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Pillars Article: Immunological Surveillance against Altered Self Components by Sensitised T Lymphocytes in Lymphocytic Choriomeningitis. *Nature*, 1974, 251: 547–548.

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Immunological surveillance against altered self components by sensitised T lymphocytes in lymphocytic choriomeningitis

THE cytotoxic activity[1,2] of immune thymus-derived lymphocytes (T cells) for ^{51}Cr-labelled fibroblasts, or macrophages infected with lymphocytic choriomeningitis (LCM) virus is restricted by the H-2 gene complex[3,4]. Specific lysis of LCM-infected monolayer cultures occurs only when targets and overlaying, sensitised T cells share at least one set of H-2 antigenic specificities.

Operationally, this restriction may reflect one of two quite distinct mechanisms[1,2]. First, H-2 compatibility is essential for sufficiently close association[3] between lymphocyte and target cell for lysis to occur. This intimacy model implies either that the H-2 gene complex specifies a product, or products, involved in self-recognition, or that there is some mutual interaction between H-2 antigens. Such a process would be additional to recognition of viral antigen by the T cell receptor. The alternative possibility is that infection with LCM virus modifies self components in a way recognised only within a H-2 compatible system. Altered self may be thought of as changes in H-2 antigens (or in structures coded for in the H-2 region) induced by the process of virus synthesis, or as some complex of viral and H-2 antigens.

Lymphocytes from F_1 immune mice lyse virus-infected targets of parent H-2 type as effectively as do syngeneic T cells[1]. If the intimacy model is correct, therefore, F_1 mice need possess only one clone of sensitised T cells, recognising viral antigen by a specific receptor and like H-2 antigen, of either parent type, in some non-immunological way (Fig. 1). The altered self hypothesis, however, requires the presence of at least two clones of T cells, each reactive to modified H-2 of one parent type.

These possibilities have been examined using the following experimental system. When LCM-immune T cells are injected into immunosuppressed[5], virus-infected recipients they home equally well to lymphoid tissue of syngeneic or allogeneic hosts, but continue to multiply only in the syngeneic system[6]. Further replication is apparently not triggered by free virus, but is dependent on thymus-derived lymphocytes being exposed to histocompatible, virus-infected target cells.

Continued proliferation of F_1 ($H\text{-}2^{k/b}$) immune spleen cells with capacity to lyse $H\text{-}2^k$ LCM-infected monolayers occurs only in recipients with $H\text{-}2^k$ antigenic specificities, and not in those possessing $H\text{-}2^d$ (Table 1). These sensitised T cells are of donor origin, as lymphocytes recovered from H-2 compatible AKR recipients adoptively immunised with CBA/H × C57Bl spleen cells were shown to bear θ C3H (Table 2). The intimacy hypothesis, therefore, is probably not correct, as the postulated single clone of F_1 lymphocytes (Fig. 1) should continue to proliferate equally well in recipients of either parent strain. The results cannot, however, exclude this model totally, the reservation being that there may be alleleic exclusion in the F_1 of this hypothetical self-recognition product. The simplest

Table 1 Cytotoxic activity of donor T cells in LCM-infected irradiated recipients*

Donor cells*	Recipient strain	H-2 type	% ^{51}Cr release† from L cells ($H\text{-}2^k$) Infected	Normal
Experiment 1				
Immune	CBA/H × BALB/c	k/d	51.2 ± 0.5	12.5 ± 1.9
	C57Bl × BALB/c	b/d	17.3 ± 0.1	13.9 ± 1.3
	BALB/c	d	16.1 ± 1.8	13.0 ± 1.3
Normal	BALB/c	d	14.4 ± 1.9	11.7 ± 1.1
Experiment 2				
Immune	CBA/H	k	83.7 ± 5.4	19.0 ± 1.4
	C57Bl	b	23.3 ± 1.3	19.1 ± 1.0
Normal	C57Bl	b	20.3 ± 1.2	18.5 ± 1.7

*Donor CBA/H × C57Bl F_1 were injected intracerebrally with 300 LD50 of WE3 LCM virus and killed when clinically affected 7 d later. Recipients were irradiated (850 r.) 24 h before i.v. injection of 10^6 LD50 of WE3 LCM virus, and inoculated i.v. with 5.0×10^7 spleen and lymph node cells 6 h later.

†% ^{51}Cr release above normal values is a measure of activity of H-2 compatible sensitised T cells[1-4]. Spleen cells from LCM-immune mice caused % ^{51}Cr release of 46.6 ± 0.9% from infected L cells and 15.2 ± 1.3% from normal L cells (experiment 1).

Table 2 Evidence that sensitised T cells are of donor origin

Donor	Recipient	Treatment	% ^{51}Cr release from L cells Infected	Normal
CBA/H × C57Bl F_1 $H\text{-}2^{k/b}$, θC3H	AKR	Anti-θ+C	22.3 ± 1.2	21.4 ± 2.5
	$H\text{-}2^k$, θAKR	Nascitic+C	89.1 ± 1.8	23.3 ± 1.2

The protocol is the same as in Table 1, except that a proportion of lymphoid cells were treated[3] with AKR anti-θ (C3H) ascitic fluid and rabbit complement or normal AKR ascitic fluid and complement.

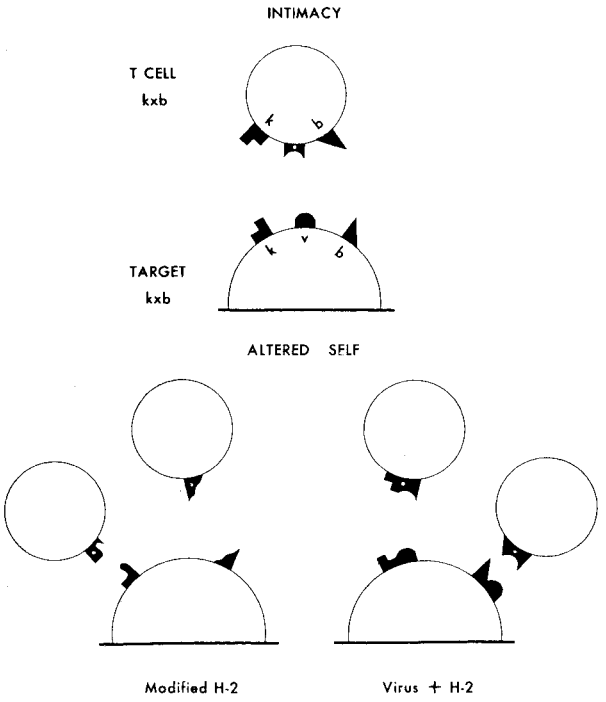

Fig. 1 Capacity of sensitised F_1 ($H\text{-}2^{k/b}$) T cells to interact only with histocompatible virus-infected target cells may be considered to reflect any one of the models shown. The intimacy concept proposes a single immunologicslly specific T cell receptor for viral (v) antigen, additional to a requirement for physiological interaction coded for by the H-2 gene complex (mutuality between either $H\text{-}2^k$ or $H\text{-}2^b$). The two models proposed for altered self postulate that, in each case, there are at least two T cell populations with receptors of different immunological specificities recognising modified H-2, or virus +H-2 of either parent type.

explanation of our results is, however, that there are sensitised T cells of at least two specificities in LCM-infected H-$2^{k/b}$ mice, each recognising a complex of virus + H-2 (or modified H-2) of one parent type. Recirculating T cells may function essentially to survey the integtity of transplantation antigens, or structures coded for by the H-2 gene complex. Recognition of cell surface changes due to virus infection, chemical modification[7] or genetic difference (alloantigens) may then be accommodated within the same model.

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