KINETIC PRINCIPLES OF GROWTH OF TRANSPLANTABLE HEPATOMAS WITH DIFFERENT DEGREES OF DIFFERENTIATION

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The kinetics of growth of three transplantable hepatomas with different rates of growth and different degrees of differentiation was studied. The graph of changes in volume and weight of the hepatomas against time consists of S-shaped curves well described by first-order equations of autocatalysis. The numerical values of the kinetic parameters characterizing the rate of growth of the tumors were determined. Correlation was obtained between the degree of differentiation and the values of the kinetic parameters.

Induced and transplantable tumors of the liver are widely used in experimental oncology as objects for the study of the fundamental biochemical differences between normal and tumor tissues. Investigations of a series of experimental hepatomas have been aimed at the elucidation of the molecular bases of tumor progression, the study of differences in the rate of proliferation of tumor cells, and the establishment of correlation between certain biochemical parameters of tumors and the characteristics of their growth. In this connection it is of great interest to study transplantable hepatomas with different rates of growth and characterized by different degrees of deviation from the structure of normal liver tissue. The most informative work in this field has been done on the Morris series of hepatomas; it has shown that the activity of various enzymes in these hepatomas undergoes regular changes as the rate of growth of the tumors increases [4, 5].

However, these correlations were largely qualitative in character, for no quantitative indices characterizing the dynamics of malignant growth as a rule were used in this case. Nowadays the dynamics of growth of most transplantable hepatomas is characterized only by such semiquantitative parameters as the latent period, the mean generation time, or the number of generations per month.

With these facts in mind there is an evident need for strict quantitative characterization of the growth parameters of hepatomas on the basis of the kinetic principles of their development. It also was decided to analyze the correlation between certain indices of the dynamics of tumor growth given in the literature and the strictly quantitative kinetic parameters of tumor growth.

TABLE 1. Kinetic Characteristics of Hepatomas

Strain of tumor	Index measured	φ (in days^{-1})	(dx/dt)·max (in days^{-1})	Induction period, days		t_{inf} (in days)	t_∞ (in days)	
				found	[1]		Found	[1]
22A	Weight	0,517	0,134	4,3	5—7	9,3	20	14—21
	Volume	0,629	0,158	4,2	5—7	9,5	20	14—21
60	Volume	0,469	0,117	23,0	19—36	27,9	40	42
46	Volume	0,104	0,026	39,0	30—90	57,6	100	90

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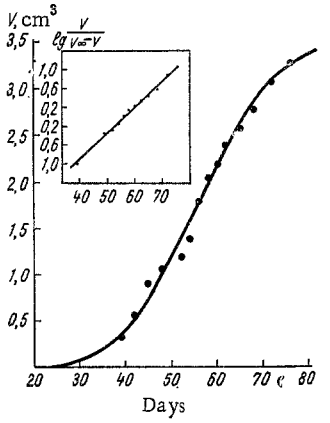

Fig. 1. Kinetic curves of increase in mean volume of tumors.

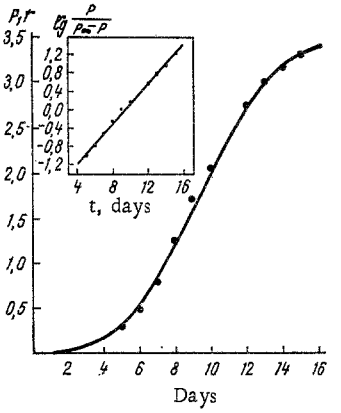

Fig. 2. Kinetic curve of change in mean weight of hepatoma 22A.

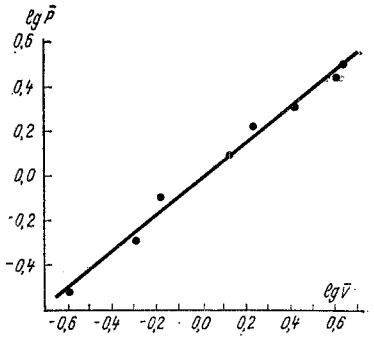

Fig. 3. Weight of tumor as a function of its volume.

The object of this investigation was to study the kinetics of growth of three transplantable hepatomas with different rates of growth and degrees of differentiation (hepatomas 22A, 60, and 46).

EXPERIMENTAL METHOD

Strains of experimental hepatomas were obtained from primary tumors arising in C3HA mice as a result of treatment with o-amino-azotoluene and they were characterized previously by Gel'shtein* [1].

The hepatomas studied in the investigation were transplanted by subcutaneous inoculation of C3HA mice with 0.3 ml of a suspension of tumor tissue in physiological saline (1 : 1). In the course of the experiments the growing tumors were measured in three mutually perpendicular directions and the value $V = a \cdot b \cdot c$ was calculated as the volume of the tumor. This method of calculating the volume of a solid tumor was suggested by McCredie [3] who, having determined the true volume of the tumor by a volumetric method, found that its shape is that of a semiellipsoid; the volume of the tumor is therefore given by the formula $(4/3)\pi \cdot a/2 \cdot b/2 \cdot c/2 \approx a.b.c$. In addition, in the case of hepatoma 22A the tumors were periodically enucleated and weighed. From the results of the measurements kinetic curves of the increase in mean volume and weight of the tumor were plotted.

EXPERIMENTAL RESULTS

Kinetic curves of the increase in mean volume of the hepatomas in the course of their development, together with the linear anamorphoses of these curves, are given in Fig. 1. Each point on these curves is the arithmetic mean of 20 separately found values for the volume or weight of the tumors. It is clear from Fig. 1 that tumor growth in these cases is characterized by S-shaped kinetic curves well described by first-order equations of autocatalysis:

$$\frac{dx}{dt} = \varphi(1-x)(x+x_0),$$

where $x = (V-V_0)/(V_\infty-V_0)$, and φ is the self-acceleration factor. Integration of this equation gives an expression for the corresponding linear anamorphoses:

$$\lg \frac{x+x_0}{1-x} = \lg x_0 + 0.4343\varphi(1-x_0)t,$$

or, alternatively

$$\lg = \frac{V}{V_\infty - V} = \lg \frac{V_0}{V_\infty - V_0} + 0.4343\varphi\left(1 - \frac{V_0}{V_\infty - V_0}\right)t.$$

*The writers are grateful to V. I. Gel'shtein for generously providing the hepatomas of strains 46 and 60.

The kinetic parameters of the relationships thus obtained were calculated on the BESM-4 computer, using all the experimentally found values of the volume of the tumors.

It will be noted that the kinetic principles can also be used to determine other characteristics of tumor growth: the induction period (time taken for the tumor to grow to palpable size), the time taken to reach the maximal rate of growth (point of inflection), and the time to reach the largest volume of the tumor (corresponding formally to the mean generation time and close to values given in the literature [1]). An important kinetic characteristic of tumors is their rate of growth, which varies in the case of autocatalytic processes so that the complete process can be divided into three stages: latent period, period of intensive growth, and final phase of slower development, in which the tumors reach a certain maximum size.

The results are summarized in Table 1.

They show that a hepatoma with a high degree of differentiation is characterized not only by a marked increase in the induction period, but also by a substantial difference in the rates of growth at the point of inflection by comparison with the hepatoma 22A, with a low level of differentiation.

In the case of hepatoma 22A the increase in weight of the tumor was studied during growth and it was shown that the kinetic curve of change in weight of the hepatoma also is described by a first-order equation of autocatalysis (Fig. 2). The kinetic parameters calculated from this curve are given in Table 1.

The changes in weight and volume of the tumor also were compared during its development. The relationship between the weight of the tumor and its volume is illustrated in Fig. 3 in logarithmic coordinates. Clearly the relationship between these parameters is described by the equation

$$\lg P = 0.82 \cdot \lg V.$$

The same type of relationship was demonstrated previously in a study of the solid form of lymphosarcoma NK/LI [2]. The kinetic parameters of growth of the experimental hepatomas thus obtained enable the biochemical indices describing the biochemical shifts to be compared with the corresponding macrokinetic parameters characterizing growth of the tumor.

LITERATURE CITED

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