IMMUNE RESPONSE GENES CONTROL T KILLER CELL RESPONSE AGAINST MOLONEY TUMOR ANTIGEN CYTOLYSIS REGULATING REACTIONS AGAINST THE BEST AVAILABLE H-2 + VIRAL ANTIGEN ASSOCIATION*

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Cytolytic T lymphocytes (CTL)[1] directed against murine sarcoma virus (MSV) tumors (1) or any other tumor bearing the C-type virus-induced Friend, Moloney, Rauscher (FMR) antigen (2) are H-2 restricted. It has been previously shown that in most cases the products of only one region of the H-2 complex are involved in the CTL to tumor target cells interaction, i.e., D^b in H-2^b and K^d in H-2^d haplotypes, K^b and D^d being not concerned (3). Similar phenomena have been observed in other systems with nononcogenic viruses (4–6), H-Y (7), other minor histocompatibility antigens (8) and hapten-modified cells (9). Several explanations of this very precise H-2 restriction can be advanced: *(a)* The association of FMR and certain H-2 molecules (i.e., K^b and D^d) never occurs on the tumor cell surface. *(b)* The CTL response is under the control of classical I region-associated immune response (Ir) genes with dominant responsiveness; H-2^b mice, for example, being low responders against K^b + FMR. *(c)* The response is directly controlled by genes mapping in the K or D regions, with complete immunodominance of some viral + H-2 associations so that in the presence of the immunodominant one (i.e., D^b + FMR or K^d + FMR), the other associations existing on the tumor cell surface are not recognized by CTL precursors. We report here experiments excluding the first hypothesis and strongly suggesting that it is the third hypothesis that is correct in the FMR tumor system.

Materials and Methods

Mice. BALB/c, C57BL/6 (B6), C57BL/10 (B10), B10.A(2R) (2R), B10.A(5R) (5R), C3H.OL, HTG, HTI, (5R × B10)F_1, and (5R × B10.WB)F_1 hybrids were obtained from our colonies. (Institut National de la Santé et de la Recherche Médicale, Paris).

Viruses. The MSV, Moloney isolate, was maintained by acellular transmission in newborn (B6 × BALB/c)F_1, and the Moloney leukemia virus (MLV) in newborn BALB/c mice.

Cells. MBL2, an MLV-induced lymphoma of B6 (H-2^b) mice, and LSTRA, an MLV-induced lymphoma of BALB/c (H-2^d) mice, were maintained by intraperitoneal passage of 10^6 cells in adult animals. Both of them bear the serologically defined viral FMR antigen. FMR(+)

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[1] *Abbreviations used in this paper:* CRT, chromium release test(s); CTL, cytotoxic T lymphocyte(s); FMR, Friend, Moloney, Rauscher; Ir, immune response; LPS, lipopolysaccharide; MHC, major histocompatibility complex; MLV, Moloney leukemia virus; MSV, murine sarcoma virus.

5R tumor cells were not available, and C-type virus-infected fibroblasts, macrophages, and lymphocytes of adult mice are relatively bad targets and stimulator cells for the FMR system. All the experiments with 5R cells were therefore set up with lipopolysaccharide (LPS) blasts of adult mice infected when newborn with MLV, as described recently (V. Duprez, Y. Hénin, and J. P. Lévy. Manuscript in preparation.). Such blast cells behave in serological and cell-mediated reactions like FMR lymphoma cells; they are, however, less sensitive to immune cytolysis.

Immune Lymphocytes. Immune spleen cells from mice inoculated intramuscularly with MSV were taken 10–15 d after inoculation for primary chromium release tests (CRT), and 3–30 wk later for in vitro restimulation by syngeneic FMR(+) cells. Restimulation was performed as previously described (2).

CRT. The CRT was performed as previously described (2) in microtiter plates (Titertek; Flow Laboratories, Paris), with each well receiving 10^4 ^{51}Cr-labeled target cells and normal or immune lymphocytes so that the effector:target cell ratio varied from 100:1 to 3:1. The chromium release was measured after 18 h of incubation in primary and 4 h of incubation in secondary reactions.

Competition Experiments. The competition experiments were performed by adding increasing amounts of unlabeled competitor cells to the CRT mixture as described previously (2).

Blocking by Anti-H-2 Sera. Blocking by anti-H-2 sera was performed with cells previously incubated for 20 min at 4°C with ½ diluted sera as targets for the CRT (3). The sera were obtained by repeated inoculations of allogenic spleen cells in recipient adult mice. Three different sera were used: anti-H-2^b: (BALB/c × C3H/He)F_1 anti-BALB.B; anti-H-$2D^b$: (B10.RIII × B10.Br)F_1 anti-B10.A(4R); and anti-H-$2K^b$: B10.A anti-B10.A(5R).

Results

Table I shows the results of a typical experiment involving in vivo primed anti-MSV T killer cells and H-2^b or H-2^d lymphoma target cells. It appears, as described previously (3), that MBL2 (H-2^b) was killed only by CTL sharing the D^b specificity, and LSTRA (H-2^d) only by attacker lymphocytes sharing d specificities at the K end of the major histocompatibility complex (MHC). On the other hand, HTI and 5R

TABLE I

Cytolysis of H-2^b and H-2^d Lymphoma Cells By In Vivo Primed Anti-MSV CTL from Different Lines

Effector cells										Target Cells	
Immune spleen cell donors*	H-2 haplotype									MBL2	LSTRA
	K	A	B	J	E	C	S	G	D	(H-2^b)	(H-2^d)
C57BL/6 anti-MSV	b	b	b	b	b	b	b	b	b	47‡	4
B10.A(2R) anti-MSV	k	k	k	k	k	d	d	—	b	36	6
BALB/c anti-MSV	d	d	d	d	d	d	d	d	d	3	32
C3H.OL anti-MSV	d	d	d	d	d	d	k	k	k	0	21
B10.A(5R) anti-MSV	b	b	b	k	k	d	d	d	d	0	0
HTG anti-MSV	d	d	d	d	d	d	d	—	b	23	19
HTI anti-MSV	b	b	b	b	b	b	b	—	d	5	3

* Effector cells have been taken from the spleen of MSV-infected mice 10–15 d after infection of 0.1 ml of 1:100 diluted MSV.

‡ Percent chromium release from target cells with effector:target cell ratio of 100:1 and after an 18-h incubation period. The mean standard errors being always between 0.4 and 2% are not given. In all cases, the activity of immune CTL was calculated by comparison with the activity of normal lymphoid cells of the same inbred strains. Practically no differences were found in the level of activity of the different normal lymphocytes.

lymphocytes (K^bD^d) failed to lyse MBL2 and LSTRA, whereas HTG (K^dD^b) CTL were efficent against both. These results show the exclusive involvement of K^d or D^b molecules in the interaction between H-2^d or H-2^b lymphocytes and their syngeneic FMR(+) target cells, as also shown by blocking experiments with monospecific anti-H-2 sera (3).

The lack of detectable reactivity of in vivo primed 5R lymphocytes against H-$2K^b$ + FMR or H-$2D^d$ + FMR could be a result of the weakness of such reactions. Secondary stimulations were therefore necessary to test this point. As mentioned in Materials and Methods, 5R lymphoma cells bearing the FMR antigen were not available. LPS blast cells of 5R mice infected with MLV at the time of birth were therefore used following a recently developed method (V. Duprez, H. Hénin, and J. P. Lévy. Manuscript in preparation.). Table II shows the results of a typical experiment: B6 lymphocytes in vivo primed with MSV and then in vitro restimulated by syngeneic FMR(+) cells lysed B6 (K^bD^b) but not 5R (K^bD^d) target cells, thus confirming that B6 mice react only with D^b + FMR. Similarly, BALB/c-immune lymphocytes lysed syngeneic (K^dD^d) targets but not 5R FMR(+) blast cells (K^bD^d), which shows that they react only with K^d + FMR. On the other hand, 5R effector cells twice stimulated in syngeneic conditions lysed both 5R and B6 FMR(+), but not BALB/c FMR(+), target cells. The 5R anti-FMR CTL cells therefore react with K^b + FMR but not with D^d + FMR. Controls with uninfected blasts demonstrate the specificity of the reactions both at the level of stimulation and at the effector steps. Anti-Thy-1.2 and complement treatment completely abolish the activity of the effector cells, which confirms their thymic origin (results not shown).

Competition experiments have been performed to confirm these results. When 5R attacker cells were tested against labeled syngeneic MBL2 cells, the chromium release was inhibited by an excess of 5R FMR(+) blast cells as well as MBL2 tumor cells but not by 4R FMR(+) blasts (K^kD^b) (Fig. 1 A), thus confirming that 5R anti-FMR lymphocytes recognized the K^b + FMR association on both 5R and B6 target cells. In contrast, when B6 anti-FMR T killer cells and labeled MBL2 target cells were

TABLE II

Cytolysis of FMR(+) Target Cells By In Vivo Primed and In Vitro Restimulated Anti-MSV CTL

Effector cells*		Effector:target cell ratios	Target cells					
Immune donor spleen cells	In vitro stimulation with		MBL2	B6 M.MuLV‡	LSTRA	BALB/c M.MuLV‡	Normal 5R‡	5R M.MuLV‡
B6 anti-MSV	MBL2	100:1	40§	16	0	0	0	0
		30:1	26	14	0	0	0	0
BALB/c anti-MSV	LSTRA	100:1	0	0	34	30	0	0
		30:1	0	0	21	18	0	0
5R anti-MSV	Normal 5R‡	100:1	0	NT‖	0	NT	0	0
		30:1	0	NT	0	NT	0	0
5R anti-MSV	5R M.MuLV‡	100:1	36	20	0	0	0	33
		30:1	19	12	0	0	0	16

* 8×10^6 spleen cells from MSV-infected mice taken 6–10 wk after infection and cocultivated 6 d with 1×10^6 irradiated stimulating cells.

‡ Spleen cells of MLV-infected mice or normal spleen cells incubated with LPS for 48 h. MuLV, murine leukemia virus.

§ Percent chromium release from target cells after 4 h of incubation.

‖ Not tested.

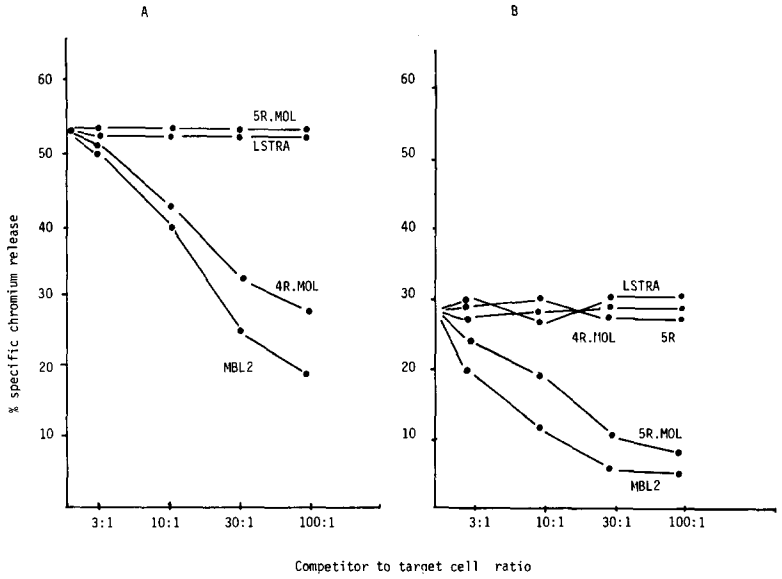

FIG. 1. Competition experiments with different unlabeled competitors and MBL2 as ^{51}Cr-labeled target cells. (A) Effector cells: B6 anti-MSV CTL in vitro restimulated by MBL2 cells. (B) Effector cells: 5R anti-MSV CTL in vitro restimulated by MLV-infected 5R LPS blast cells. Effector:MBL2 target cell ratio: 100:1.

TABLE III

Cytolysis of MBL2 Target Cells By 5R or B6 Effector Cells: Selective Effect of Anti-H-2K^b and Anti-H-2D^b Sera

MBL2 target cells preincubated with		Effector cells	
Serum	Specificity	B6*	5R‡
—	—	30§	11
Normal mouse serum	—	32	13
(BALB/c × C3H)F$_1$ anti-BALB.B	Anti-H-2^b	2	0
(B10.RIII × B10.BR)F$_1$ anti-B10.A(4R)	Anti-H-2D^b	4	12
B10.A anti-B10.A(5R)	Anti-H-2K^b	41	0

* B6 anti-MSV CTL in vitro restimulated by MBL2. Effector:target cell ratio of 20:1.

‡ 5R anti-MSV CTL in vitro restimulated by MLV-infected 5R LPS blast cells. Effector:target cell ratio of 100:1.

§ Percentage of specific chromium release of the target cells calculated by comparison with the activity of normal lymphoid cells in the presence of the same normal or immune serum.

used, competitions were obtained by B6 or 4R FMR(+) blasts or by MBL2 cells, but not by 5R FMR(+) cells, (Fig. 1 B), thus showing that B6 lymphocytes react exclusively with D^b + FMR on B6 target cells.

Finally, blocking experiments were done with anti-H-2K^b and anti-H-2D^b sera. Table III shows that the cytolysis of MBL2 target cells by 5R CTL was inhibited by anti-K^b but not by anti-D^b antibodies. As expected, the reverse was observed with B6 effectors and the same MBL2 target cells.

These results show that both K^b + FMR and D^b + FMR antigenic associations exist on B6 FMR(+) tumor cells. The K^b + FMR association might be, however, less

antigenic because it can be revealed only after secondary stimulation. The weakness of this antigen is also emphasized by the rapid disappearance of memory cells: whereas anti-D^b + FMR T killer lymphocytes are easily induced in B6 mice by secondary stimulation at least up to 8 mo after immunization, anti-K^b + FMR responses have been rarely detected in 5R mice later than 2 mo post-inoculation (Table IV).

The ability to react or not react with K^b + FMR is thus genetically determined; B6 and B10 mice being nonresponder in contrast to 5R mice. Table V shows that (B10 × 5R)F_1 cells in vivo primed with MSV react at a good level against MBL2 targets, like the B10 parent, whereas 5R cells never produced detectable primary response. After secondary in vitro stimulation by MBL2, ($K^{b/b}D^{b/d}$)F_1 hybrids produced a very high anti-MBL2 response, which contrasts with a weak and possibly insignificant reaction against 5R FMR(+) blast cells. Therefore, they react preferentially, if not exclusively, with D^b + FMR. When in vitro restimulated with 5R FMR(+) blast cells instead of MBL2, (B10 × 5R)F_1 mice produced only a weak anti-K^b + FMR cytolysis that was hardly detectable on 5R target cells, whereas 5R mice produced a good level of anti-K^b + FMR activity. (5R × B10.WB)F_1 hybrids, which share with B10 and (5R × B10)F_1 mice the H-2D^b private specificity but differ by the other regions of the MHC, behave exactly like (5R × B10)F_1 mice.

Discussion

We have previously shown that the anti-FMR response of H-2^b or H-2^d mice is very precisely restricted so that the FMR antigen is seen associated with H-2D^b or H-2K^d molecules but never with H-2K^b or H-2D^d (3). The above reported results show at first that this is not a result of the absence of association between H-2K^b and FMR because 5R-immune CTL cells react exclusively with K^b + FMR, not only on 5R FMR(+) blast cells, but also on MBL2 (H-2^b) tumor cells. Both K^b + FMR and D^b + FMR antigenic associations, therefore, exist on the surface of B6 tumor cells, and the choice of the reacting association depends only upon the 5R or B6 origin of the

TABLE IV

Secondary Anti-FMR CTL Response in B6 and B10.A(5R) Mice at Different Times After MSV Inoculation

Effector cells*	Stimulator cells‡	Time after MSV inoculation	Target cells					
			MBL2		LSTRA		5R M.MuLV§	
			100:1	30:1	100:1	30:1	100:1	30:1
B6 anti-MSV	MBL2	1 mo	73	55	37	9	0	0
		3 mo	75	66	10	0	0	0
		6 mo	70	59	12	0	0	0
		10 mo	57	47	20	3	0	0
5R anti-MSV	5R MLV-infected blast cells	1 mo	31	26	0	0	33	24
		2 mo	23	17	0	0	12	7
		4 mo	5	0	0	0	0	0
		6 mo	0	0	0	0	0	0

* Spleen cells from MSV-infected mice taken 1 to 10 months after virus inoculation.

‡ 8 × 10^6 effector cells cultivated 6 days with 1.10^6 stimulating cells.

§ Spleen cells from neonatally infected mice incubated with LPS for 48 h. MuLV, murine leukemia virus.

TABLE V

Cytolytic Activity of Anti-MSV CTL from (5R × B10)F1 or (5R × B10.WB)F1

	Effector cells		Target cells					
	Immune spleen cell donors*	In vitro restimulation with‡	MBL2		LSTRA		5R M.MuLV§	
			100:1	30:1	100:1	30:1	100:1	30:1
Experiment A	B10 anti-MSV	—	32*	13	6	0	NT‖	NT
	BALB/c anti-MSV	—	0	0	27	11	NT	NT
	5R anti-MSV	—	0	0	0	0	NT	NT
	(5R × B10)F1 anti-MSV	—	29	8	0	0	NT	NT
	(5R × B10.WB)F1 anti-MSV	—	38	11	2	0	NT	NT
Experiment B	B10 anti-MSV	MBL2	49	36	5	0	5	0
	BALB/c anti-MSV	LSTRA	0	0	60	43	0	0
	5R anti-MSV	5R MLV-infected blast cells	35	28	0	0	18	13
	(5R × B10)F1 anti-MSV	MBL2	51	39	3	0	6	0
	(5R × B10)F1 anti-MSV	5R MLV-infected blast cells	8	5	0	0	6	0
	(5R × B10.WB)F1 anti-MSV	B10.WB MLV-infected blast cells	22	11	0	0	0	0
	(5R × B10.WB)F1 anti-MSV	5R MLV-infected blast cells	3	0	0	0	0	0

* Spleen cells from MSV-infected mice taken 8–10 wk after virus inoculation.
‡ 8×10^6 effector cells cultivated 6 d with 1×10^6 stimulating cells.
§ Spleen cells of neonatally infected mice incubated with LPS for 48 h. MuLV, murine leukemia virus.
‖ Not tested.

attacker cells used. In other words, the mechanism of H-2 restriction must be related to the problem of T cell repertoire and cannot be explained by a phenomenon arising only on the target cell surface, such as a specific association between H-2 and FMR antigens. This conclusion is apparently at variance with previously published observations that suggest that a specific association exists between D^b and viral structures, because H-$2D^b$, but not H-$2K^b$, molecules have been detected in Friend virions produced in H-2^b cells (10). This discrepancy can be explained in at least two ways: (*a*) The presence of H-2 molecules in the virions does not necessary correlate the existence of a specific CTL-reacting structure on the virus-producer cell surface. (*b*) The relative unsensitivity of the method used to detect virion-associated H-2 antigens could explain that a lesser but significant amount of K^b molecules might have been missed in the virions. A specific cocapping of H-$2D^b$ and FMR molecules has also been reported (11, 12), although not confirmed in other experiments with the same or other methodologies (2, 13). Quantitative problems or the use of different cells perhaps explain this discrepancy. Furthermore, the cocapping phenomenon might be unrelated to the CTL-reacting structure of the cell surface that is directly explored by the present experiments.

There exists an obvious hierarchy of FMR + H-2 antigenic associations, and

whatever the nature of this association D^b is preferred to K^b, K^b to D^d, and K^d to D^d. The mouse CTL response is, however, not obligatorily limited to a unique H-2 + FMR association as shown in HTG mice that react with both D^b + FMR and K^d + FMR. It cannot be excluded that D^d antigens can be seen in association with FMR in other H-2 haplotypes because H-2D^d-restricted CTL responses have been observed in other tumors (14, 15). It is, however, interesting to observe that the D^d + antigen association was only weakly antigenic in these cases, not being revealed in a primary response. Similar response hierarchies have now been observed in all kinds of T killer cell-mediated syngeneic reactions as with nononcogenic viruses (4–6), H-Y antigens (7) and hapten-modified cells (9). The reason for this phenomenon is unclear. In the FMR system, the possible existence of low responder alleles of Ir genes that control the nonreacting associations in all inbred strains tested appears unlikely because: (*a*) previously published results have shown that the non-H-2 background is not involved in the restriction phenomenon (3) excluding the role of non-H-2-linked Ir genes; (*b*) the use of H-2 recombinants and experiments with multiple F_1 hybrids of different H-2 specificities failed to reveal any complementation of the response, which could suggest the role of I region-associated Ir genes (E. Gomard, Y. Hénin, and J. P. Lévy. Unpublished data.); and (*c*) furthermore, the above reported observation that the ability to respond against K^b + FMR is recessive in (5R × B10)F_1 hybrids argues against the existence of a classical I region-associated Ir gene with dominant responsiveness in K^b + FMR responder 5R mice. On the other hand, the anti-K^b + FMR response appears to be observed only in mice not bearing the D^b specificity. The results obtained with (5R × B10)F_1 show that the anti-K^b + FMR response is recessive in these hybrids. With similar results being obtained with (5R × B10.WB)F_1, which share only the D region with B10, one may suppose that the responsible gene maps to this D region. Further experiments are now in progress to further demonstrate this point. A similar interpretation has been proposed for D or K region-associated genes that control CTL responses in nononcogenic systems (4, 5). Such genes could provoke an immunodominance of certain H-2 + viral antigen associations. In other words, the presence of D^b + FMR, for example, could abolish the possibility to respond against K^b + FMR. Such a selection of a subpopulation of responder T killer cells might be compared with the dominant idiotype clones in certain antibody responses (16, 17). In terms of altered self, the receptor for D^b + FMR could be more efficient that any other. In terms of dual recognition, it could be imagined that CTL that bear an H-2D^b self receptor would be able to develop an antigen receptor specific for FMR of higher affinity than the precursors that bear a receptor for H-2K^b or H-2D^d self. The results observed in the FMR system might be especially interesting, because they suggest that the antigenic association chosen for the response is the one providing the higher level of protection: mice that respond against D^b + FMR regularly produce a good level of CTL after primary immunization, and they possess memory cells at least 8 mo later. In contrast, 5R mice that are obliged to respond against a weaker antigenic association (i.e., K^b + FMR) produce CTL activity after secondary stimulation only. Furthermore, memory cells disappear early in this case. (5R × B10)F_1 hybrids are low responders against K^b + FMR, responsiveness against this association being recessive, but they produce a primary anti-FMR response associated to D^b, like the high-responder B10 patient, the high level of antiviral responses is therefore dominant.

The apparent discrepancy existing between the usual dominant responsiveness at Ir genes of the antibody responses and the dominant unresponsiveness against certain H-2 + viral antigens (i.e., K^b + FMR) for K or D region-associated CTL that control genes (Results [4]) is probably a result of the double subsets of precursors that exist in the latter case even in homozygous mice. As a matter of fact, CTL precursors can respond against the antigen associated to either H-2D or H-2K. The situation is similar to that of an F_1 hybrid between responder and nonresponder parents in the antibody response. In this case, F_1 hybrids respond preferentially with the antigen associated to Ia of the responder parent (18, 19). Ir genes that control CTL or antibody responses, therefore, are both characterized by (*a*) dominant high-responder phenotype and (*b*) the choice of the best possible MHC product + antigen association, explaining unresponsiveness against certain associations and permitting dominance of the higher response. They seem to differ only by their mapping to different regions of the H-2 complex.

Summary

Cytolytic T lymphocytes (CTL) specific for the virus-induced and leukemia-associated Friend, Moloney, Rauscher (FMR) antigen are easily detected in the spleens of primary and secondary stimulated H-2^b or H-2^d mice. They react, respectively, with H-$2D^b$ + FMR and H-$2K^d$ + FMR; D^d and K^b never being involved. On the other hand, recombinant (K^bD^d) mice are relatively low responders that produce CTL only after secondary stimulation. Competition and blocking experiments with monospecific anti-H-2 antibodies have demonstrated that on the same H-2^b tumor cells, C57BL/6 (H-2^b) lymphocytes recognize D^b + FMR, whereas B10.A(5R) lymphocytes recognize K^b + FMR, the restriction cannot, therefore, be explained by a specific association of viral molecules with certain H-2 products. The CTL response of (B10 × 5R)F_1 hybrids is (*a*) easily detected in primary reaction, the high responder anti-FMR phenotype being dominant and (*b*) directed against D^b + FMR, F_1 mice being low responder against K^b + FMR like the B10 parent. These results suggest that a D region-associated immune response gene controls the cell-mediated anti-FMR reaction, the best available H-2 + FMR antigenic association being chosen by CTL precursors.

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