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Immunology

Cognate peptides induce self-destruction of CD8$^+$ cytolytic T lymphocytes

(antigen presentation/target cell lysis/histocompatibility antigens/CD8 T cells/peptide vaccines)

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ABSTRACT **Cytotoxic T lymphocytes (CTLs) have been shown to be relatively resistant to cytolytic attack by other CTLs. We show here, however, that cloned CTLs, in the absence of other cells, are destroyed by exposure to their cognate peptides (defined as those that in association with major histocompatibility complex proteins are recognized by the antigen-specific receptor of the T cell). Destruction is proportional to peptide concentration and can be prevented by a second peptide that competes with the cognate peptide for presentation by the class I major histocompatibility complex proteins of the CTLs. The speed and extent of peptide-induced changes in the appearance of CTLs suggest that the destruction may be due primarily to self-recognition and self-destruction of individual CTLs (suicide) rather than to the destruction of some CTLs by others of the same clone in the same culture (fratricide). This effect may also take place *in vivo* because the appropriately timed injection of a cognate peptide into ovalbumin-immunized mice appeared to deplete their spleens of primed anti-ovalbumin CTLs. The results point to a possible physiologic mechanism for postthymic elimination of cytolytic T cells that recognize their own peptides in association with their own major histocompatibility complex protein. The results also raise the possibility that cognate peptides might eventually prove therapeutically useful for eliminating CTL clones that cause pathological cell destruction, as in some autoimmune diseases and some viral infections.**

Considerable evidence suggests that the antigens recognized by CD8$^+$ cytotoxic lymphocytes (CTLs) are complexes formed on target cells by the association of peptide fragments of protein antigens with proteins encoded by genes of the class I major histocompatibility complex (termed MHC-I proteins). It is likely that the peptide moiety of the complex normally arises within the target cell itself from proteolysis of its recently synthesized proteins. However, short synthetic peptides (typically 8–25 amino acids in length) that resemble the natural peptide moiety are also effective in creating antigenic complexes because cells that express an appropriate MHC-I protein become susceptible to lysis simply upon incubation with an appropriate peptide (1), here termed the cognate peptide.

CTLs and their target cells usually express the same MHC-I proteins (i.e., they are syngeneic). Hence, when a synthetic cognate peptide is added to a mixture of CTLs and syngeneic target cells, the peptide should associate not only with an appropriate MHC-I on the target cell but on the CTL as well. Nevertheless, in the standard 4-hr assay used to measure cytolysis it has been repeatedly observed with many different peptides, CTLs, and syngeneic target cells that the addition of a cognate peptide induces the CTLs to lyse the target cells but not apparently to lyse themselves. This asymmetry appears not to have attracted much attention, probably because of current ideas on how CTLs kill target cells. According to an extensively studied mechanism, when a CTL recognizes and adheres to the antigen on a target cell, the CTL is stimulated to release cytotoxic granules into the synapse-like cleft between it and the target cell (2, 3). When isolated from CTLs, these granules readily lyse a wide variety of normal and transformed cells, but CD8$^+$ T cells and especially cloned CD8$^+$ CTL cell lines are relatively resistant (4); hence, lysis of the target cell, and not the CTL, is understandable.

The recognition of an antigen on the target cell stimulates the CTL not only to release its cytolytic components but also to proliferate. Accordingly, cultured CTLs are usually maintained by periodically incubating them with target cells having the appropriate surface antigen (because target cells express either the corresponding genomic gene, are infected with an appropriate virus, or are "pulsed" by briefly incubating them with synthetic cognate peptides and then washing them to remove unbound peptides). In view of these circumstances it seemed reasonable to attempt to maintain CTLs in culture simply by periodically adding cognate synthetic peptides to mixtures of these cells and syngeneic target cells. Surprisingly, however, we found that this simple procedure decreased the number of CD8$^+$ CTLs. To analyze this unexpected observation, we examined the effects of synthetic peptides on CTL clones. We show here that in all cases examined self-recognition of a cognate peptide stimulates CTLs to destroy themselves. The effect was seen consistently *in vitro* (with five clones specific for three peptides, see Table 1), and preliminary results suggest that it can also occur *in vivo*.

METHODS

Mice, Antigens, and Immunizations. C57Bl/6 and DBA/2 mice were obtained from The Jackson Laboratory. Chicken ovalbumin was grade VI (lot 29F-8040) from Sigma; although purified further by ion-exchange chromatography on TSK650-DEAE, it contained trace amounts of many peptides (≈2–20 kDa on silver-stained SDS/PAGE). The peptides OVA-2, pp89, and T1 (Table 1) were synthesized in the Biopolymers Lab of the Howard Hughes Medical Institute (Massachusetts Institute of Technology). Mice were primed by injecting 10^7 viable EG7-OVA cells [EL-4 tumor cells transfected with the ovalbumin gene (5)] in 20 μl of phosphate-buffered saline into hind footpads, or 200 μg of OVA-2, or 2 mg of ovalbumin in 0.5 ml of 150 mM NaCl i.p. The mice were boosted at the indicated times (Fig. 3) by injecting the same quantities of cells, protein, or peptide in 0.5 ml of saline i.p. Spleen cells from these mice were restimulated *in vitro* at

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Abbreviations: CTL, cytotoxic T lymphocyte; FCS, fetal calf serum; MHC-I, class I major histocompatibility complex.

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Table 1. CTL clones and their specificities

Clone	Cognate peptide	Presented by MHC-I	Stimulator cell*
4G3, 2H7, and 3G12	OVA-2 (IINFEKLTEWTSSNVMEER)	K^b	EG7-OVA
12D3	T1 (ISTQNHRALDLVA)	L^d	P911
IE1†	pp89 (YPHFMPTNL)	L^d	

*EG7-OVA cells (H-2^b) are EL-4 tumor cells transfected with the ovalbumin gene (5). P911 cells (H-2^d) are mutagenized P815 tumor cells in which the histidine residue of the T1 sequence replaced a wild-type arginine residue in a gene of unknown function (6).
†The IE1 CTL responds to the pp89 peptide, a sequence in the pp89 protein of murine cytomegalovirus, in association with L^d (7).

5- to 7-day intervals with 10^7 irradiated (6000–18,000 rads; 1 rad = 0.01 Gy) EG7-OVA cells in α modified Eagle's medium/10% fetal calf serum (FCS); the cells were tested for cytotoxic activity 5 days after restimulation (see Fig. 3, below).

Cell Lines. The thymoma EL-4 (H-2^b), the mastocytoma P815 (H-2^d), and the tum$^-$ variant P911 tumor cell line were grown in Dulbecco's modified Eagle's medium/10% FCS. EG7-OVA cells were cultured in the presence of 400 μg of G418 per ml (5). The CTL clone IEI was grown in α modified Eagle's medium/10% FCS and recombinant interleukin 2 at 100 units per ml, as described (8). CTL clone 12D3 was established in this laboratory by K. Udaka according to ref. 9; it was maintained by stimulating the cells every 4 or 5 days with irradiated (6000 rads) P911 cells and irradiated syngeneic spleen cells in DMEM/10% FCS in 5% rat Con A supernatant as described (10). The OVA-2-specific CTL clones 4G3, 2H7, and 3G12 were established in this laboratory by C. Nagler-Anderson according to ref. 5; they were maintained by weekly restimulation with irradiated EG7-OVA cells in RPMI 1640/10% FCS/5% rat Con A supernatant.

Cytotoxicity Assay. Five thousand ^{51}Cr-labeled target cells (EL-4, EG7-OVA, P815, or P911) were incubated with various numbers of CTLs in a total volume of 200 μl of RPMI 1640/10% FCS in round-bottom microtiter plates. After 4 hr the plates were centrifuged briefly, and 100-μl portions of supernatants were analyzed in a γ counter. Percent specific lysis was calculated as $100\ (a - b)/(c - b)$, where a is cpm released due to CTLs, and c, maximum release, was determined by treating the labeled cells with 0.05% Nonidet P-40. Spontaneous release (b) was consistently <10% of the maximal release.

RESULTS

Effect of Peptides on Cell Survival. During attempts to elicit antiinfluenza virus CTLs from human peripheral blood cells, the repeated addition to cultures of an immunodominant influenza virus peptide (matrix protein peptide 55-73) led to a gradual disappearance of CD8$^+$ T cells and persistence of CD4$^+$ T cells (P.W., unpublished data). To verify this observation we followed cell counts of murine CD8$^+$ CTL clones cultured with and without cognate peptides at various concentrations. Fig. 1*A* shows what happened when a cognate peptide (OVA-2, see Table 1) was added to an antiovalbumin CD8$^+$ CTL clone (2H7) that had been stimulated for the preceding 3 days by incubation with irradiated target cells (EG7-OVA, see Table 1). When no peptide was added (0, Fig. 1*A*), there were 1.4×10^6 CTLs per ml on day 3 and 2×10^6 CTLs on day 4; however, in cultures to which the OVA-2 peptide was added at 20 μg/ml, the number of CTLs per ml dropped to 0.2×10^6 on day 3, and to too few cells to count ($<0.1 \times 10^6$) on day 4. Decrease was proportional to concentration of peptide (Fig. 1*A*).

Similar effects were seen with four other CD8$^+$ CTLs: 3G12 and 4G3, both antiovalbumin clones; 12D3, an antitumor clone; and IE1, a clone specific for mouse cytomegalovirus-infected cells (Table 1). In all cases, the decline in cell numbers was proportional to the concentration of the cognate peptide.

Destruction of CTLs Can Be Inhibited by a Peptide That Blocks Lysis of a Conventional Target Cell. The foregoing results imply that CTLs recognize their cognate peptides in association with their own MHC-I protein. To determine whether this self-recognition resembles the recognition of a peptide on a conventional target cell, 20 unrelated peptides were screened, and one that blocked sensitization of EL-4 cells by the OVA-2 peptide for lysis by antiovalbumin CTLs was identified (Jan Dutz, personal communication). Such inhibitory peptides appear to compete with cognate peptide for presentation by the MHC-I protein of the target cells (K^b in this instance) (6, 11, 12). Fig. 1*B* shows that the inhibiting peptide (pp89) also blocked the OVA-2-induced self-destruction of an antiovalbumin CTL clone (4G3 cells). The extent of inhibition increased with increased concentrations of blocking peptide. Thus, CTLs appear to recognize cognate peptides on themselves in the same way as on conventional target cells.

Effect of Peptides on Cytolytic Activity. To extend the observations on CTL survival we followed the effect of peptides on cytolytic activity. After several clones were maintained for 3 days with or without various peptides, they were tested for cytolytic activity. When no peptide had been added (Fig. 2, column at extreme left), the cytolytic activity defined the specificity of the clones. Virtually all antiovalbumin CTLs raised in C57BL/6 mice (H-2^b) by the immunization program used to derive clone 4G3 (see *Methods*) have been shown (5, 13) to recognize the OVA-2 peptide in association with K^b. This specificity (OVA-2/K^b) agrees with the activity of clone 4G3 (Fig. 2, *Left upper*) as well as the other anti-OVA CTL clones studied here (Table 1). Similarly,

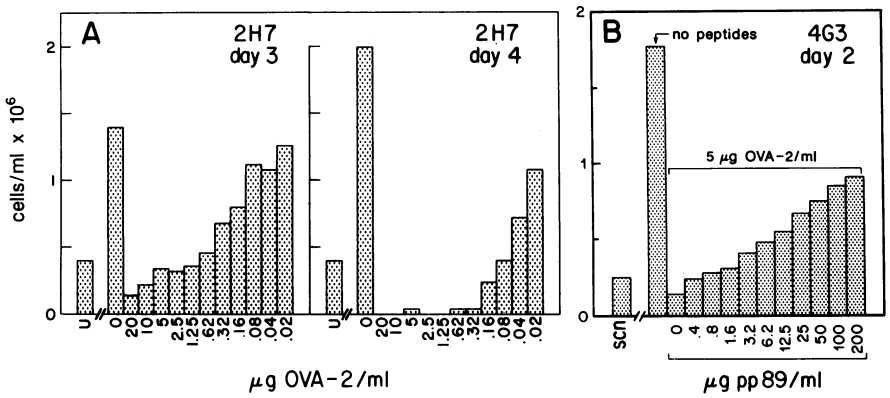

FIG. 1. Destruction of CTLs by a cognate peptide (*A*) and inhibition of the destruction by a competing peptide (*B*). (*A*) Cells of clone 2H7 were incubated for 3 or 4 days with stimulator cells (EG7-OVA) in the absence (0) or presence of the cognate peptide (OVA-2) at various concentrations. Control 2H7 cells, incubated for 3 or 4 days in the absence of EG7-OVA and OVA-2, are at extreme left (U, unstimulated cells). (*B*) Clone 4G3 was incubated without any peptide (no peptides) or with their cognate peptide (OVA-2) at 5 μg per ml plus the competing peptide pp89 at 0–200 μg per ml. Cell counts are after 48 hr. scn, Starting cell number, is the initial number of 4G3 cells.

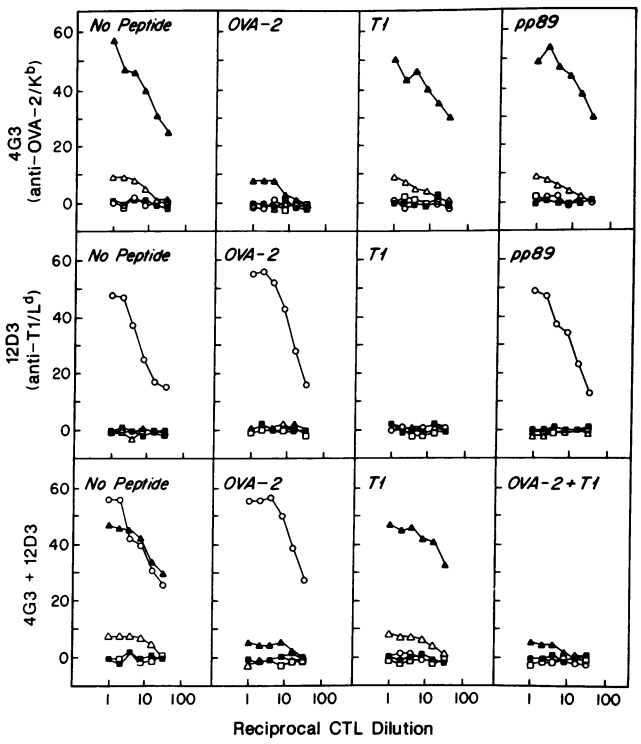

FIG. 2. Self-destruction of CTLs and loss of cytolytic activity. Freshly stimulated cells of clones 4G3 and 12D3 (MHC haplotypes H-2^b and H-2^d and specific for OVA-2 with K^b and T1 with L^d, respectively, see Table 1) were incubated with no peptide or with the peptides shown at the top of each panel and then tested for cytolytic activity by the standard 4-hr assay against the following four ^{51}Cr-labeled targets: △, EL-4; ▲, EL-4 + OVA-2 at 5 μg per ml; □, P815; ○, P815 + T1 at 1 μg per ml; and ■, P815 + pp89 at 1 μg per ml. In the bottom row 4G3 and 12D3 were cultured together with no peptide or with OVA-2 or T1 or both OVA-2 and T1 at the concentrations noted above. Successive twofold dilution of the CTL cultures were used to titrate CTL/target cell ratios.

the specificity of clone 12D3 for a tumor-derived peptide (T1) in association with L^d agrees with Lurquin *et al.* (6). When these clones were incubated for 3 days with each of several peptides and then tested for cytotoxic activity, it was evident (Fig. 2) that only a clone's cognate peptide eliminated that clone's activity: the OVA-2 peptide inactivated only clone 4G3, and the T1 peptide inactivated only clone 12D3. A third clone, IE1, was similarly inactivated by pp89, its cognate peptide (data not shown). However, pp89 had no effect on clones 12D3 and 4G3 (Fig. 2), even though it prevented the recognition by clone 4G3 of its cognate peptide (Fig. 1*B*).

To determine whether the response of a CTL to its cognate peptide affects CTLs of different specificity in the same culture, two clones were cultured together with their respective cognate peptides, added singly or together. As shown in the bottom row of Fig. 2, each peptide inactivated only the clone that recognized it (in association with the appropriate MHC-I protein) without affecting the other clone in the same culture (i.e., OVA-2 inactivated 4G3 cells but not 12D3 cells, and T1 inactivated 12D3 cells but not 4G3 cells); with both peptides in the same culture, both clones were inactivated.

Do Cognate Peptides Inactivate CTLs *in Vivo*? To elicit CTLs against many antigens (including ovalbumin, ref. 13 and Fig. 3, below) it is necessary to obtain activated precursor ("primed") CTLs from animals immunized with the antigen in appropriate form and to restimulate these cells in culture. If a cognate peptide induces self-destruction of CTLs *in vivo*, as it does *in vitro* (Figs. 1 and 2), then injecting the immunized animals with the peptide at an appropriate time and in appropriate amount should eliminate or substantially reduce the level of cytolytic activity that can be demonstrated *in vitro*. To measure antiovalbumin CTL activity *in vitro* we stimulated isolated spleen cells in culture one or more times with irradiated EG7-OVA cells and then tested for cytolytic activity on three target cells: (*i*) EG7-OVA, (*ii*) EL-4 cells sensitized by incubating them with the OVA-2 peptide (termed EL-4 + OVA-2 targets), and (*iii*) EL-4 cells alone (termed nonsensitized targets). Greater lysis of the EL-4 + OVA-2 targets than of nonsensitized EL-4 measured OVA-2-specific CTL activity.

Fig. 3 shows that spleen cells from naive mice exhibited no cytolytic activity when stimulated in culture (Fig. 3*A*, but they did manifest low-level activity against some epitopes of EL-4 cells), as expected (13). In contrast, anti-OVA-2 activity was pronounced in spleen cells obtained from mice that had been primed with EG7-OVA cells (Fig. 3*B*) or with ovalbumin (data not shown). This activity was also elicited in spleen cells of mice that had been primed by two injections of the OVA-2 peptide, ≈30 days apart but not mice given a single injection of the peptide (Fig. 3 *C* and *D*).

To determine whether the cognate peptide (OVA-2) could decrease the effect of priming the CTLs *in vivo*, the peptide was injected into mice at different times after injections of (irradiated) EG7-OVA cells and ovalbumin. When the peptide was injected once 14 days after the primary injection and 16 days before the booster injection, it had no obvious effect: i.e., the spleen cells subsequently obtained exhibited pronounced anti-OVA-2 activity (Fig. 3*E*). When, however, the peptide was also injected 4 days after the booster injection, the spleen cells appeared to have been depleted of primed anti-OVA-2 CTLs because this activity was not subsequently

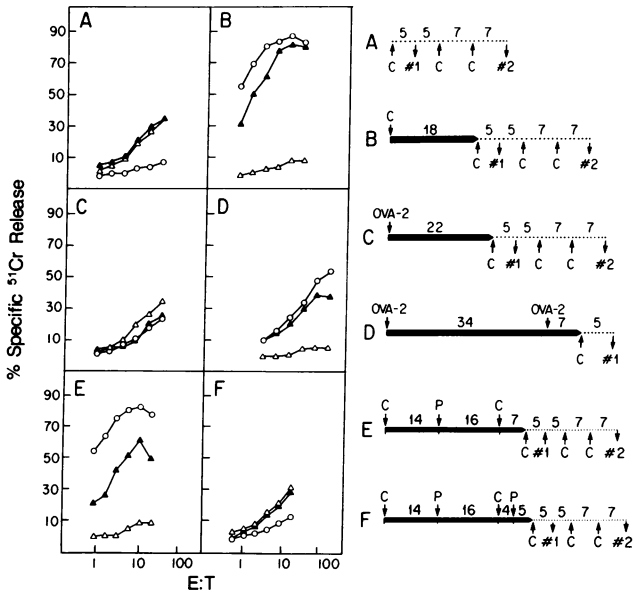

FIG. 3. Inactivation of primed splenic CTLs *in vivo*. (*A–F*) Cytolytic assays of spleen cells derived from naive mice (*A*) or mice immunized according to the protocols shown (*B–F*). In the immunization protocols shown at right, the heavy horizontal line indicates when (in days) C57Bl/6 mice were injected with EG7-OVA cells (C) or the OVA-2 peptide (termed OVA-2 or P). Dotted line at extreme right indicates when and at what intervals (days) the isolated spleen cells were boosted in culture with EG7-OVA cells (C) and tested for cytolytic activity (either 5 days after the first boost, assay #1, or 7 days after the third boost, assay #2). For all cytolytic assays the ^{51}Cr-labeled target cells were EL-4 (△), EL-4 + OVA-2 at 5 μg per ml (▲), and EG7-OVA (○). Mice were naive (*A*) or primed with EG7-OVA (*B*, *E*, and *F*) or with the OVA-2 peptide (*C* and *D*), and their spleen cells were assayed after having been boosted in culture once with EG7-OVA (assay #1 in *D*) or twice more (assay #2, in *A–C*, *E*, and *F*). E:T, effector/target cell ratio.

elicited in culture (cf. Fig. 3 *E* and *F*). In other mice primed with EG7-OVA cells (irradiated) and boosted 22 days later with ovalbumin, the peptide was injected once 1–5 days after the booster injection. Mice that had received no peptide at all or that had been injected with the peptide on day 1 or 5 after the booster injection had substantial and indistinguishable levels of OVA-2-specific CTL activity (as in Fig. 3*B*), but the injection of peptide on day 2 eliminated OVA-2-specific cytolytic activity; injection of peptide on day 3 or 4 resulted in a reduction but not in a complete elimination of anti-OVA-2 activity (data not shown). Thus, appropriately timed injections of immunized mice with cognate peptide appeared to delete or inactivate the corresponding CTLs from the spleen. These preliminary results lead us to suggest that (*i*) a cognate peptide can specifically inactivate the corresponding CTLs *in vivo*, (*ii*) the inactivation probably occurs only when the peptide achieves a critical concentration for a critical period in the immediate vicinity of cells that are cytolytically active, and (*iii*) resting CTL precursors are probably unaffected.

Is Peptide-Induced Destruction of CTLs Due to Fratricide or Suicide? The destruction of cloned CTLs by their cognate peptide could come about because the cells attack each other (fratricide) or because individual cells are induced to undergo self-destruction (suicide). A distinction between these possibilities is suggested by the appearance of the cells in a light microscope after exposure to peptides. In contrast to the highly irregular, elongated normal shape of control CTLs (Fig. 4*A*), virtually all antiovalbumin (4G3) CTLs became round and highly refractile within 1 hr of adding a cognate (OVA-2) peptide (Fig. 4*B*); many were also aggregated into large clumps. By the next morning most of the cells were dead, suggesting that most of the round cells seen after 1 hr went on to die. Specificity of this striking change was evident from the pronounced delay brought about by including in the medium an inhibiting peptide (pp89) at a 20-fold molar excess over the cognate (OVA-2) peptide (Fig. 4*C*). Because virtually all cells were so rapidly affected, it is possible that cell–cell contact is not required. Instead, it seems more likely that the individual CTL, upon recognition by its antigen-specific receptor of the cognate peptide in association with the MHC-I protein on the same cell is triggered to undergo a prompt change in shape and to eventually self-destruct. Such a mechanism is consistent with standard models of antigen recognition because the surface proteins of a single cell (in this instance MHC-I and the T-cell receptor) can probably interact with one another.

DISCUSSION

This study shows that CTLs can be destroyed by exposing them to their cognate peptides. The destruction is proportional to peptide concentration, and it can be blocked by a second peptide that blocks MHC-presentation of the cognate peptide. The findings suggest, therefore, that CTLs destroy themselves when their antigen-specific receptors recognize their cognate peptide in association with their own MHC-I protein. It is quite possible that the effect results from the self-destruction of individual CTLs (suicide), rather than from their destruction by other CTLs of the same clone (fratricide).

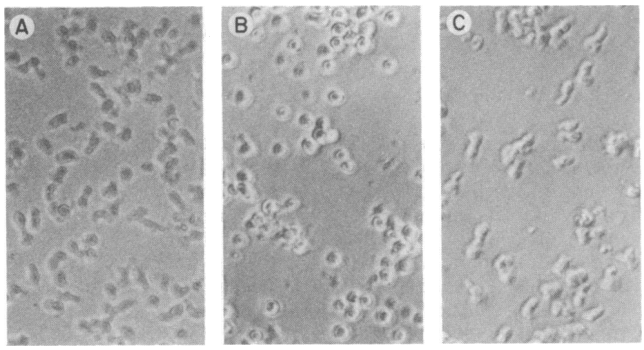

FIG. 4. Change in appearance of CTL upon exposure to their cognate peptide. Antiovalbumin CTLs of clone 4G3 were photographed under an inverted phase-contrast Nikon microscope ≈1 hr after addition of no peptide or the pp89 peptide (*A*), or their cognate peptide OVA-2 at 10 μg/ml (*B*), or a mixture of OVA-2 at 10 μg per ml and the competing peptide pp89 at 200 μg/ml (*C*). (×210.)

Cloned CTLs maintained in culture by periodically stimulating them with target cells are generally highly resistant to cytolytic attack by other CTLs (14–16). The resistance was also evident in this study when two clones having the same MHC (12D3 and IE1) were cultured together with the cognate peptide for one of them (peptide pp89 for clone IE1; see Table 1). The IE1 cells are exceptional in their susceptibility to lysis in the standard 4-hr assay (probably because of the way they are cultured; ref. 8): they killed themselves but not the 12D3 cells (data not shown). Because 12D3 cells express L^d, the MHC-I protein that can present the pp89 peptide, they should have been recognized and lysed by the cytolytically active IE1 cells were it not for their resistance.

If a CTL, such as 12D3, resists destruction by another CTL, why should it not resist self-destruction? The answer probably lies in two considerations: (*i*) while CTLs are highly resistant as target cells they are not totally resistant (e.g., they can be inactivated in mixed lymphocyte cultures when recognized as targets by multiple alloreactive CTLs) (14, 17, 18) and (*ii*) self-destruction of CTLs and lysis of conventional target cells differ kinetically. In conventional reactions between CTLs and target cells the two cells adhere to each other as "conjugates" only transiently, as briefly as 6 min (19) and usually much less than an hour. This transience is evident from the low frequency of conjugates in CTL–target cell mixtures (e.g., ref. 20) and from the well-known migration of CTLs from one target cell to another. In contrast, when a single CTL serves as its own target, by presenting a cognate peptide via its own MHC-I molecules to its own antigen–receptor molecules, the interactions are probably long-lasting as long as the peptide is present. The chronicity of this self-attack is probably responsible for the eventual death of the CTL, which occurs much more slowly (Fig. 1) than is seen in lysis of conventional target cells.

Many peptides, when injected into mice, stimulate the development of $CD4^+$ T helper cells but commonly fail to elicit the development of $CD8^+$ CTLs (21). This failure, of obvious importance to peptide vaccine development efforts, is puzzling because many of the peptides probably associate with MHC-I proteins. In contrast, target cells that express endogenously derived peptides in association with surface MHC-I are potent immunogens for $CD8^+$ T cells. It is possible that exogenous peptides are presented much less effectively than endogenously derived ones, perhaps because of large differences in the surface density on target cells of the relevant peptide–MHC-I complexes. Another possibility is suggested by the evidence that a cognate peptide can induce self-destruction of activated CTLs *in vivo* (Fig. 3). Thus, when mice are immunized by repeated injections of a cognate peptide, any $CD8^+$ T cells that are successfully primed by one injection would be at risk of self-destruction if a subsequent injection led to an adequate peptide concentration in the immediate environment of the cytolytically competent CTLs. Nevertheless, when some peptides are administered under special conditions, they can elicit the corresponding $CD8^+$ CTLs (13, 22, 23). Likewise, in the present study a low level of OVA-2-specific cytolytic activity was induced by widely spaced injections of the OVA-2 peptide (Fig. 3*D*): we surmise that under these conditions cells primed by the first injection would not have been cytolytically active when the peptide was injected a second time, leading to their further priming

and eventually to their successful restimulation in culture with EG7-OVA cells.

In several previous reports, cognate peptides have been observed to cause unresponsiveness of the corresponding T-cell clones, without inducing their self-destruction as described herein (24–26). Of particular note, Vitiello *et al.* (27) recently observed that the addition of cognate peptides to murine $CD8^+$ CTLs reduced their cytolytic activity. However, they did not describe self-destruction of these CTLs; instead, they attributed their diminished cytolytic activity to "cold-target inhibition" (in which unlabeled CTLs having bound cognate peptide competed with ^{51}Cr-labeled target cells, also having bound cognate peptide, for recognition by the CTLs). However, as the present work was being readied for publication, a report appeared by Pemberton, Wraith, and Askonas (28), describing peptide-induced lysis of $CD8^+$ CTL clones, almost exactly as in the present report. Human $CD4^+$ CTL clones have also been very recently reported (29) to lyse peptide-pulsed cells of the same clone (or other class II MHC-matched cells).

CTLs that can recognize an individual's self-peptides in association with self-MHC-I proteins are potentially pathogenic. Much evidence suggests that the precursors of such cells are normally deleted as they develop in the thymus, but if some were to escape, it is possible that they would self-destruct in the periphery as they respond to cognate peptides that associate with their own MHC proteins. Thus, the process described here and in ref. 28 could serve as the basis for a postthymic mechanism that contributes to the elimination of anti-self CTLs.

The evidence that synthetic peptides can eliminate activated CTLs *in vivo* also suggests that such peptides might be useful therapeutically—e.g., to destroy CTLs that cause pathological cell destruction, as probably occurs in some autoimmune diseases and viral infections. Because the requirements for the effective administrations of such peptides are stringent (Fig. 3), their therapeutic application is likely not to be simple. Nevertheless, their potential ability to eliminate critical clones, while leaving the immune system as a whole intact, suggests that cognate peptides, once identified and properly administered, could contribute to the realization of a long-term goal of immune therapy.

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