Genetic Control of the Antibody Response to a Synthetic Polypeptide: Transfer of Response with Spleen Cells or Lymphoid Precursors*

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THE ANTIBODY responses of certain strains of mice to a series of multi-chain synthetic polypeptide antigens are quantitative traits under a dominant, determinant-specific type of genetic control.[1,2] That is, a given strain of mouse may respond poorly if at all to one of the antigens while a second strain will respond quite well. The antigens[2] are composed of a polylysine backbone with side chains of poly-DL-alanine terminating in short, random sequences of either tyrosine and glutamic acid, (T,G)-A—L, or histidine and glutamic acid, (H,G)-A—L. Recently reported studies[3] with congenic strains of mice, segregating back-cross populations and crossover strains supplied by Stimpfling indicate that the genetic control of the ability to respond to either of these antigens is localized in the right hand half of the H-2 locus, or just to the right of this. It was found that H-2^b and some H-2^d strains of mice respond well to (T,G)-A—L and poorly to (H,G)-A—L; the reverse was true with regard to H-2^a and H-2^k strains. While these differences are clearly quantitative, high responder mice will to be termed responders, and low responder mice will be termed nonresponders. The experiments reported here were performed in an effort to determine if the genetic control of the responses to these antigens is directly related to the process of antibody formation, and if so through which cell type(s) this control is expressed.

As previously reported,[3] when spleen cells from mice which respond well to (T,G)-A—L are transferred to lethally irradiated thymectomized or nonoperated mice which normally respond poorly, the antibody responses elicited in these chimeras are characteristic of the donor strain (Table 1). This is true whether the mice are immunized on the day of irradiation or 21 days later. These results show that there is no property of the nonresponder host which renders it incapable of supporting

Table 1.—Adoptive transfer of primary response to (T,G)-A—L with spleen cells.*

Donor	Host	No. responding /total	Mean % antigen ppt.
NR	NR	0/27	4
RF_1	RF_1	10/10	63
RF_1	NR	12/16	46
R	TxR	6/10	56
RF_1	TxNR	6/12	40

* R, responder; NR, nonresponder; RF_1, F_1 hybrid responder; Tx, thymectomized. These data have been reported previously.[3]

Table 2.—Inability to transfer primary response to (T,G)-A—L with thoracic duct cells from responder mice.*

Donor Sensitized	No. Cells Transferred (x 10^6)	Number Responding 1°	2°	Donor γG_{2a} Present †
No	20–40	0/9	0/7	7/9
No	50–70	0/11	0/11	10/11
Yes	28	3/4	3/4	3/4

* Donors, (C3H x C57B1/6)F_1; hosts, C3H. The hosts were also given C3H fetal liver cells i.p. and immunized on the day of irradiation (1°) and 45 days later (2°).

† C57B1/6 allotype.

* Methods detailed in ref. 1–4.

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a response to (T,G)-A—L, and that the thymus is not essential for a primary response by mature lymphoid cells. Attempts to transfer a primary response to (T,G)-A—L with thoracic duct cells (20 to 70x10^6 cells) from responder mice were unsuccessful (Table 2). Donor γG_{2a} immunoglobulins were detected in the sera of the hosts in almost all cases, suggesting that the transferred cells remained functionally active. When thoracic duct cells (28x10^6) from sensitized donors were transferred, 3 of 4 mice responded well to a booster injection of (T,G)-A—L. These results indicate that the cell type(s) essential for a primary response to (T,G)-A—L while present in the spleen cell population of responder mice are absent or deficient in thoracic duct drainage.

Thymectomized lethally irradiated mice which normally respond well to (T,G)-A—L were given liver cells and a thymus graft from nonresponder fetuses and then immunized with (T,G)-A—L 60 and 100 days after irradiation. All chimeras failed to respond to (T,G)-A—L but 12 of 13 responded well to (H,G)-A—L (Table 3). Host type γG_{2a} immunoglobulin levels were extremely low in the sera of these chimeras. When fetal liver cells from a responder strain were transferred to thymectomized or normal, lethally irradiated syngeneic hosts, only those chimeras in which the thymus was intact responded to (T,G)-A—L (14/15 vs 0/26 (Table 4a). When fetal liver cells from a responder strain were transferred to lethally irradiated nonresponder hosts, 15 of 21 chimeras responded well to (T,G)-A—L. The γG_{2a} antibodies were predominantly donor in origin in 8 of 17 mice, of both host and donor-type in 6 and of host type in 3 (Tables 4a and 4b). When fetal liver cells from nonresponder mice were transferred to responder hosts 23 of 31 chimeras responded well to (T,G)-A—L. The allotype of the γG_{2a} antibody was predominantly donor in origin in 12 of 22 mice and of both host and donor type in the other 10. These data indicate that the genetic control

Table 3.—Response to (T,G)-A—L and (H,G)-A—L by thymectomized lethally irradiated B6D2F_1 mice given CBA fetal liver cells and thymus graft.*

Thymus implant intact	No. responding to (T,G)-A—L 1°	2°	No. responding to (H,G)-A—L
Yes	0/19	0/16	12/13
No	0/4	0/4	0/4

*B6D2F_1 mice respond well to (T,G)-A—L and poorly to (H,G)-A—L; the reverse is true with CBA mice. The mice were immunized with (T,G)-A—L 60 days (1°) and 100 days (2°) after irradiation.

Table 4a.—Transfer of response to (T,G)-A—L with lymphoid precursors from the livers of responder and nonresponder embryos.*

Fetal Liver Donor	Host	Day first immunization given (No. responding/total) 45	60	100	Response to second immunization
NR	NR	0/3	0/5	0/13	0/7
R	R	0/11	14/15		12/14
R	TxR		0/26		0/11
R	NR	2/27		6/10	15/21
NR	R	6/24	7/24	9/16	23/31

* R, responder; NR, nonresponder; Tx, thymectomized.

Table 4b.—Allotype of antibody (γG_{2a}) to (T,G)-A—L (see Table 4a).*

Fetal Liver Donor	Host	Predominant antibody allotype Donor	Host	Both
R	NR	8/17	3/17	6/17
NR	R	12/22	0/22	10/22

* R, C57B1/6 or $B6D2F_1$; NR, CBA.

of the ability to respond to the synthetic polypeptides (T,G)-A—L and (H,G)-A—L is exerted through a mechanism directly related to antibody formation and suggest that this control is expressed through a cell type(s) other than those produced by the thymus or the antibody forming cell or its direct precursor. That is, lymphoid precursors (from fetal liver) from nonresponder mice are capable of responding well to (T,G)-A—L when transferred to a responder strain and lymphoid stem cells obtained from responder mice mature normally under the influence of the thymus of a nonresponder stain. While it is apparent that the reticulo-epithelial thymus promotes the maturation of the precursors of antibody forming cells, the data suggest that its role with regard to these antigens is nonspecific. It would appear that the cell(s) which mediates this genetic control is present in the fetal liver and in certain lymphoid tissues of the adult mouse.

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