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Staphylococcus-Mediated T-Cell Activation and Spontaneous Natural Killer Cell Activity in the Absence of Major Histocompatibility Complex Class II Molecules†

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We used major histocompatibility complex class II antigen-deficient transgenic mice to show that in vitro natural killer cell cytotoxicity and T-cell activation by staphylococcal exotoxins (superantigens) are not dependent upon the presence of major histocompatibility complex class II molecules. T cells can be activated by exotoxins in the presence of exogenously added interleukin 1 or 2 or in the presence of specific antibody without exogenously added cytokines.

Staphylococcal exotoxins, often referred to as superantigens, stimulate T cells expressing specific Vβ region-containing T-cell receptors (9). This occurs through a mechanism thought to be dependent on toxin binding to nonpolymorphic regions of major histocompatibility complex (MHC) class II molecules on accessory cells (7, 15, 23). Recent work suggests that non-MHC receptors may be present on cells that allow the toxin to bind and activate cells (1, 8, 22, 25). However, the nature of these toxin-binding ligands has yet to be fully elucidated.

Our laboratory used C2D (*H-2*^{b}) transgenic mice (GenPharm, Int., Mountain View, Calif.), deficient in the expression of MHC class II molecules, to investigate the activation and function of various lymphocyte subpopulations. We used cells from C1D (*H-2*^{b}; GenPharm) MHC class I-deficient mice, normal B6 (*H-2*^{b}) mice, and/or C3HeB/FeJ (*H-2*^{k}) mice (Jackson Laboratory, Bar Harbor, Maine) as controls. C3HeB/FeJ mouse cells were used as controls because of our familiarity with the responses of the T cells and macrophages of this strain (11, 18). Normal B6 cells were used as an unmanipulated, syngeneic control. C1D mice served as an additional syngeneic control but were subjected to genetic manipulation of a knockout distinct from MHC class II molecules. We confirmed that C1D and C2D mice lacked MHC class I or class II molecules, respectively, by using flow cytometric analysis of thymocytes or spleen cells. A concomitant decrease occurred in CD8- or CD4-expressing cells from C1D or C2D mice, respectively.

Animals used in these experiments were handled in accordance with procedures approved by the Animal Care and Use Committee at Kansas State University.

We evaluated whether splenic natural killer (NK) cells needed to express class II molecules to lyse Yac-1 tumor cells. ^{51}Cr-labelled Yac-1 tumor cells (10^4) were incubated with splenic cells from C1D, C2D, and normal B6 mice in a 5-h cytotoxicity assay (6). The data in Table 1 confirm that MHC class I-deficient mice lack NK cell activity, as has been shown previously (19). However, there was no apparent difference between C2D mice and B6 mice in NK cell activity. Therefore, although the level of MHC class I expression is important on both effectors and targets (4, 16) for NK cell-mediated killing, there does not appear to be a requirement for MHC class II molecules on NK effector cells.

Several recent studies have questioned the absolute role in and contribution to the toxin-mediated T-cell activation process of MHC class II molecules (8, 12, 22, 25). Salamon et al. have also suggested that cytokines are important for the T-cell response to toxin (24). Because T cells may not necessarily require MHC class II molecules to respond to toxin, and cytokines may contribute to activation, we tested the capacity of T cells to respond to toxin in the absence of MHC class II molecules. Table 2 shows experiments confirming that the activation of T cells by staphylococcal enterotoxin B (SEB) and exfoliative toxin A (ETA) is dependent upon the expression of class II molecules by spleen cells when cultures are not supplemented with cytokines. We also demonstrate that exfoliative toxin B (ETB) exhibits stimulatory properties similar to those of the more extensively studied toxins SEB and ETA.

Although it appears that MHC class II molecules are required under normal, in vitro activation conditions, preliminary experiments indicated that exogenous cytokines could induce C2D T cells to proliferate in response to staphylococcal superantigens. When interleukin 1 (IL-1) and IL-2 were added together, stimulation indices of 3.8 and 4.2 were observed when C2D T cells were stimulated by ETA and SEB, respectively (Table 3). This proliferative response

TABLE 1. In vitro NK cell activity is normal in MHC class II transgenic animals

Spleen cells	% Specific ^{51}Cr release[a] at effector/target cell ratio of:		
	300:1	200:1	100:1
B6	31 ± 2	27 ± 1	21 ± 1
C1D	8 ± 2[b]	6 ± 1[b]	8 ± 2[b]
C2D	29 ± 2	32 ± 3	26 ± 0

[a] Values represent $\bar{x}$ ± standard errors of the means of triplicate determinations; data are representative of two experiments. Yac-1 target cells (10^4 per well of microtiter plate) were assayed in a 5-h assay.

[b] Significantly different from B6 and C2D mice as determined by Student's *t* test ($P < 0.01$).

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TABLE 2. MHC class II-deficient murine spleen cells do not proliferate in response to staphylococcal exotoxins without additives

Expt	Mouse strain	Proliferation in response to[a]: No toxin (cpm)	ETA cpm	ETA SI	ETB cpm	ETB SI	SEB cpm	SEB SI
1	C1D	14,919 ± 789	ND[b]	ND	65,312 ± 7,314[c]	4.4 ± 0.5	92,085 ± 5,197[c]	6.2 ± 0.3
	C2D	7,006 ± 1,008	ND	ND	13,209 ± 2,063	1.9 ± 0.3	8,199 ± 878	1.2 ± 0.1
	C3H/FeJ	12,600 ± 2,091	ND	ND	143,059 ± 13,236[c]	11.4 ± 1.1	164,744 ± 4,795[c]	13.1 ± 0.4
2	C1D	5,985 ± 45	27,662 ± 1,287[c]	4.6 ± 0.2	13,131 ± 1,295[c]	2.2 ± 0.2	38,153 ± 894[c]	6.4 ± 0.1
	C2D	6,378 ± 1,163	6,787 ± 631	1.1 ± 0.1	10,783 ± 645[c]	1.7 ± 0.1	7,041 ± 223	1.1 ± 0
	B6	14,329 ± 663	27,101 ± 1,488[c]	1.9 ± 0.1	18,262 ± 852[c]	1.3 ± 0.1	40,821 ± 1,268[c]	2.8 ± 0.1
	C3H/FeJ	13,597 ± 760	95,725 ± 1,198[c]	7.0 ± 0.1	57,847 ± 2,127[c]	4.3 ± 0.2	75,941 ± 1,491[c]	5.9 ± 0.1

[a] Toxin concentration was 10 μg/ml; toxins were prepared as described previously (11). Absolute counts (cpm) and stimulation indices (SI) were obtained in 60-h assays done as described previously (18). Stimulation indices were calculated from cells incubated in medium alone.
[b] ND, not determined.
[c] Significantly different from unstimulated control as determined by Student's t test ($P < 0.05$).

was significantly better than that of cells incubated in the absence of toxin ($P < 0.05$). Splenic T cells from C1D and B6 mice had qualitatively similar proliferative responses to ETA and SEB (Tables 2 and 3). T cells from C1D and B6 mice proliferated well in the presence of IL-1 alone and had much better responses in the presence of both IL-1 and IL-2 (Table 3). Therefore, it appeared that exogenous cytokines might play a role in toxin-induced T-cell proliferation for all three T-cell types (B6, C1D, and C2D). Furthermore, the absence of MHC class I molecules did not affect the proliferative response of T cells in response to superantigens. We next determined the contributions of IL-1 and IL-2 to T-cell proliferation in more closely controlled experiments. Both IL-1 and IL-2 significantly enhanced ($P < 0.05$) class II-positive (B6) and -negative (C2D) mouse spleen cell proliferation in the absence of toxin (Table 4). ETA and SEB induced minimal proliferative responses by T cells in the absence of exogenous IL-1 and IL-2. However, both IL-1 and IL-2 significantly enhanced the toxin-induced proliferative response of C2D and B6 mouse T cells. Proliferation was significantly greater in these cells than in cells stimulated by toxin alone or by cells incubated in cytokines without toxin (Table 4; $P < 0.05$). Furthermore, there appeared to be an additive effect between IL-1 and IL-2 on C2D mouse T-cell proliferation (Table 4). Therefore, in the absence of MHC class II molecules, either IL-1 or IL-2 could promote superantigen-induced T-cell responses. Other studies in our laboratory indicate that peritoneal macrophages from C2D mice are able to bind both ETA and SEB (1). It is possible that the added cytokines worked in concert with toxin that was presented by this alternate receptor. However, it is possible that ETA and SEB bound directly to the T cells, as has been suggested by others (25). Nevertheless, the lack of MHC class II molecules does not preclude the activation of T cells by staphylococcal superantigens. However, the amount of proliferation is significantly lower than that of cells that express MHC class II molecules incubated under similar culture conditions (Tables 2 to 4).

One possible explanation for the greater efficiency of toxin-induced T-cell proliferation in the presence of class II molecules could be that class II molecules have a higher affinity for toxins than the alternative receptor (1). The higher-affinity toxin-MHC binding possibly enhances toxin–T-cell receptor interactions and augments T-cell proliferation. If this hypothesis is true, other molecules which bind toxin without interfering with the T-cell epitope should substitute for MHC-expressing cells to activate T cells. Table 5 illustrates that antibody, complexed to polystyrene in microtiter plate wells, achieved such a result in an antibody- and toxin-specific fashion. Neither SEB nor polyclonal antibody, specific for SEB, was able to stimulate high levels of C2D thymic T-cell proliferation. Anti-SEB antibody and ETA together also induced modest proliferation of C2D T cells. Soluble SEB, in the presence of anti-SEB antibody complexed to plastic, induced very high levels of proliferation (significantly higher than those of various controls, $P <$

TABLE 3. Exogenous cytokine and toxins induce T-cell proliferation in the absence of MHC class II-positive cells

Expt	Mouse strain	Cytokine treatment[a] IL-1	IL-2	Proliferation in response to[b]: No toxin (cpm)	ETA cpm	ETA SI	SEB cpm	SEB SI
1	B6	+	−	5,811 ± 615	19,974 ± 350[c]	3.4 ± 0.1	20,859 ± 1,140[c]	3.6 ± 0.2
	C1D	+	−	16,263 ± 1,680	44,409 ± 560[c]	2.7 ± 0.1	41,434 ± 3,394[c]	2.5 ± 0.2
	C2D	+	−	13,244 ± 397	11,737 ± 567	0.9 ± 0	12,623 ± 1,120	1.0 ± 0.1
2	B6	+	+	22,241 ± 674	134,647 ± 13,220[c]	6.1 ± 0.6	215,837 ± 10,998[c]	9.7 ± 0.5
	C1D	+	+	19,338 ± 424	143,943 ± 14,603[c]	7.4 ± 0.8	145,543 ± 14,297[c]	7.5 ± 0.7
	C2D	+	+	16,878 ± 2,262	64,937 ± 2,265	3.8 ± 0.2	70,698 ± 2,665	4.2 ± 0.1

[a] Splenic T cells were stimulated with 7 pg of recombinant murine IL-1 per ml and 10 U of recombinant murine IL-2 per ml.
[b] Cells were stimulated with 20 μg of ETA or SEB per ml. Numbers represent $\bar{x}$ ± standard errors of the means of triplicate determinations. Stimulation indices (SI) were calculated from cells incubated without toxin.
[c] Significantly different from unstimulated control as determined by Student's t test ($P < 0.05$).

TABLE 4. Effects of IL-1 and -2 on C2D mouse T-cell proliferation

Mouse strain	Cytokine treatment[a]		Proliferation in response to[b]:				
			No toxin (cpm)	ETA		SEB	
	IL-1	IL-2		cpm	SI	cpm	SI
B6	−	−	2,046 ± 52	41,237 ± 3,527[c]	20.2 ± 1.7	21,100 ± 1,262[c]	10.3 ± 0.6
B6	+	−	34,747 ± 3,474[d]	228,686 ± 15,902[c,d]	111.8 ± 7.8	284,794 ± 21,612[c,d]	139.2 ± 10.6
B6	−	+	24,812 ± 2,006[d]	163,702 ± 14,168[c,d]	80.8 ± 6.9	200,859 ± 22,760[c,d]	98.2 ± 11.1
B6	+	+	40,235 ± 5,208[d]	196,158 ± 12,250[c,d]	95.9 ± 6.0	254,104 ± 22,078[c,d]	124.2 ± 10.8
C2D	−	−	2,784 ± 463	6,787 ± 224[c]	2.4 ± 0.1	3,099 ± 244	1.1 ± 0.1
C2D	+	−	20,079 ± 2,264[d]	33,144 ± 1,059[c,d]	11.9 ± 0.4	46,972 ± 1,812[c,d]	16.9 ± 0.7
C2D	−	+	18,725 ± 736[d]	29,586 ± 1,632[c,d]	10.6 ± 0.6	34,544 ± 3,872[c,d]	12.4 ± 1.4
C2D	+	+	43,682 ± 2,857[d]	55,142 ± 966[c,d]	19.8 ± 0.3	60,717 ± 873[c,d]	21.8 ± 0.3

[a] Splenic T cells were stimulated with 10 pg of recombinant murine IL-1 per ml and 10 U of recombinant murine IL-2 per ml.
[b] Cells were stimulated with 20 μg of ETA or SEB per ml. Numbers represent $\bar{x}$ ± standard errors of the means of triplicate determinations. Stimulation indices (SI) were calculated from cells incubated in medium alone. One representative experiment of two is presented.
[c] Significantly different from unstimulated controls incubated in the same cytokine as determined by Student's t test ($P < 0.05$).
[d] Significantly different from toxin-stimulated cells incubated without exogenous IL-1 or IL-2 as determined by Student's t test ($P < 0.05$).

0.05), with stimulation indices of 7.0 and 5.8 recorded in two experiments (Table 5). Interestingly, polyclonal antibodies raised against ETA did not have a similar ability to present toxin, suggesting that some antibodies may interfere with the epitope recognized by the T cell. When epitopes important for T-cell recognition are blocked by toxin-specific antibody, T-cell responses are abrogated (5). However, additional experiments with C2D mouse T cells will be needed to confirm this hypothesis. The importance of the immobilization of the antibody is also exemplified in Table 5. When anti-SEB and SEB were added to thymic T cells in solution, T-cell proliferation was minimal. These data suggest that the conditions under which molecules that present toxin to T cells are very specific but that other molecules may substitute for MHC class II antigens.

TABLE 5. Antibody and SEB induce T-cell proliferation in the absence of MHC class II-positive cells

Expt	Antibody treatment[a]	Toxin	Proliferation	
			cpm	Stimulation index
1	None	None	1,041 ± 363	
	None	ETA	966 ± 180	0.9 ± 0.2
	None	SEB	1,229 ± 367	1.2 ± 0.4
	Anti-SEB(C)	None	1,663 ± 119	1.6 ± 0.1
	Anti-SEB(C)	ETA	2,058 ± 89.9[b]	2.0 ± 0.1
	Anti-SEB(C)	SEB	7,251 ± 1,669[b,c,d]	7.0 ± 1.6
	Anti-ETA(C)	None	715 ± 75.7	0.7 ± 0.1
	Anti-ETA(C)	ETA	1,145 ± 324	1.1 ± 0.1
	Anti-ETA(C)	SEB	1,427 ± 295	1.4 ± 0.3
2	None	None	677 ± 55	
	None	ETA	925 ± 250	1.4 ± 0.4
	None	SEB	1,002 ± 298	1.5 ± 0.4
	Anti-SEB(C)	None	1,627 ± 274[c]	2.4 ± 0.4
	Anti-SEB(C)	ETA	1,375 ± 167[c]	2.0 ± 0.2
	Anti-SEB(C)	SEB	3,939 ± 916[b,c,d]	5.8 ± 1.4
	Anti-ETA(C)	None	738 ± 57	1.1 ± 0.1
	Anti-ETA(C)	ETA	784 ± 142	1.2 ± 0.2
	Anti-ETA(C)	SEB	785 ± 117	1.2 ± 0.2
	Anti-SEB(S)	None	950 ± 215	1.4 ± 0.3
	Anti-SEB(S)	SEB	1,574 ± 1,051	2.3 ± 1.6

[a] Corning 96-well flat-bottom ELISA plates were complexed (C) with polyclonal rabbit (anti-ETA) or goat (anti-SEB) serum at a 1:80 or 1:20 dilution, respectively, and diluted in sterile phosphate-buffered saline (PBS), and 200 μl was added per well. Plates were incubated overnight at 4°C. Untreated wells were blocked with 1% bovine serum albumin-PBS overnight at 4°C. Prior to the addition of cells, wells were washed twice with sterile PBS and toxin was added to appropriate wells (20-μg/ml final concentration). Soluble (S) antibody was added at similar concentrations without the overnight complexing step, blocking step, or washes. Antibody and toxin remained in the wells for the entire proliferation assay under S and C conditions. Thymocytes were from C2D mice.
[b] Significantly different from treatment with toxin alone as determined by Student's t test ($P < 0.05$).
[c] Significantly different from untreated cells as determined by Student's t test ($P < 0.05$).
[d] Significantly different from cells treated with antibody alone as determined by Student's t test ($P < 0.08$).

We have demonstrated that toxin-mediated T-cell proliferation can be induced in the absence of one of the members of the trimolecular complex thought to be important for the activation of T cells by staphylococcal superantigens, class II molecules. Because T cells could be activated in the presence of exogenous IL-1 or IL-2 or when toxin was presented by immobilized antibody, we hypothesize that class II molecules are necessary only to immobilize and efficiently mediate toxin binding to T cells via the T-cell receptor. The observations that correlate toxin binding to MHC class II molecules with the ability of the toxin to activate T cells (14) would support this hypothesis. Others have reported that IL-1 and IL-2 act synergistically to induce T-cell proliferation in the presence of suboptimal concentrations of mitogen (2, 20). Green et al. found that purified human T cells needed both toxin and a costimulant anti-CD28 antibody to activate the T cells in the absence of accessory cells (13). Together, these findings suggest that toxin presentation to T cells in the absence of class II-positive cells is less efficient and supports our proposed role for MHC class II molecules. The hypothesis is further supported by our data indicating that cytokines are not needed to activate T cells in response to toxin when the toxin molecules are presented by appropriate antibodies. Perhaps there are two classes of toxin-binding molecules: (i) those that can bind toxin but require accessory cytokines or signals to complete T-cell activation, perhaps by up-regulating IL-2 receptors (21) and IL-2 secretion (5), and (ii) receptors like MHC class II molecules on cells or immobilized antibody that bind toxin with relatively high affinity, do not interfere with the T-cell epitope, and do not require the presence of exogenous cytokines.

Because thymocytes responded to SEB presented by anti-SEB, it is clear that the cell population responding is the T cell. However, we did not have reagents available to us

during this study to determine whether anti-SEB antibody–SEB complexes induced T-cell proliferation in a Vβ-specific manner. Such an experiment would confirm whether the Vβ-specific nature of the T-cell expansion induced by superantigens is determined at the T-cell receptor level (17) or is MHC molecule dependent as suggested by others (3, 10).

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