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DEPENDENCE OF STRAIN DIFFERENCES IN ANTIBODY RESPONSE TO SHEEP RED BLOOD CELLS AND RESPONSIVENESS OF F_1 HYBRIDS ON DOSE AND METHOD OF ADMINISTRATION OF THE ANTIGEN

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KEY WORDS: immune response; sheep's red cells; strain differences.

Investigations into genetic control of the immune response have revealed strains of mice which give opposite responses to sheep's red blood cells and inheritance of a strong type of response has been shown to be dominant in character [2, 3]. In all these investigations high doses of antigen were given and were injected either intraperitoneally or intravenously. It was shown that genetic control over the immune response is effected at the level of immunocompetent cells [3, 4, 7]. It is a familiar fact, however, that besides immunocompetent cells, mononuclear phagocytes also play an essential role in immunogenesis. This suggests that under certain conditions the level of the immune response may be limited by macrophages. Such conditions are perhaps created by immunization with small doses of antigen and by the use of methods of immunization (such as intramuscular injection of antigen) dependent on access of antigen to the lymphoid organs, for which macrophages are evidently responsible.

The object of this investigation was to study dependence of strain differences in the height of the antibody response to sheep's red blood cells in strains of mice responding in opposite directions to this antigen, and also to examine how the character of inheritance of responsiveness depends on the immunizing dose and mode of administration of the antigen.

EXPERIMENTAL METHOD

Experiments were carried out on inbred CBA, C57BL/6, and BALB/c mice and on (CBA × BALB/c)F_1 and (CBA × C57BL/6)F_1 hybrids, aged 3-4 months. All animals were obtained from the animal house of the Institute of Cytology and Genetics, Siberian Branch, Academy of Sciences of the USSR. The mice were immunized by a single intravenous or intramuscular injection of sheep's red blood cells (SRBC) in doses of 5×10^5 to 1×10^9 cells. The immunoreactivity of the animals was assessed by the number of antibody-forming cells (AFC) in the spleen by Cunningham's method of local immune hemolysis in the liquid phase [6], in the modification of Kaledin et al. [1]. The number of AFC was counted at the peak of the immune response, namely on the 4th day after intravenous and on the 6th day after intramuscular injection of FRBC.

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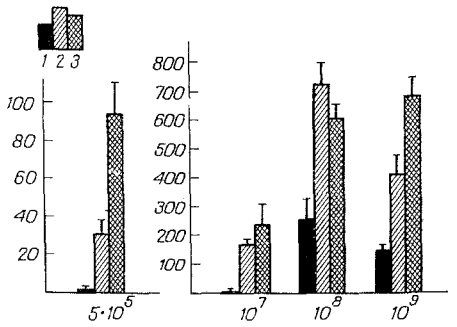

Fig. 1

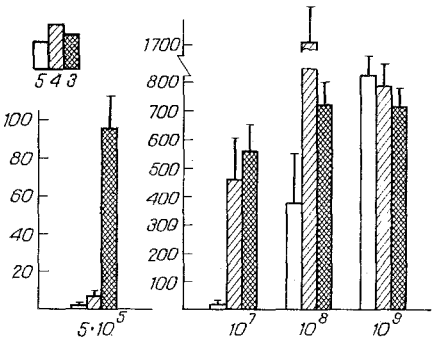

Fig. 2

Fig. 1. Height of antibody response to SRBC in CBA and C57BL/6 mice and in (CBA × C57BL/6)F_1 hybrids in relation to dose of intravenously injected antigen: 1) C57BL/6; 2) (CBA × C57BL/6)F_1; 3) CBA. Here and in Figs. 2 and 3: abscissa, dose of SRBC; ordinate, number of AFC per 10^6 nucleated spleen cells.

Fig. 2. Height of antibody response to SRBC in CBA and BALB/c mice and (CBA × BALB/c)F_1 hybrids in relation to dose of intravenously injected antigen: 3) CBA; 4) (CBA × BALB/c)F_1; 5) BALB/c.

EXPERIMENTAL RESULTS

CBA and C57BL/6 mice, strains responding in opposite direction to SRBC [3] and characterized by differences in phagocytic activity of their macrophages with respect to this antigen (high in C57BL/6 and low in CBA [8]), and BALB/c mice, whose system of mononuclear phagocytes is distinguished by high phagocytic activity against several antigens [5], were chosen for the investigation.

In the experiments of series I the dependence of the height of the antibody response to SRBC in mice of the test strains and their first generation hybrids on the immunizing dose of intravenously injected antigen was studied. Results reflecting the dose dependence of the height of the antibody response to SRBC in CBA and C67BL/6 mice and their hybrids are given in Fig. 1. They show that immunization with large doses of antigen (10^8, 10^9) revealed two- to threefold differences in the level of antibody production, in agreement with data in the literature [3], and they demonstrate the dominant character of inheritance of a high type of response. With a decrease in the immunizing dose of antigen these differences increased substantially: in response to injection of 5×10^5 SRBC the number of AFC in CBA mice was 83 times greater than the number in C57BL/6 mice. The type of immune response of the hybrids also changed with a decrease in the dose. As Fig. 1 shows, the response of the F_1 hybrids to an immunizing dose of 5×10^5 SRBC was of the weak type. Similar results were obtained in the next experiment, in which the antibody response of CBA and BALB/c mice to intravenous immunization with SRBC within the same dose range (5×10^5 to 1×10^9) was compared.

Immunization with small doses of antigen also revealed considerable (30-fold) differences in the height of the antibody response in the mice of these strains and a weak type of response in the F_1 hybrids (Fig. 2). With an increase in the dose of antigen these differences gradually diminished, and after immunization with a dose of 10^9 SRBC they disappeared. The dominant type of response in F_1 hybrids immunized with large doses of antigen was high. BALB/c mice were found to give a low response only to small and average doses of SRBC.

In the next experiment the immune response to SRBC was studied in mice of the same strain and in their hybrid in the case of intramuscular immunization. It will be clear from Fig. 3 that with this method of administration and with an average dose of antigen (5×10^7) significant differences were found in the height of the antibody response (84-fold between CBA and BALB/c mice and 183-fold between mice of strains CBA and C57BL/6). When this scheme of immunization was used the dominant type of response in the F_1 hybrid was weak, and the degree of its dominance depended on the phenotype of the weakly responding parent. In (CBA × BALB/c)F_1 hybrids dominance of the low type of response was more marked than in (CBA × C57BL/6)F_1 hybrids. Doubling the immunizing dose of SRBC led to weakening of dominance of a low level of response in the hybrids and to a decrease in the strain differences in the height of the antibody response in mice of opposite strains.

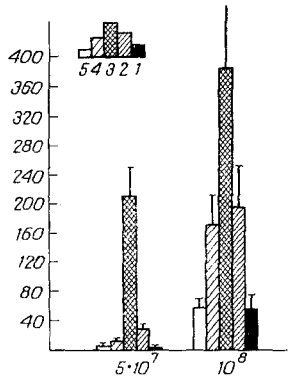

Fig. 3. Height of antibody response in CBA, C57BL/6, and BALB/c mice and in (CBA × C57BL/6)F_1 and (CBA × BALB/c)F_1 hybrids to intramuscular injection of SRBC. 1) C57BL/6; 2) (CBA × C57BL/6)F_1; 3) CBA; 4) (CBA × BALB/c)F_1; 5) BALB/c.

The results suggest that the weakly responding strains of mice investigated in these experiments possess a certain factor which is manifested within the zone of low immunizing doses of SRBC and is dominant in F_1 hybrids; the most likely cellular substrate of this factor, in the writers' view, is the macrophages. Direct proof of the role of macrophages is the manifestation of the immunologic phenomena described above may be obtained in experiments with transfer of macrophages of opposite parental lines to first generation hybrids.

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EFFECT OF THYMOSIN ON SPLENIC EXOCOLONY FORMATION IN ALLOGENEIC AND SYNGENEIC SYSTEMS

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Investigation of the role of the thymus in splenic colony formation probably ought not to be confined to an examination of the parts played by thymus-dependent cells only in this process, because the thymus not only produces T-lymphocytes but also secretes a humoral factor (or more than one). This factor, which is most frequently called thymosin, as the results of recent investigations have shown, plays an important role in the proliferation and, in particular, the differentiation of thymus cells [1]. In previous investigations the writers used two models with which to study the role of thymus cells in splenic colony growth. It was shown previously that injection of the synthetic polyribonucleotide polyI:polyC into recipient mice (F_1 hybrids) simultaneously with donor's bone marrow (C57BL mice) significant-

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