J., E. M. Smith, W. J. Meyer, G. M. Fuller, and J. E. Blalock.** 1985. Corticotropin-releasing factor activity of monokines. Science **230:**1035.
39. **Yin, T., T. Taga, M. L.-S. Tsang, K. Yasukawa, T. Kishimoto, and Y.-C. Yang.** 1993. Involvement of IL-6 signal transducer gp130 in IL-11-mediated signal transduction. J. Immunol. **151:**2555–2561.

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