IMMUNITY AND THE STAGE OF PROGRESS OF CARCINOGENESIS (AN EXPERIMENTALLY BASED CONCEPT)

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In carcinogenesis, as a rule, suppression of the immune system is observed, and for that reason attempts have been made to use this phenomenon in the early diagnosis of tumors.

The aim of this investigation was to study experimentally the role of immunomodulation (immunosuppression and immunostimulation) in the prevention of tumor development during exposure to a combination of two chemical carcinogens.

EXPERIMENTAL METHOD

Experiments were carried out on 1480 noninbred albino rats, subjected to chemical loading with two carcinogens, namely one amino and one nitroso compound, for 22 months, starting from the age of 1.5 months. Two levels of exposure to the substances were tested, namely high and low, the concentrations for the two levels differing by 2-3 orders of magnitude.

To study the possibility of protection against carcinogenesis by immunomodulators, vitamin preparations (pyridoxin hydrochloride, decamevit), and also preparations stimulating (sodium nucleate) and inhibiting (metalcaptase) the immune system were tested. The animals were given these compounds by addition to the food throughout the period of poisoning. Pyridoxin (vitamin B_6 – 25 mg/day), decamevit (DCV – two tablets), and sodium nucleate (SN – 20 mg/kg) were given to the animals in mean therapeutic doses; metalcaptase (MCP) was given in the maximal daily (180 mg/kg) and therapeutic (15 mg/kg) doses for man. The animals serving as the positive control received the carcinogens without the addition of the drugs. The intact control group received drinking water alone. The state of homeostasis of the animals was studied 3-18 months after the beginning of poisoning, on the basis of a number of parameters including assessment of the general state of the animal, determination of key components of protein, carbohydrate, and lipid metabolism, and investigation of the immune status.

EXPERIMENTAL RESULTS

Prevention of the general toxic effect was best achieved with the aid of SN, and was characterized by the smallest number of altered biochemical and immunologic tests, the most favorable characteristics of the animals' general state and the morphological picture under the influence of the carcinogens. No such a marked degree of prevention of the general toxic effect was observed in animals receiving vitamin B_6 or decamevit.

Immunosuppression (MCP) had no protective effect against poisoning by the chemical carcinogens studied. To compare results obtained in different series of experiments in order to study modification of the carcinogenic effect, taking account of differences in spontaneous tumor formation, the "pure" effect of the substances was deter-

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TABLE 1. Frequency of Tumor Formation under Influence of Different Modifiers

Levels of carcinogens acting in combination	Modifiers	Frequency of tumor formation, %	Localization of tumors	
			specific	nonspecific
High	Positive control	11	2	11
	SN	26	16*	16
	MCP (180 mg/kg)	17	17*	4
	MCP (15 mg/kg)	9	3	9
	B_6	10	5	8
	DCV	4	2	1
Low	Positive control	16	3	17
	SN	17	3	14
	MCP (180 mg/kg)	3	0	3
	MCP (15 mg/kg)	—	—	—
	B_6	14	3	12
	DCV	10	3	8
	MCP (180 mg/kg)	2	2	0

Legend. Values for which $p < 0.05$ compared with positive control marked by an asterisk.

mined [1] with a correction for spontaneous neoplasia. Our initial hypothesis in this case was that the action of carcinogens and of factors inducing spontaneous tumor formation is independent.

Table 1 gives the "pure" effects of the carcinogens and modifiers studied.

It follows from Table 1 that B_6 had virtually no effect on the yield of tumors. With DCV a tendency was observed for tumor formation to be depressed, mainly in localizations nonspecific for the particular carcinogens. For instance, these two modifiers could be rated as carcinogenically passive with respect to the chosen carcinogens, and as not possessing a carcinoprotective effect against them.

Unlike B_6 and DCV, SN and MCP in a dose of 180 mg/kg exhibited definite cocarcinogenic activity during exposure to high concentrations of carcinogens. An unexpected observation in this case was that the action of the immunostimulator (SN) and of the immunosuppressor (MCP) was identical in direction: both increased the yield of tumors with localization specific for the carcinogens tested.

Meanwhile, with low concentrations of carcinogens the parameters characterizing tumor formation under the influence of SN were virtually identical to the positive control.

To explain the cocarcinogenic effect of SN we analyzed the results of the experiment in which low and high concentrations of carcinogens were used, and also studied certain aspects of the mechanism of action of the carcinogens themselves and of SN. Consideration was paid to the fact that, according to data in the literature, the carcinogens chosen for these experiments involved cytochrome P-450 in their metabolism, with the formation of reactive metabolites, responsible for tumor formation [3]. As regards the carcinogenic effect of combined action of high concentrations of these substances antagonism has been observed, but potentiation with low concentrations, as was recorded in our own case also (see the positive control). The cocarcinogenic effect of SN in this case was connected with activation of the cytochrome P-450 system and abolition of competition of the test xenobiotics for it. With low concentrations of carcinogens no competitive effect arises, and additional activation of the cytochrome P-450 system by SN had no effect on the yield of carcinogenically active metabolites. The validity of this explanation also is confirmed by the influence of SN on the general toxic effect. This explanation might be considered acceptable if the cocarcinogenic effect of SN were not combined with its immunostimulating effect, which ought to be accompanied by increased elimination of transformed cells and a reduced yield of tumors.

This illogicality can be overcome by introducing the concept of functional (eliminational) limit of the immune system, in other words, the limit of ability to perform the elimination function, the exceeding of which by antigenic loading makes its performance impossible. It can be tentatively suggested that for this particular organism, this limit is assigned, and immunostimulation cannot alter it.

An increase in the number of animals with established tumors under the influence of high concentrations of carcinogens and against the background of an evident immunostimulating effect of SN, fits in well with this suggestion.

In an attempt to explain the cocarcinogenic effect of SN, the ability of the latter to stimulate proliferation cannot be completely ruled out, and together with the increase in the number of cells undergoing spontaneous mutations on account of the mutagenic effect of the carcinogens, accompanying active proliferation, this may lead to exceeding of the eliminational limit of the immune system and the creation of conditions for realization of the phase of clinical manifestation of carcinogenesis.

In our opinion, the validity of elimination must be awarded the decisive role in the logical conclusion of carcinogenesis up to the stage of clinical attributes.

Mutagenesis is natural and is evolutionarily justified in the multicellular organism undergoing continuous renewal of cell populations. It must be supposed that the presence of a definite number of transformed cells also is natural, but their complete elimination creates a state of dynamic equilibrium, which can be disturbed either by exceeding the limit of elimination of the immune system because of activation of mutagenesis, or by suppression of the immune system, when the leading role belongs to disturbance of recognition or direct inhibition of the elimination function. From these standpoints, the potentiation of carcinogenesis in old age is not necessarily connected with carcinogenic initiations from outside. It can happen through spontaneous mutations or lowering of the elimination limit due to age-related immunosuppression.

As already stated, in the presence of high concentrations of carcinogens the use of MCP in a dose of 180 mg/kg increased the yield of tumors in the specific location for these carcinogens. The use of MCP in a dose of 15 mg/kg, against this background, led to a distinct tendency for the yield of tumors to decrease. A particularly clear tendency toward reduction of tumor formation predominantly in the specific location, was observed when MCP was used together with low concentrations of carcinogens. MCP can thus be characterized as a compound with a definite effect on processes of carcinogenesis, and with different action depending on the dose of the compound and the concentration of the carcinogens.

In our opinion, the effect of MCP revealed by this investigation can be explained only by accepting a dual mechanism of action of the preparation, namely immunosuppression and inhibition of proliferation.

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