GENETIC ASPECTS OF THE IMMUNOMODULATIONG ACTION OF INTERFERON

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Conclusive evidence has now been obtained that interferons (IFN) are important factors in the maintenance of cellular homeostatis [5]. The study of the concrete mechanisms of action of IFN aimed at maintaining homeostasis is necessary from the standpoint of identification of the lace and role of the IFN system in the general order of control and regulatory mechanisms.

Recent research has shown that IFN production and reception by the body cells is under genetic control and linked with the presence of genes located in chromosome 3 in mice and chromosome 21 in man [11, 13]. Genetic structures determining the sensitivity of the body to the action of orthomyxoviruses and endogenous IFN have been discovered [6].

The aim of this investigation was to study the effect of murine α/β IFN on migration of hematopoietic stem cells (HSC) from a screened region of bone marrow, and also on parameters of antibody-forming cells (AFC) and rosette-forming cells (RFC) in the spleen of mice belonging to different lines.

EXPERIMENTAL METHODS

CBA, C57Bl/6, and (CB × C57Bl/6)F_1 mice (from the Stolbovaya nursery) aged 2-2.5 months and weighing 18-20 g were used. Murine α/β IFN was obtained by the method of Solov'ev, et al. [1] by injecting Newcastle disease virus (NDV), a powerful interferonogen. Activity of IFN was (32-65) × 10^3 U/ml.

To study the effect of IFN on migration of HSC, mice were subjected to whole-body irradiation on the RUM-17 apparatus in a dose of 850 R, with partial screening of the right thigh and leg. IFN was injected intraperitoneally into the mice in a volume of 1 ml simultaneosly with irradiation; the dose of IFN was 500-5000 U per mouse.

To estimate the effect of IFN on AFC and RFC production, it was injected into animals simultaneously with antigenic stimulation by 5% sheep red blood cells (SRBC) (0.5 ml, intraperitoneally). The number of AFC and the number of immune RFC were determined on the 5th day after injection of the antigen and IFN by the standard methods of Jerne and Nordin [12] and Zaalberg [14], respectively. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Mice of two lines with opposite reactions to SRBC were used: CBA ($H\text{-}2^k$) and C57Bl/6 ($H\text{-}2^b$), as well as their first generation hybrids ($H\text{-}1^k/H\text{-}2^b$).

Migration of HSC from bone marrow and their settling in the peripheral organs of the immune system constitute an important stage in the development of the immune response [3]. Since the height of the immune response is largely determined by the number of lymphocytes taking part in this process, inhibition of the process of HSC migration alone, even without inhibition of their proliferation, may be sufficient to involve the immune response. It has also been shown that migration of HSC is sharply stimulated in the initial period of tumor

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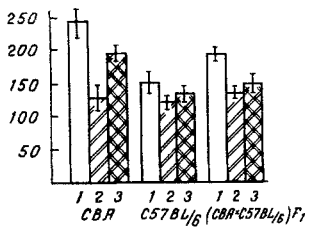

Fig. 1

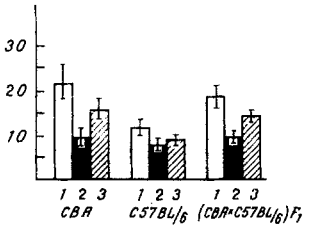

Fig. 2

Fig. 1. Effect of murine α/β IFN on antibody production in mice with opposite responses to SRBC. Ordinate, number of AFC per 10^6 splenic karyocytes. Number of animals in group 21. 1) Control (without IFN); 2) IFN, 500 U/mouse; 3) IFN, 100 U/mouse.

Fig. 2. Inhibitory action of α/β IFN on immune rosette formation in mice of different lines (M ± m). Ordinate, number of RFC per 10^3 spleen cells. Remainder of legend as to Fig. 1.

TABLE 1. Action of Different Doses of IFN on HSC Migration from Screened Region of Bone Marrow (M ± m)

Dose of IFN, U per mouse	No. of HSC in spleen migrating from bone marrow	
	(CBA×C57BL/6)F_1	CBA
5000	15,6±0,5 (*n*=15)	5,8±0,8 (*n*=13)
500	22,4±0,7 (*n*=17)	18,1±0,3 (*n*=19)
Control (without IFN)	20,8±1,1 (*n*=12)	11,0±0,6 (*n*=15)

Legend. n) Number of mice in group.

growth [4], and for that reason the study of the effect of IFN on this process is particularly interesting. It will be clear from Table 1 that injection of IFN in high doses (5000 U) reduced the number of colonies in the spleen. Injection of low doses either had no action on the migration process (F_1 mice) or stimulated it (CBA mice). The rate of migration of HSC was lower in CBA mice than in (CBA × C57Bl/6)F_1 mice, and the effects of different doses of IFN were of a more marked degree, suggesting that the action of endogenous IFN on this process depends on the animals' genotype. Similar results were obtained with simultaneous injection of viral interferonogens (in particular, NDV) with irradiation.

Dependence of the action of α/β IFN on the genotype of the mice was demonstrated also on another model, namely the study of AFC and immune RFC. Splenocytes of C57Bl/6 mice were found to be less sensitive to the inhibitory action of IFN than spleen cells from CBA and (CBA × C57Bl/6)F_1 mice. When IFN was given in a dose of 100 and 500 U/mouse very slight depression of AFC and RFC, depending on the dose of the preparation, was observed (Figs. 1 and 2). Injection of IFN in the same doses into CBA and (CBA × C57Bl/6)F_1 mice simultaneously with the antigen likewise led to reduction of the number of AFC and RFC, and the reduction was greater with a dose of 500 U/mouse, i.e., the effect also depended on the dose of IFN (Figs. 1 and 2).

It can be concluded from analysis of the experimental results that the action of IFN on cells of the immune system is under genetic control. The existence of genetic differences in sensitivity to IFN was first described by Braun and Levy [7]. The work of De Maeyer, et al. [9] demonstrated that administraiton of IFN to BALB/c mice which were recipients of a skin allograft from C57Bl/6 mice prolonged the survival of the graft, whereas in the opposite version IFN did not change the survival time of the skin graft. It is also known that the immunodepressive action of IFN on the development of the delayed type hypersensitivity reaction also is determined by the animal's line [10]. In some cases the sensitivity of lymphoid cells to the actions of endogenous IL can be explained by dependence of its action on the level of endogenous IFN production: the higher the level of endogenous IFN production in

response to NDV, the less sensitive are the animal's cells to the action of exogenous IFN [8]. In our view, this restriction of sensitivity of cells to IFN is essential, for it may perhaps "protect" the animal against the antiproliferative action of endogenous IFN even when administered artificially, thereby helping to preserve the proliferative powers of the cells. Meanwhile, as the present experiments showed, CBA and C57Bl/6 mice did not differ significantly in their level of endogenous IFN production in response to NDV [2], but they give opposite responses to SRBC. It can be postulated that in this experimental model of interaction of IFN with cells of the immune system, the end result of this interaction is evidently not only determined by the level of endogenous IFN production, but is also polygenic in character.

Dependence of the effect of IFN on genotype may thus have a quite broad spectrum of application. This dependence must be taken into account when interferon therapy is planned and during the analysis of the results of research, when allowance must be made for the effect of the genetic factor on the end result of interaction of IFN with the cells of the body and, in particular, cells of the immune system.

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