DEPENDENCE OF THE COCARCINOGENIC ACTION OF INFLUENZA VIRUS ON THE CHARACTER OF INFLUENZAL INFECTION

Z. D. Savtsova, Yu. A. Grinevich, I. N. Shevchenko, and I. S. Nikol'skii

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Stimulation of spontaneous and induced carcinogenesis (principally in the lungs) in experimental influenzal infection has been described by several workers [10, 12, 13], but not only the mechanisms of this phenomenon, but also the conditions under which the cocarcinogenic activity of influenza virus is exhibited, have nevertheless received very little study. In mice of inbred lines, infected with influenza virus, long tumors arise with different frequencies [10], which correlate in some cases with the frequency of development of chronic infection [7]. This parallel suggests that the cocarcinogenic activity of influenza virus is realized most fully when the latter persists in the body. However, for this hypothesis to be firmly proved, experiments ruling out any possible effect of differences among mice of inbred lines in their genetic predisposition to spontaneous tumors and sensitivity to induced tumors must be undertaken. The writers showed previously that stimulation of cellular immunity to influenza by thymosin prevents the formation of chronic influenzal infection in CC57W mice [8].

The aim of the present investigation was to study the effect of influenza virus on the appearance of tumors in mice of this line with experimental models of different types (acute and chronic) of infection.

EXPERIMENTAL METHOD

Allantoic strain A/PR8/34 of influenza virus with an infectious activity of $10^{7.5}$ EID_{50}/0.2 ml was used. Experiments were carried out on 200 CC57W mice, aged 2 months at the beginning of the experiment. The animals were divided into three groups by the method of random selection. Mice of group 1 were infected intranasally with influenza virus (dose 10^3 EID_{50}/0.2 ml). The mice of group 2 received thymosin for 2 weeks before infection with the same dose of virus. The characteristics of the thymosin, data on its biological activity and dose, and the schedule and methods, of administration were given previously [1, 8]. Group 3 (control) consisted of intact animals. The character of the infection was judged from the results of titration of 10% (w/v) lung homogenates from mice of each group, prepared by the method in [5], 1, 3, 5, and 6 months after infection with the virus, on chick embryos. The isolated virus was titrated in the hemagglutination inhibition test with rat antiserum against reference strain A/PR8/34. The experiment was terminated 9 months after infection. Lungs from mice of each group were examined histologically. Meanwhile, in some animals (6 mice from each group) the proliferative activity of the bronchial and alveolar epithelium was studied by autoradiography [3]. A histological investigation also was made of the lungs of all mice which died in the course of the experiment.

EXPERIMENTAL RESULTS

Infectious virus could be isolated in the late stages from the lungs of mice receiving thymosin before infection with influenza virus much less frequently than from mice of the same strain, infected with virus without preliminary immunostimulation (Table 1). Histological study of the lungs also revealed significant differences between the two experimental groups. In most mice of group 1, characterized by a chronic course of infection, different kinds of inflammatory and proliferative changes were observed in the lungs, and against this background,

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TABLE 1. Frequency of Appearance of Lung Tumors and Changes in Proliferative Activity of Alveolar and Bronchial Epithelium in CC57W Mice with Different Types of Course of Influenza

Experimental conditions	Isolation of infectious virus from lungs at late stage after infection	Discovery of lung tumors	Labeling index (M ± m), per cent	
			alveolar epithelium	bronchial epithelium
Control	0/20 (0)	4/57 (7)	0.30±0.10	0,15±0,10
Infection with A/PR8/34 virus	18*/24 (75)	26*/52 (50)	0,96±0,05*	0,57±0,15*
Infection with A/PR8/34 virus after administration of thymosin	2**/20 (10)	8**/50 (16)	0,74±0,10*	0,28±0,10**

Legend. Numerator — number of positive results, denominator — number of animals tested; numbers in parentheses give number of animals from which virus was isolated or in which tumors were found, in percent of total numbers of animals studied. *P < 0.05, compared with control, **P < 0.05 compared with group 1. Significance of differences in frequency of persistence of virus and discovery of tumors was calculated by Pearson's test (fourfold), significance of differences in labeling index by Student's test.

starting with 6th month after infection, solitary and multiple adenomas, adenocarcinomas, and solid adenocarcinomas were discovered. This phenomenon was studied in detail and described previously [6]. The frequency of tumors in this group was 50%. In mice of group 2, which developed an acute infection after administration of the virus, inflammatory changes in the lungs were virtually absent, tumors developed later (9 months after infection), and they were found in far fewer animals (16%). In this group, just as in the control mice, mainly solitary and multiple adenomas were discovered, with no signs of malignant change.

Some investigators interpret hyperplastic proliferation of the epithelium as the initial stage of development of adenomas of the lungs [2]. We therefore also investigated the proliferative activity of the alveolar and bronchial epithelium of mice of the experimental and control groups. The labeling index in mice developing the acute infection was significantly lower (especially in epithelium of the bronchi) than in animals developing the chronic infection with influenza virus (Table 1).

The results are evidence that influenza virus significantly affects the development of spontaneous lung tumors only if it persists a long time in the body. Dependence of the cocarcinogenic action of influenza virus on the character of infection is evidently determined by the fact that some of the changes which, in the modern view, are mechanisms of participation of infectious viruses in carcinogenesis [11] (stimulation of mitotic activity of infected cells, activation of endogenous oncoviruses in them, the development of a lasting immunodeficiency facilitating progression of tumors), arise specifically in chronic infection by this virus [4, 6, 9].

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*Reference incomplete in Russian original — Publisher.