EXPERIMENTAL GENETICS

Interstrain Peculiarities of the Secondary Immune Response in Mice

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CBA, CC57BR, C57Bl/6, BALB/c, and outbred white mice were intraperitoneally or subcutaneously (C57Bl/6 strain) immunized with sheep red cells in a dose optimal for the development of delayed-type hypersensitivity but subthreshold for antibody production. Seven days later the mice were reimmunized with sheep red cells in various doses subcutaneously (CBA, C57Bl/6, BALB/c, outbred mice) or intraperitoneally (CBA, CC57BR, outbred mice), and 5 days after reimmunization the intensity of antibody production and delayed-type hypersensitivity was assessed. Intact mice were controls. The immunization was found to selectively enhance delayed-type hypersensitivity in C57Bl/6, CC57BR, and BALB/c mice and to intensify antibody production in CBA mice; both phenomena were observed in outbred mice.

Key Words: *antibody production; delayed-type hypersensitivity; secondary immune response*

Previously [1,3,5] we demonstrated two genetically determined types of immune response to sheep red cells (SRC) injected in various doses. In mice with the type 1 response (C57Bl/6, CC57BR, BALB/c, DBA/2) delayed-type hypersensitivity (DTH) prevailed over antibody production (ABP), whereas in the type 2 response (CBA, C3H, outbred mice) the effect was the contrary. The principal differentiating criterion is a lower threshold of antigenic sensitivity for DTH or ABP. Intraperitoneal immunization of C57Bl/6 mice with SRC in a dose optimal for DTH but subthreshold for ABP boosts DTH and suppresses general, but not local ABP in response to reinjection of various doses of the antigen [2,3]. It is not clear, however, whether this phenomenon is universal, determined by the specific features of induction of a generalized immune reponse, or is due to a certain type of genetic control.

In the present study we attempted to assess the genetic features of the generalized and local immune response under conditions of development of primary ABP in the presence of secondary induction of T effectors of DTH.

MATERIALS AND METHODS

A total of 700 C57Bl/6, CC57BR, BALB/c, CBA, and outbred mice weighing 18 to 22 g were used. For primary immunization the animals were intraperitoneally (or subcutaneously in the foot pad - C57Bl/6 mice) injected SRC in doses subthreshold for ABP but effective for the development of DTH. This dose [1,3,5] was 2×10^5 SRC for CBA mice, 5×10^5 SRC for CC57BR and BALB/c mice, and 1×10^6 SRC for outbred mice. For subcutaneous immunization of C57Bl/6 mice a dose of 1×10^5 SRC was used, which, according to our

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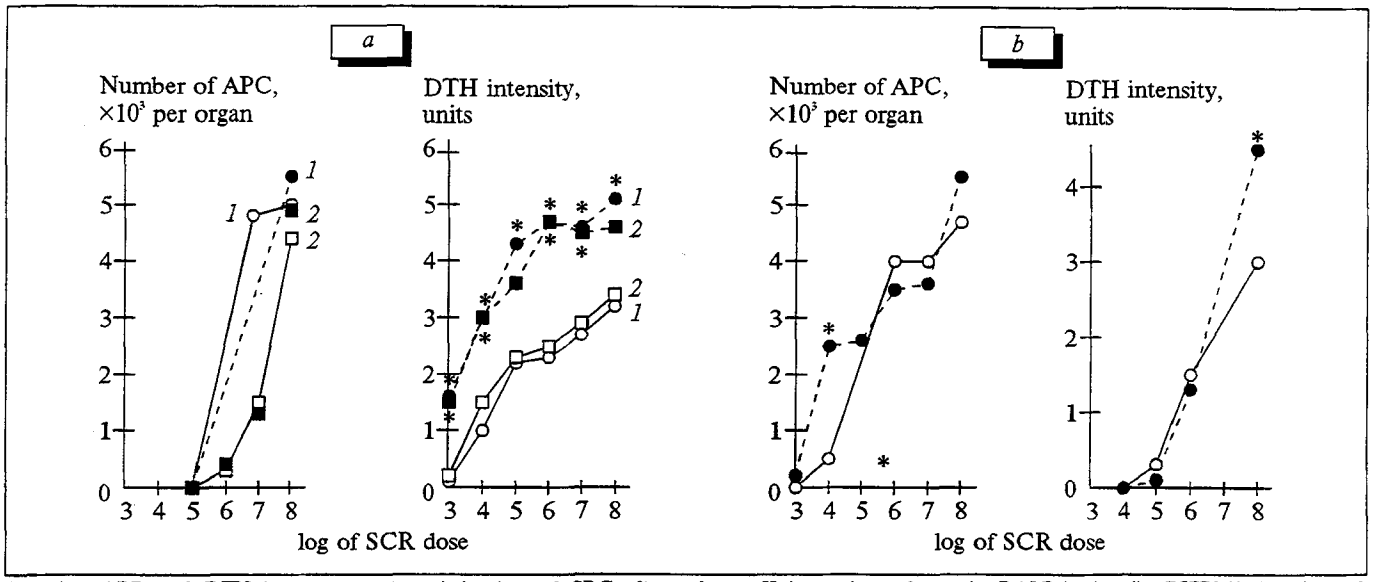

Fig. 1. ABP and DTH in response to reinjection of SRC after scheme II in various doses in BALB/c (*a*, *1*), C57Bl/6 (*a*, *2*), and CBA (*b*) mice. Here and in Fig. 2: a continuous line denotes the primary immune response (control) and a broken line the secondary immune response. Asterisk shows data reliably ($p<0.05$) differing from the corresponding parameter in the control.

findings [1,3], induces only local DTH-type reactivity. Seven days after primary immunization the mice were reinjected SRC in various doses, from 1×10^3 to 1×10^8, according to two schemes: scheme I, intraperitoneally, to assess the generalized response (CBA, CC57BR, outbred mice) and scheme II, subcutaneously in the foot pad (outbred, CBA, BALB/c mice). C57Bl/6 mice were injected the antigen after scheme II. The ABP level was assessed 5 days after reimmunization in the spleen (after SRC injection after scheme I) or in the popliteal lymph node (after SRC injection after scheme II) from the count of antibody-producing cells (APC) per organ by the direct local hemolysis method [6]. For the assessment of DTH, a resolving dose of SRC (1×10^8) was injected in the paw 1 day before sacrifice and the reaction was assessed from the degree of pad edema: a difference of 0.1 mm was taken as 1 unit, edema developing in response to primary injection of SRC

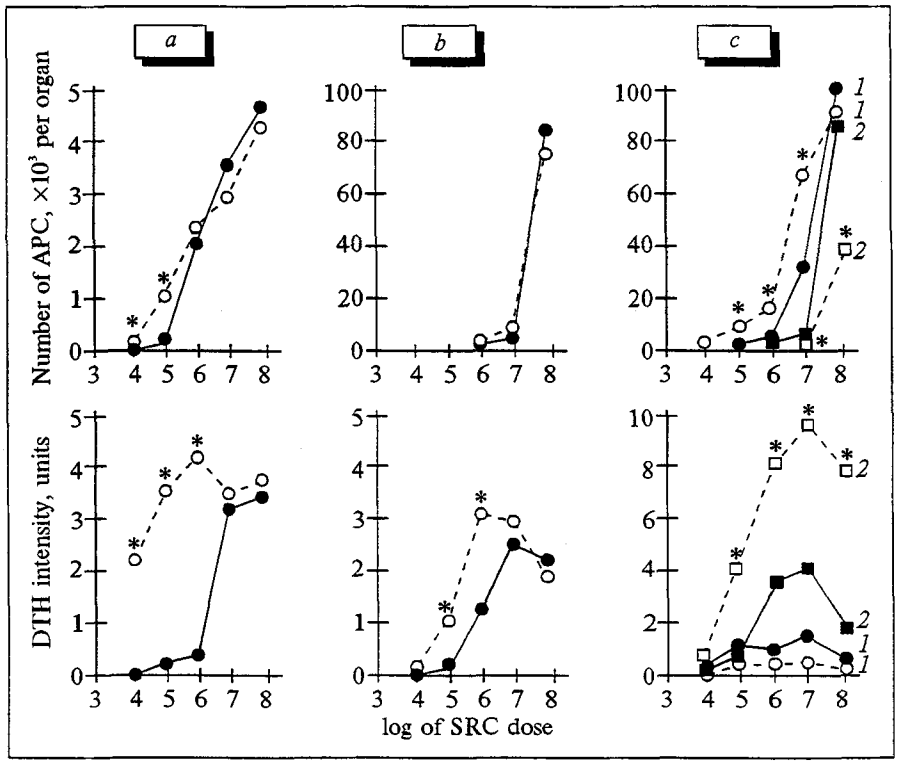

Fig. 2. ABP and DTH in response to reinjection of SRC in outbred, CBA, and CC57BR mice. Immunization of outbred mice after schemes II (*a*) and I (*b*); *c*) immunization of CBA (*1*) and CC57BR (*2*) mice after scheme I.

in a dose of 1×10^8 being taken as the zero DTH level. Control animals were injected 0.5 or 0.05 ml normal saline instead of being subjected to immunization after schemes I or II, respectively. Results were statistically processed using the Student *t* test.

RESULTS

Control curves on Figs. 1 and 2 clearly show the above-mentioned differences between the types of primary immune response. These differences stand out still more clearly under conditions of the secondary immune response. In mice with the type I response a reduction of the antigenic threshold of DTH by approximately one order of magnitude and intensification of this reaction in response to virtually all immunogenic doses of SRC are observed both in the local (BALB/c and C57Bl/6 mice, Fig. 1, *a*) and in the generalized (CC57BR mice, Fig. 2, *c*) response. These effects are associated with a reduction of the intensity and increase of the threshold of sensitivity to the antigen in the generalized humoral response, this being paralleled by stable ABP parameters in the local response. The lowered ABP intensity in the spleen in this case may be explained by the influence of T effectors of DTH on APC via activation of a specific T-suppressor population in the territory of this organ [4].

Conversely, in CBA mice immunization causes a lowering of the antigenic threshold for ABP in both the local (Fig. 2, *b*) and generalized (Fig. 1, *c*) response in the absence of DTH under conditions of secondary immunization after scheme I and a stimulation of DTH in scheme II immunization only if the maximal SRC dose, 1×10^8, is used.

In outbred mice the secondary immune response is characterized by an intermediate type of reaction: in the local response (Fig. 2, *a*) a drop of the antigenic threshold for both ABP and DTH (to a greater degree) is observed, whereas in the generalized response this threshold is lowered only for DTH (Fig. 2, *b*). Hence, on the whole, the immune response of outbred mice to SRC may be characterized as a "false-humoral" type of reaction.

Apparently, a specific T-cell response forms after immunization with the antigen doses subthreshold for ABP, one of the aims of this response being the priority boosting of the humoral or cellular immune response after repeated contact of the lymphoid tissue with the antigen. Therefore, the type of immune reaction to even a reinjection of a xenoantigen permits us to confirm the existence of two genetically determined patterns of response, which determine the ratio of the effector components, humoral and cellular.

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