MECHANISM OF THE ANTIMUTAGENIC ACTION OF INTERFERON: ITS ABILITY TO PROTECT THE REPAIR SYSTEM OF HUMAN CELLS

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Interferon (IF) gives rise to pleiotropic effects: it possesses antiviral activity, ability to inhibit cell proliferation, antitumorigenic properties, and ability to activate the immune system of the host [1].

The writers have discovered a new property of IF, linked with its antimutagenic activity. This property is exhibited in chick embryonic cells when chick IF is used after exposure to a number of physical and chemical mutagens, and also in human cells exposed to fast neutrons and 4-nitroquinoline 1-oxide (4-NQO) [2, 3, 6].

It has been suggested that the mechanism of action of IF is linked with derepression of the genes which control various stages of the DNA repair system in cells. It has been shown experimentally that IF can potentiate activity of the excision repair system [4] and that it can perhaps also induce the repair system, repressed under normal conditions, which can repair primary DNA lesions and, in particular, double-stranded breaks formed in cells under the influence of fast neutrons [2].

This paper describes a study of the antimutagenic action of IF after exposure to various doses of gamma-irradiation, using the formation of chromosomal aberrations and sister chromatid exchanges (SCE) after a single dose as the criterion.

EXPERIMENTAL METHOD

All experiments were carried out on human leukocytes cultured in vitro by the following scheme: 4-5 h after addition of phytohemagglutinin (PHA) IF was added in final titers of 10, 50, and 100 IU/ml. Treatment with mutagen was given 52 and 90 h after stimulation by PHA. In the last case the cells were cultured after treatment with the mutagen and until the time of fixation in medium containing 5 μg/ml of 5-bromodeoxyuridine. Chromosomal aberrations were analyzed in C-metaphase plates stained with acetic orcein. SCE were recorded in preparations stained by the FPG technique [7].

TABLE 1. Effect of Leukocytic IF on Frequency of Chromosomal Abberations Induced by Gamma-Irradiation in Human Leukocytes

Dose of irradiation, Gy	Dose of IF, IU/ml	Total		Cells with chromosomal aberrations (M ± m), %	Total	Chromosomal aberrations				
						per 100 cells (M ± m)	isochromatid deletions	chromosome exchanges	chromatid deletions	chromatid exchanges
Control		200	4	2,0±0,9	4	2,0±0,9	3	—	1	—
0,5	—	200	11	5,5±1,6	11	5,5±1,6	9	—	2	—
0,5	10	200	10	5,0±1,5	10	5,0±1,5	8	—	2	—
0,5	100	160	8	5,0±1,7	8	5,0±1,7	8	—	—	—
1	—	200	22	11,0±2,3	22	11,0±2,3	18	—	4	—
1	10	300	28	10,0±1,7	30	10,0±1,7	27	—	2	1
2	—	300	100	33,4±2,7	115	38,4±2,8	89	12	9	4
2	10	740	142	19,2±1,4	164	22,1±1,5	142	13	3	6
2	100	150	30	20,0±3,3	33	22,0±3,4	22	4	4	3
4	—	200	94	47,0±3,5	106	53,0±3,5	100	4	—	2
4	10	200	65	32,5±3,2	70	35,0±3,4	66	—	4	—
—	10	150	2	1,3±0,9	3	2,0±1,2	3	—	—	—
—	100	100	2	2,0±1,4	2	2,0±1,4	2	—	—	—

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TABLE 2. Frequency of SCE Induced by Gamma-Irradiation and 4-NQO in Human Leukocytes Cultured in vitro in the Presence of IF (M ± m)

Experimental conditions	No. of SCE per 100 chromosomes (gamma-irradiation)	No. of SCE per 100 chromosomes (4-NQO)
Control	24,8±2,0	17,4±1,8
IF + 4-NQO	28,7±2,1	29,6±1,8
4-NQO	48,7±2,7	42,7±2,3
IF	27,5±2,1	24,4±2,3

EXPERIMENTAL RESULTS

Table 1 gives data on the formation of chromosomal aberrations in human lymphocytes pretreated with IF in concentrations of 10 and 100 IU/ml and exposed to gamma-irradiation. Table 1 shows that with a dose of 2 Gy maximal protection of the cells against the action of radiation was observed, whereas with small doses (0.5 and 1 Gy) no decrease was found in the number of chromosomal aberrations.

Data on induction of SCE formed as a result of exposure to gamma-irradiation (2 Gy) and to 4-NQO ($2.5 \cdot 10^{-7}$ M) are given in Table 2. The level of SCE in cells pretreated with IF and irradiated, was lowered to the level of exchanges in control cells treated with IF only. A significant decrease in the number of SCE in cells with IF was observed in experiments with 4-NQO.

These results can be explained either by the true antimutagenic action of IF or the predominant elimination of injured cells pretreated with IF. To exclude the second hypothesis, experiments were undertaken to determine the survival rate of the cells. With a dose of 2 Gy the survival rate of cells with IF was 89.0 ±1.7%, whereas the survival rate of irradiated cells untreated with IF was 73.3 ± 2.3%, compared with 92.3 ± 1.8% in the control and 85.4± 1.5% in experiments with treatment with IF only. In the experiments with 4-NQO these figures were 90.3 ± 2.1% in cells after treatment with the mutagen and pretreated with leukocytic IF, 58.4 ± 2.8% in cells treated with 4-NQO without pretreatment with IF, 89.5 ±1.6% in the control cells, and 85.3 ± 1.4% in cells treated with IF only. IF thus induces a true antimutagenic effect.

It follows from these results that one mechanism of action of IF is associated with its ability to protect the repair system in cells [5]. In fact, with small doses of irradiation, when the repair system is undamaged, no effect of IF is exhibited. The protective effect of IF is reduced also if large doses are used, when the repair system is damaged. There is thus a definite dose range within which IF can exhibit its maximal protective action, recorded by the use of both chromosomal aberrations and SCE as criteria. By contrast with known antimutagens of chemical nature it is extremely effective.

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