IMMUNOMODULATING ACTION OF INTERFERON IN MICE WITH CONGENITAL AND EXPERIMENTAL THYMUS-DEPENDENT IMMUNODEFICIENCY

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It has now become evident that the system of interferons (IF) controls many processes in infectious pathology as well as a wide range of biological functions of normal and transformed cells both in vivo and in vitro. IF not only possess a unique property, namely antiviral activity, but they also have a marked immunoregulatory action. Knowledge of the mechanisms of the immunomodulating action of IF is exceptionally important for their use as immunotherapeutic preparations.

A central role in the realization of the majority of immunologic phenomena is known to be played by the T system of immunity, but the degree to which it is involved in the immunomodulating action of IF has virtually not been studied. Only fragmentary data indicating that production of endogenous IF depends on the presence of a functionally normal thymus have been obtained [4].

The aim of this investigation was to study the action of mouse α/β-IF on activity of effector lymphocytes in the hematopoietic stem cell (HSC) inactivation reaction, and also on antibody production and rosette formation in mice with congenital and experimentally created immunodeficiency of the T system.

EXPERIMENTAL METHOD

Experiments were carried out on CBA, C57BL/6, and (CBA × C57BL/6)F_1 mice and also on mice with congenital absence of the thymus (nude; based on C57BL/6) and on HRS mice (based on CBA), with a disturbance of T lymphocyte differentiation. Mice thymectomized at the age of 6-8 weeks by the method in [7] were used in some experiments. IF-containing blood serum obtained after intravenous injection of Newcastle disease virus (NDV) into mice weighing 20-25 g was used as the exogenous IF preparation. The preparation of murine IF was stable at pH 2.0, did not change its activity on heating to 56°C for 30 min, and could be classed as IF of α/β-type. The effect of IF on effector cell activity was studied on a model of inactivation of nonsyngeneic HSC [2]. The donors of lymph node and spleen cells were given an intramuscular injection of IF 1-2 h before the experiment began, and later a mixture of lymph node cells with allogeneic bone marrow cells was transplanted into recipients [2]. On the 7th-8th day the receipients were killed, the spleens were extracted, and the number of macrocolonies counted. The reaction was evaluated as the inactivation index, calculated by the equation:

$$II = \left(1 - \frac{\text{number of colonies in experiment}}{\text{number of colonies in control}}\right) \times 100\%.$$

To study the effect of IF on antibody-forming and rosette-forming cells (AFC and RFC, respectively) mice were given an intraperitoneal injection of 500 U of IF simultaneously with antigenic stimulation by 5% sheep's red blood cells (SRBC). On the 5th day after immunization and injection of the preparation, the spleen cells were isolated and the number of AFC counted by the usual test [5] and the number of immune RFC determined as in [10]. The results were subjected to statistical analysis by Student's t test.

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TABLE 1. Effect of Murine α/β-IF on Degree of Inactivation of Nonsyngeneic HSC

Interacting cells	Ratio of cells	Inactivation, %	
		intact mice	injection of IF
Nude LNC + CBA BMC	10:1	5,2	3,6
	20:1	10,4	8,5
C57Bl/6 LNC + CBA BMC	10:1	17,5	51,5
	20:1	34,1	51,1
Nude SC + CBA BMC	10:1	2,7	2,4
	20:1	4,3	4,0
C57BL/6 SC + CBA BMC	10:1	19,2	19,7
	20:1	36,1	35,8

Legend. LNC) Lymph node cells, SC) spleen cells, BMC) bone marrow cells.

TABLE 2. Immunomodulating Action of IF in Mice with Congenital Deficiency of the T System

Line of mice	Number of AFC per 10^6 splenocytes		Number of RFC per 10^3 splenocytes	
	without IF	treatment with IF	without IF	treatment with IF
nude	98,4±10,1	155,2±13,2	3,5±0,15	7,8±1,2
C57Bl/6	169,7±16,5	103,5±9,9	14,2±2,2	11,3±2,1
HRS	215,4±13,3	213,8±14,2	9,4±1,4	8,9±1,7
CBA	288,5±21,3	200,2±17,3	21,2±3,0	15,0±2,6

EXPERIMENTAL RESULTS

It was shown previously that the principal cells inhibiting HSC proliferation are T effector lymphocytes, whose genesis and differentiation are controlled by the thymus. Absence of the thymus in animals can influence the character of inactivation of HSC, as is shown by both weakening and complete abolition of this phenomenon [1]. We studied the effect of α/β-IF on inactivation of nonsyngeneic HSC in nude mice with congenital absence of the thymus, which are a convenient model of the natural thymus-dependent deficiency. For this purpose the mice which were donors of the effector cells were treated with IF in vivo, after which cells were obtained from their spleen and lymph nodes, thoroughly washed with medium 199, and transplanted in various doses (from 10^5 to $2 \cdot 10^6$ cells) together with bone marrow cells from CBA mice (10^5 cells). Lymphoid cells of nude mice are known to have weak killer activity. Injection of IF into these mice did not affect the killer activity of their spleen cells and the weak killer effect of their lymph node lymphocytes was inhibited (Table 1).

Meanwhile injection of IF in a similar dose into phenotypically normal C57BL/6 mice, from which the nu/nu gene mutation was obtained, strengthened the killer activity of the lymphoid cells (Table 1). This effect of IF can evidently be explained by the fact that the presence of the thymus is essential for cells to acquire sensitivity to IF. A similar role was discovered previously for thymus hormone: treatment of lymph node and spleen cells of nude mice with a thymus extract had virtually no effect on their activity [3]. It will be clear from the facts described above that the killer activity of lymphoid cells is determined by the presence of a functionally normal thymus, and in that case absence of the thymus also affects the action of IF. We postulated that the same dependence exists also for other manifestations of the immunomodulating effect of IF.

To test this hypothesis, mice were thymectomized at the age of 6-8 weeks and, 1 month after the operation, they were given an intraperitoneal injection of 500 U of IF simultaneously with 5% SRBC. In the thymectomized animals a decrease of 15% in the number of AFC and inhibition of RFC formation in the spleen by 40% were observed 1 month after the operation.

Injection of IF into these animals restored the parameters studied to normal. A single injection of IF into intact animals caused only slight inhibition of AFC and of immune RFC in the spleen.

To study the action of IF under conditions of a natural deficiency of the T system of immunity, nude and HRS mice were treated with the same dose of IF and simultaneously immunized. Injection of IF into nude mice increased the number of AFC and RFC. Meanwhile treatment of the control animals with IF depressed these parameters only slightly (Table 2). A considerable degree of disproportion of cells carrying Lyt-markers was observed in HRS mice aged 3-3.5 months, with predominance of the Lyt $1^{+}.2^{-}.3^{-}$ T lymphocyte population [8]. Treatment of HRS mice had virtually no effect on the quantitative parameters studied (Table 2).

The results are thus evidence that the action of IF in these experimental models differs from the normal function of the T system. Inhibition of the T component (thymectomy on adult animals) or a congenital T deficiency (nude and HRS mice) has a significant effect on the end result of interaction between IF and cells of the immune system. In the presence of a partial or congenital defect of the T component, IF acts as a stimulator of the disturbed antibody-forming and receptor function of the cells. By contrast, the killer effect is unchanged or depressed to a small degree under the influence of IF. Evidence of the importance of the role of normal thymic function for realization of the antitumor activity of IF is given by data showing that injection of murine β-IF inhibits metastasization of fibrosarcoma, and that this effect is much weaker in nude mice and in the presence of a partial lesion of the T component [6]. The need to take into account the T system of immunity will be evident also from the practical point of view, for there have been reports that IF preparations are ineffective in children with immunologic insufficiency [9]. The study of interaction of IF and the thymus, in our view, is a promising trend, the development of which will lay the foundations of the proper clinical use of IF.

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