CYTOTOXICITY BY NONIMMUNE ALLOGENEIC LYMPHOID CELLS

Specific Suppression by Antibody Treatment of the Lymphoid Cells*

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(Received for publication 13 April 1967)

The central role of immune lymphoid cells in the manifestation of diverse immunological reactions in delayed hypersensitivity, transplantation, and autoimmunity is well established, but the mechanism by which the sensitized cells exert their effect is still largely unknown. The introduction of tissue culture methods represents a major advance in this area, and cell-mediated immunity against histoincompatible target cells can now be demonstrated by the capacity of specifically sensitized lymphoid cells to kill normal or neoplastic target cells in vitro (1-8).

Cytotoxicity by sensitized cells fulfils requirements for immunological specificity (9), is preceded as a rule by aggregation of the lymphoid cells around the target cells, and is abolished if the two cell types are separated by impermeable diffusion membranes (8).

However, not only specifically sensitized cells but normal allogeneic (though not syngeneic) cells were also found to kill H-2 incompatible target cells of mouse origin in vitro (10–12) if heterologous antibodies or phytohemagglutinin was present in the medium. Although this reaction may represent the induction of a primary immune response in vitro, this seemed less probable since lymphoid cells, which would be genetically unable to react immunologically against the targets, were still capable of mediating target cell death (11). The only variable that determined cytotoxicity in this case seemed to be the presence of foreign histocompatibility antigens on the lymphoid cells. Presumably, target cells were damaged by close confrontation with cells carrying incompatible surface isoantigenic determinants. An analogous concept was also put forward by Hellström et al. (13) as an explanation of the phenomenon of reduced tumor growth in semisyngeneic F_1 hybrid mice as compared to tumor growth in syngeneic hosts (14). The reaction was termed "allogeneic inhibition".

In the present study, attempts have been made to test the validity of the above hypothesis concerning contact-induced cytotoxicity by incompatible lymphoid cells. Interest has been directed to the demonstration of cytotoxocity

* This work was supported by grants from the Swedish Cancer Society and the Swedish Medical Research Council.

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with lymphoid cells genetically unable to react immunologically against target cells and with X-irradiated lymphoid cells. Furthermore, the concept that target cell death is caused by confrontation with foreign histocompatibility antigens has been investigated by experiments aimed at the suppression of cytotoxicity by blocking the antigens on the lymphoid cells with specific isoantibodies. Part of this work has been published in preliminary form (11, 12, 15).

Materials and Methods

Mice.—The following inbred strains of mice were used in the present study: A/Sn (*H-2*^{a}); C57BL/KL and C57L/Kl, both (*H-2*^{b}); DBA/Kl (*H-2*^{d}); A.CA/Kl (H-2^f); C3H/Kl (H-2^k) and A.SW/Kl (*H-2*^{s}); and F_1 hybrids produced by crossing two of the strains.

Tumors.—Tumors MC57G, MC57S, and MC57T are methylcholanthrene-induced sarcomas which originated in the C57BL strain. They were serially passaged by the subcutaneous inoculation of trypsinized cells in the C57BL strain. Tumor MCAG is a methylcholanthrene-induced tumor which originated in an (A × A.CA)F_1 hybrid mouse. A parental strain variant, specific for strain A/Sn, was isolated from this tumor. Transplantation and serological studies have revealed that this tumor, designated MCAGA, behaves phenotypically as an A strain tumor (16). Tumor MACD is a methylcholanthrene-induced sarcoma indigenous to the (A × A.CA)F_1 hybrid. Sarcoma MDHC was induced by methylcholanthrene in a (C3H × DBA)F_1 hybrid. None of the above tumors grew nonspecifically in H-2 incompatible recipients.

Antiserum.—Antiserum was prepared by weekly intraperitoneal injections of spleen and lymph node cell suspensions. After 6-10 injections, blood was collected from the retroorbital sinus and allowed to clot at room temperature. The sera were pooled and stored at −20°C before use. The various antisera against different H-2 isoantigens used in the present study were tested for their content of hemagglutinating (HA) antibodies by the technique of Gorer and Mikulska (17) as modified by Stimpfling (18). For tissue culture experiments, all sera were diluted so that the final HA titer in the medium would average 1/10—1/20.

Lymph Node and Spleen Cells.—These were obtained from nonimmune adult mice. Cell suspensions were obtained by pressing the organs through stainless steel screens into Eagle's in Earle's medium. The cells were washed twice and counted in a Bürker hemocytometer.

Tissue Culture Technique.—Viable cell suspensions from various target sarcomas were obtained by trypsinizing solid tumors [0.25% trypsin in balanced salt solution (BSS)] cut into small pieces with a pair of scissors. Trypsinization was carried out for 45 min at 37°C. Thereafter the cells were washed twice, and the number of viable tumor cells estimated by the trypan blue dye exclusion test in a Bürker chamber. The tumor cells were diluted, and 10^6 viable cells were cultivated in 13 × 100 mm tubes kept at an angle of 15° in the presence of 2 ml of Eagle's in Earle's medium containing 15% fetal calf serum (Microbiological Associates, Bethesda, Md.). Mycostatin (30 IU/ml), penicillin (500 IU/ml), and streptomycin (0.1 g/ml) were present in the medium. After 24–48 hr incubation at 37°C, the tumor cells were used for the experiment. Medium was changed and 10 g/ml of phytohemagglutinin (PHA) (Wellcome Research Laboratories, Beckenham, England) was added. 30 min later, 0.1 ml lymphoid cell suspension containing 10^7 viable lymphoid cells was added to the tubes. In some experiments where serum was used, the lymphoid cells were first mixed with antiserum at 37°C for 30 min prior to addition to the target cells. After 48 hr, the tubes were centrifuged and the supernatant discarded, 2 ml of 0.25% trypsin was added for 30 min at 37°C, and the cells were washed once. Most of the supernatant was carefully withdrawn and the cells were resuspended in a small volume of medium. The total number of tumor cells per tube was calculated. At least five tubes were counted in each experimental group.

RESULTS

Cytotoxic Effect of Allogeneic and Semisyngeneic Nonimmune Lymphoid Cells.—Nonimmune allogeneic lymphoid cells are capable of causing cytotoxic damage to H-2 incompatible normal and neoplastic cells in the presence of PHA. Since syngeneic cells were not active in the presence of PHA, an alternative explanation of the reaction would be that a primary immune response was initiated in the lymphoid cells leading to the death of the target cells. In order to study this possibility, lymphoid cells from F_1 hybrid mice were added to target tumor cells derived from one of the parental strains.

F_1 hybrid cells were not expected to react immunologically against parental cells since recessively determined histocompatibility antigens have not been demonstrated in the H-2 systems of the mouse (19, 20). Therefore, the hybrid cells contain all histocompatibility factors present in the parental cells. However, lymphoid cells derived from F_1 hybrid mice were found to be able to kill H-2 incompatible tumor cells (Table I). In fact, they were equally, or only slightly less, efficient compared to homozygous allogeneic cells. It was concluded that at least one component of this reaction was not related to immunological phenomena analogous to those observed in vivo. It seems more likely that target cell damage was caused by contact with foreign isoantigens carried on the surface of the added lymphoid cells.

As demonstrated previously (12), other strain differences not related to histoincompatibility at the H-2 locus could not explain the effect, since cytotoxicity occurred in cells from congenic resistant lines different only with regard to their H-2 isoantigens.

Cytotoxicity of Parental Nonimmune Lymphoid Cells on F_1 Targets.—In view of the above findings, it was considered important to investigate whether lymphoid cells from a parental strain would kill target cells derived from an F_1 hybrid strain produced by crossing the parental strain with an H-2 incompatible strain. In this case, the target cells would not meet any foreign antigens on the added cells, since the targets contain all antigens present on the lymphoid cells. The results of some tests of this design are summarized in Table II. In all experiments, a significant cytotoxic effect of parental lymphoid cells on F_1 targets was observed. In Experiments 2 and 3, this cytotoxic effect was qualitatively comparable to that obtained with allogeneic cells, whereas in other experiments (1, 4, and 5) it was somewhat lower.

Effect of X-Irradiation on Cytotoxicity.—In these experiments, the possibility of the induction of a primary immune response exists since the lymphoid cells were confronted with foreign transplantation antigens present on the target cells. However, this was considered less probable since pretreatment of the lymphoid cells with X-ray doses of 1500–3000 R did not reduce their cytotoxic potency (Tables I and II). Similar doses of X-rays did not abolish cytotoxicity of homozygous allogeneic or semisyngeneic lymphoid cells.

As shown previously (21), DNA synthesis in lymphoid cells was completely inhibited by these X-ray doses as determined by the incorporation of thymidine-^{14}C into the lymphoid cells even after stimulation with PHA. Since semisyngeneic and X-irradiated allogeneic lymphoid cells were able to damage target

TABLE I

Cytotoxic Effect of Nonimmune Allogeneic and Semisyngeneic F_1 Hybrid Lymphoid Cells on Parental Target Tumor Cells

Exp. No.	Tumor	Strain of origin	Lymphoid cells derived from	Pretreatment of lymphoid cells	No. of living tumor cells $\times 10^3 \pm$ SE	Living cells in comparison with controls
						%
1	MCAGA	A	A	—	132 ± 22	100
			C57BL	—	44 ± 5	33.3
			A × C57BL	—	73 ± 5	55.3
2	MCAGA	A	A	3000 R	200 ± 18	100
			A.CA	"	93 ± 7	46.5
			C57BL	"	80 ± 9	40.0
			A × C57BL	"	92 ± 8	46.0
			—		188 ± 14	94.0
3	MC57S	C57BL	C57BL	1500 R	283 ± 31	100
			A	"	180 ± 18	63.6
			A × C57BL	"	181 ± 15	64.0
			A.CA	"	173 ± 16	61.1
			A.CA × C57BL	"	197 ± 14	69.0
			—		317 ± 14	>100
4	MC57S	C57BL	C57BL	—	84 ± 7	100
			A	—	32 ± 3	38.1
			A × C57BL	—	58 ± 7	69.0
			—		110 ± 21	>100
5	MC57S	C57BL	C57BL	—	105 ± 6	100
			A.CA	—	61 ± 12	58.1
			A.CA × C57BL	—	69 ± 11	65.7
			—		137 ± 15	>100
6	MC57S	C57BL	C57BL	—	41 ± 10	100
			A.CA	—	15 ± 2	36.6
			A.CA × C57BL	—	13 ± 1	31.7
			—		38 ± 4	92.3
7	MC57T	C57BL	C57BL	—	79 ± 12	100
			A	—	31 ± 6	39.2
			A × C57BL	—	27 ± 3	34.2
			C3H	—	45 ± 5	57.0
			C3H × C57BL	—	41 ± 7	51.9

TABLE II

Cytotoxic Effect of Nonimmune Allogeneic and Parental Lymphoid Cells on F_1 Hybrid Target Tumor Cells

Exp. No.	Tumor	Strain of origin	Origin of lymphoid cells	Pretreatment of lymphoid cells	No. of living tumor cells $\times 10^3 \pm$ SE	Living cells in comparison with controls
						%
1	MCAG	A × A.CA	A × A.CA	—	206 ± 12	100
			A	—	130 ± 9	63.1
			A.SW	—	57 ± 8	27.7
			—		204 ± 14	99.0
2	MCAG	A × A.CA	A × A.CA	3000 R	186 ± 18	100
			A	"	91 ± 16	48.9
			A.CA	"	95 ± 10	51.1
			C3H	"	100 ± 10	53.8
			A × C3H	"	83 ± 12	44.6
3	MDHC	C3H × DBA	C3H × DBA	3000 R	97 ± 10	100
			C3H	"	44 ± 8	45.4
			A	"	54 ± 1	55.7
			—		114 ± 10	>100
4	MDHC	C3H × DBA	C3H × DBA	1500 R	499 ± 118	100
			C3H	"	396 ± 70	79.4
			DBA	"	347 ± 42	69.5
			A	"	299 ± 43	59.9
			C57BL	"	386 ± 82	77.4
			A.CA	"	338 ± 77	67.7
5	MDHC	C3H × DBA	C3H × DBA	1500 R	55 ± 4	100
			C3H	"	43 ± 5	78.2
			DBA	"	36 ± 10	65.5
			A.SW	"	34 ± 8	61.8
			C57BL	"	24 ± 7	43.6
6	MDHC	C3H × DBA	C3H × DBA	1500 R	112 ± 9	100
			C3H	"	87 ± 6	77.7
			DBA	"	76 ± 15	67.9

cells, immune reactions appear unlikely, whereas the allogeneic inhibition concept explains the findings adequately. Parental cells killed F_1 targets to the same extent as allogeneic lymphoid cells did and their effect was not abolished by X-irradiation. It seems likely, in view of these findings, that an analogous mechanism operates in the latter case. Since F_1 target cells are not confronted with foreign antigens on parental lymphoid cells, allogeneic inhibition in the in the real sense cannot be applied as an explanation. However, the structural

TABLE III

Suppression of Target Cell Death by Pretreatment of the Allogeneic Lymphoid Cells with Specific Isoimmune Sera

Exp. No.	Target cells		Lymphoid cells derived from strain	Immune serum	Immune serum directed against the following lymphoid cells H-2 isoantigens	No. of surviving tumor cells × 10^3 ± SE	Living cells in comparison with controls
	Designation	Strain of origin					
							%
1	MC57S	C57BL	C57BL	—	—	128 ± 14	100
			A	C57L-A	1, 3, 4, 8, 10, 11, 13, 23	116 ± 11	90.6
			A	DBA × C57BL-A	1, 11, 25	62 ± 7	48.4
			A	C3H × C57BL-A	4, 10, 13	68 ± 15	53.1
			A	A.CA-A	3, 4, 5, 11, 13, 25, 28, 29	47 ± 9	36.7
2	MC57G	C57BL	C57BL	C57BL-A	None	181 ± 10	100
			C57BL	—	—	185 ± 17	>100
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	151 ± 24	83.4
			A	DBA × C57BL-A	1, 11, 25	88 ± 9	48.6
			A	CBA × C57BL-A	4, 10, 13	74 ± 10	40.9
			A	—	—	46 ± 8	25.4
3	MC57G	C57BL	C57BL	C57BL-A	None	81 ± 25	100
			C57BL	A × C57BL-ACA	None	88 ± 16	>100
			C57BL	—	—		
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	62 ± 16	76.5
			A	DBA × C57BL-A	1, 11, 25	61 ± 9	75.3
			A	CBA × C57BL-A	4, 10, 13	63 ± 11	77.8
			A	A × C57BL-ACA	None	34 ± 3	42.0
4	MC57G	C57BL	C57BL	C57BL-A	None	149 ± 25	100
			C57BL	A × C57BL-ACA	None	129 ± 9	86.6
			C57BL	—	—	124 ± 15	83.2
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	123 ± 14	82.6
			A	DBA × C57BL-A	1, 11, 25	90 ± 10	60.4
			A	CBA × C57BL-A	4, 10, 13	94 ± 9	63.1
			A	A × C57BL-ACA	None	90 ± 5	60.4
5	MC57G	C57BL	C57BL	C57BL-A	None	149 ± 24	100
			C57BL	A × C57BL-ACA	None	150 ± 15	>100
			C57BL	—	—	132 ± 17	88.6
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	120 ± 17	80.5
			A	DBA × C57BL-A	1, 11, 25	72 ± 8	48.3
			A	CBA × C57BL-A	4, 10, 13	81 ± 20	54.4
			A	A × C57BL-ACA	None	76 ± 12	51.0
			A	—	—	55 ± 6	36.9
6	MC57S	C57BL	C57BL	C57L-A	None	126 ± 24	100
			C57BL	—	—	145 ± 12	>100
			A	C57L-A	1, 3, 4, 8, 10, 11, 13, 25	71 ± 9	56.3
			A	DBA × C57BL-A	1, 11, 25	64 ± 10	50.8
			A	CBA × C57BL-A	4, 10, 13	63 ± 6	50.0
			A	—	—	70 ± 7	55.6
7	MC57T	C57BL	C57BL	C57L-A	None	170 ± 11	100
			C57BL	—	—	56 ± 8	80.0
			A	C57L-A	1, 3, 4, 8, 10, 11, 13, 25	43 ± 6	61.4
			A	—	—	12 ± 4	17.1
8	MC57T	C57BL	C57BL	C57BL-A	None	151 ± 17	100
			C57BL	C57BL ns	—	202 ± 15	>100
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	116 ± 23	76.8
			A	C57BL ns	—	89 ± 8	58.9

TABLE III-*Continued*

Exp. No.	Target cells		Lymphoid cells derived from strain	Immune serum	Immune serum directed against the following lymphoid cells H-2 isoantigens	No. of surviving tumor cells × 10^3 ± SE	Living cells in comparison with controls
	Designation	Strain of origin					
							%
9	MC57T	C57BL	C57BL	C57BL-A	None	75 ± 8	100
			C57BL	A × C57BL-ACA	None	98 ± 17	>100
			A	C57BL-A	1, 3, 4, 8, 10, 11, 13, 25	86 ± 7	>100
			A	DBA × C57BL-A	1, 11, 25	62 ± 11	82.7
			A	CBA × C57BL-A	4, 10, 13	47 ± 7	62.7
			A	A × C57BL-ACA	None	62 ± 11	82.7
10	MC57T	C57BL	C57BL	A-A.CA	None	78 ± 15	>100
			C57BL	C57L-A	None	70 ± 10	100
			A	C57L-A	1, 3, 4, 8, 10, 11, 13, 25	81 ± 7	>100
			A	DBA × C57BL-A	1, 11, 25	30 ± 4	42.9
			A	CBA × C57BL-A	4, 10, 13	52 ± 7	74.3
			A	A-A.CA	None	33 ± 6	47.1

arrangements of H-2 isoantigens are necessarily different on parental and hybrid cells. It seems possible that structurally and/or antigenically incompatible lymphoid cells can cause target destruction by close confrontation.

Specific Suppression of Cytotoxicity by Isoantibodies against the Allogeneic Lymphoid Cells.—In terms of the allogeneic inhibition concept, it would be expected that cytotoxicity is suppressed by blocking the antigenic receptors on the allogeneic lymphoid cells. It seemed possible that this could be achieved by treating the lymphoid cells with isoantibodies produced in the target strain and directed against the lymphoid cells. Tumors MC57G, MC57S, and MC57T indigenous to the C57BL strain were used for this study. Antisera against the allogeneic lymphoid cells of strain A origin were produced in the tumor host strain. Antibodies in C57BL mice against strain A are supposed to react with all the antigens on A cells that are different from the C57BL strain. Two other sera were also produced which are expected to contain antibodies only to some of the antigens present on the lymphoid cells and absent from the targets. Such sera were produced in (C3H × C57BL), (CBA × C57BL)F_1, and (DBA × C57BL)F_1 hybrids against strain A. Since C3H and CBA mice on the one hand and DBA on the other contribute antigens present in strain A and absent from C57BL, these sera will react only against some antigens in strain A which are absent in C57BL. For details of antiserum specificities see Table III. The results of 10 experiments of this design are shown in Table III. In all experiments but one (Exp. 6), pretreatment of the A lymphoid cells with C57BL or C57L anti-A serum before addition to the C57BL tumor cells resulted in a partial (Exps. 2, 3, 7, and 8) or almost complete (Exps. 1, 4, 5, 9, and 10) inhibitior of the cytotoxic reaction in comparison with the effect by untreated strain A lymphocytes or the same cells treated with isoantibodies not recognizing any of the relevant A antigens present on the lymphoid cells.

Antisera expected to react with some but not all of the A histocompatibility antigens absent in C57BL caused a partial suppression of cytotoxicity in some experiments, whereas in others there was no detectable protective effect. Although these sera contained antibodies against the lymphoid cells, complete inhibition of the reaction did not occur. Thus, suppression by the C57BL or C57L anti-A sera was specific and could not be explained by steric hindrance, lymphoid cell death, or leukoagglutination, all of which could occur theoretically. It seems likely, therefore, that inhibition of the cytotoxic reaction obtained in the present experiments was due to specific blocking by antibody of the antigenic determinants of the lymphoid cells, thereby interfering with the recognition of incompatibility by the target cells.

DISCUSSION

Cytotoxic effects of nonimmune lymphoid cells on incompatible target cells in vitro have recently been described by different authors (11, 12, 22–26). In some of these publications, syngeneic (or autochthonous) controls demonstrated that the effect was related to antigenic discrepancies rather than to various nonspecific influences (11, 12, 23, 26).

The presence of PHA or heterologous antibodies was found to be necessary for cytotoxicity with nonimmune allogeneic lymphoid cells (11, 12, 23, 24) or to accelerate cytotoxicity (26). Although this reaction could represent the induction of a primary immune response in vitro, several findings suggested that at least one component of the reaction was nonimmunological. As documented above, semisyngeneic F_1 hybrid lymphoid cells, generally assumed unable to carry out immune reactions against parental targets for genetical reasons, were as efficient as allogeneic cells. Since several experiments of this type have been performed in congenic resistant lines of mice, being different only with regard to histocompatibility antigens of the H-2 system, it was concluded that target cell confrontation with foreign histocompatibility antigens was the relevant variable for cytotoxicity (allogeneic inhibition) (12). This conclusion was strengthened in the tests described here by the finding that isoantibodies capable of reacting with all the lymphoid cell antigens which were foreign to the targets suppressed cytotoxicity, whereas antisera still reacting with the lymphoid cell antigens, but not blocking all antigens foreign to the target cells, did not suppress cytotoxicity.

Hellström and his collaborators (13, 14, 27, 28) have put forward evidence indicating that the reduced growth of tumors in semisyngeneic F_1 hybrids, as compared to syngeneic hosts, is dependant upon the confrontation of the tumor with foreign antigens present in the tumor recipients. In vitro studies revealed that antigenic extracts of allogeneic cells were able to inhibit the growth of cells in tissue culture, as compared to the effect of syngeneic antigenic extracts (14). From Hellström's and our own data, the conclusion was drawn that allo-

geneic inhibition is a cytotoxic and/or growth-inhibiting reaction induced by foreign histocompatibility antigens in a number of different target cells, such as normal embryo cells (12, 23), lymphoma (27), and sarcoma cells (11). As postulated before (10), the allogeneic inhibition phenomenon may contribute to the cytotoxic effect of immune lymphoid cells. According to this hypothesis, sensitized lymphoid cells would be equipped with specific receptors, presumably of antibody nature, making recognition and attachment possible to the targets, whereas actual target death would be caused by the allogeneic inhibition phenomenon.

A cytotoxic reaction mediated by nonimmune lymphoid cells has also been observed in human systems; Holm and Perlmann have shown that normal lymphocytes from peripheral blood can kill human Chang liver cells in culture in the presence of PHA (29). Their experiments suggested that the lymphocytes were probably not inactive during the cytotoxic process. Thus they demonstrated that lymphocytes which have been pretreated with PHA, with staphylococcal toxin, or with incompatible lymphocytes are more able to kill target cells than untreated cells. Furthermore, they have showed that lymphocytes from peripheral blood of leukemic patients were less capable of inflicting target cell damage (30). Such cells do not undergo blast transformation as easily as cells from healthy donors. Experiments with various metabolic inhibitors suggested that inhibition of RNA or protein synthesis did not affect the potency of the lymphocytes in causing target cell death, whereas certain drugs that interfered with oxygen uptake and energy-consuming processes were suppressing (31).

Other experiments with human cells have shown that allogeneic lymphocytes are more potent in causing destruction of human fibroblast cell cultures than cells obtained from the autochthonous patient (26). However, in some tests, autochthonous lymphocytes gave cytotoxic reactions, although these reactions were always lower in intensity than those from allogeneic cells. The autochthonous reactions were caused to a large extent by contaminating granulocytes which became degranulated in tissue culture and presumably released lysosomal substances toxic to the target cells. Pure lymphocytes such as those obtained from the thoracic duct were highly cytotoxic in the presence of PHA to allogeneic cells.[1] Further studies on these problems are in progress.

SUMMARY

Nonimmune lymphoid cells were capable of causing cytotoxicity of H-2 incompatible mouse tumor cells in vitro in the presence of PHA, whereas syngeneic cells were not. Semisyngeneic and X-irradiated (1500–3000 R) F_1 hybrid lymphoid cells were cytotoxic for target cells derived from one of the parental

[1] Möller, G. Personal communication.

strains. In addition, parental nonimmune and X-irradiated lymphoid cells damaged hybrid target cells. It was concluded that one component of cytotoxicity was not related to an induction of a primary immune response in vitro, since F_1 hybrid cells are not capable of reacting immunologically against parental type target cells. It seemed probable that cytotoxicity was caused by target cell confrontation with antigenically and/or structurally incompatible lymphoid cells. This conclusion was strengthened by the demonstration that isoantibodies produced in the target strain and directed against the allogeneic lymphoid cells specifically suppressed cytotoxicity. Isoantibodies reacting against some but not all of the antigenic determinants of the lymphoid cells differentiating them from the target cells did not suppress cytotoxicity. The specific suppression of cytotoxicity by specific isoantibodies against the lymphoid cells support the allogeneic inhibition concept.

The author wishes to thank Mrs. Lill-Britt Andersson for excellent technical assistance.

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