TUMOR PROGRESSION AS A FACTOR IN VARIABILITY OF THE STRUCTURE OF CIRCADIAN RHYTHMS OF PHOSPHORUS METABOLISM IN TUMORS

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The study of circadian rhythms in malignant neoplasms meets with considerable difficulties due to the known phenomenon of tumor progression. Fluctuations detected at some times of development of a tumor may significantly change or even disappear completely at other times [3, 8]. The study of this phenomenon has not been further developed, although it is very important from the standpoint of additional characterization of a tumor as an extraordinarily dynamic biosystem.

EXPERIMENTAL METHOD

A Pliss lymphosarcoma was transplanted subcutaneously into male and female albino rats weighing 80-100 g. The animals were then divided into three groups, and on the 7th day (44 rats), the 9th day (25 rats), and the 10th day (27 rats) after transplantation, when the volume of the neoplasms in each group was 2.7-2.9, 7.0-9.0, and 12.5-14.0 cm^3 respectively in each group, they were given a subcutaneous injection of ^{32}P in a solution of sodium phosphate, each in a dose of $3.7 \cdot 10^3$ Bq. After 3 h, and again every 3 h for 24 h, the level of radioactivity was measured in vivo at three or four points of the tumor in each animal by means of an end-type "Comet" radiometer. The results were analyzed by computer using a specially prepared program [2] for carrying out averaged "Cosinor" analysis [11].

EXPERIMENTAL RESULTS

Attention was first directed to the fact that on all days of tumor growth, besides a circadian rhythm of the radiophosphorus concentration (with a period of 20.6-28.0 h), there were also ultradian components of the oscillations with periods of 8.0-18.0 h, correlation between which varied at different times of development of the lymphosarcoma (Table 1). In the ultradian interval, there was a shift toward longer periods: whereas on the 7th day three wave contours could be identified with a period of 8.0, 12.0, and 14.4 h, by the 9th day of tumor growth the 8-h period had disappeared, and on the 10th day, only the 14.4-h rhythm remained, and a new 18-h component appeared.

It also follows from Table 1 that within the circadian interval a strictly 24-hourly period was found only on the 9th day after transplantation, whereas two other periods, namely 20 and 28 h, remained stable throughout the 3 days of growth of the neoplasm.

The amplitude of fluctuation of the radiophosphorus concentration in the neoplasm likewise did not remain constant, for it was low on the 7th day, rose sharply on the 9th day, and fell significantly on the 10th day. Less marked changes were found on analysis of the acrophases of the waves during the periods of growth of the lymphosarcoma examined. Acrophases of the 24- and 28-h rhythms were virtually unchanged, whereas for other rhythms some displacement of the acrophases could be observed to later hours by the 9th day of tumor development.

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TABLE 1. Structure of Ultradian and Circadian Rhythms of ^{32}P Concentration in Pliss Lymphosarcoma during Its Growth

Day of tumor growth	Period discovered, h	Amplitude, cpm	Acrophase, h
7-	8,0	13,2(1,7—24,6)	6,5(5,3—7,9)
	12,0	14,1(1,7—26,5)	1,1(11,2—3,6)
	14,4	93,1(79,6—106,6)	12,3(11,9—12,7)
	18,0	Absent	Absent
	20,6	63,5(52,6—74,4)	9,3(8,7—9,8)
	24,0	Absent	Absent
	28,0	88,3(76,6—100,0)	19,4(18,7—20,2)
9-	8,0	Absent	Absent
	12,0	108,4(70,9—145,9)	4,5(3,9—5,0)
	14,4	176,9(136,3—217,5)	14,3(13,8—0,4)
	18,0	Absent	Absent
	20,6	119,9(82,9—156,9)	12,6(11,1—13,9)
	24,0	89,4(35,6—143,2)	15,4(13,1—16,7)
	28,0	173,2(127,3—210,2)	18,0(17,3—19,2)
10-	8,0	Absent	Absent
	12,0	Absent	Absent
	14,4	95,3(55,6—134,9)	14,0(12,9—0,4)
	18,0	106,1(73,0—139,2)	12,5(11,7—13,3)
	20,6	68,2(41,0—95,4)	12,2(10,9—13,5)
	24,0	44,7(15,9—73,5)	16,2(14,2—18,9)
	28,0	112,7(88,7—136,7)	18,9(17,6—20,3)

Legend. Limits of variations shown in parentheses.

Thus in a transplanted tumor rhythms with different periods were discovered, and the ratio between them changed significantly during development of the neoplasm. Two basic questions arise: how can such a diverse pattern of oscillatory processes affecting the radiophosphorus concentration in the tumor be explained, and what determines its dynamics during tumor growth?

An essential feature of malignant neoplasms is their polyclonal structure [1, 5], which is manifested as the presence of genetically different cell populations in tumors, each developing in accordance with its own internal laws, and adapting itself differently to the changing conditions of the host—tumor system. If we accept that rhythmic fluctuations are the basis of any vital activity [7], the characteristics of function of each clonal cell population in a tumor must also include oscillatory processes that are peculiar to them. This was in fact found by spectral analysis of the rhythm of radiophosphorus concentration in the lymphosarcoma. In all probability, those seven periods which were discovered reflect the uniqueness of the fluctuations of metabolic, proliferative, and other processes, in which phosphorus participates, characteristic of individual clonal populations in a neoplasm.

Another important property of tumors is progression [10], which means the development of a neoplasm by means of stable qualitative changes in one or more features. One such qualitative shift is characterized by a change in the cytogenetic structure during the period of tumor growth [4], reflecting replacement of some cell populations by others, better adapted for survival in the course of tumor progression. It is perfectly admissible that the dynamics of restructuring of the clonal architectonics of a neoplasm also involves alternation of the parameters of oscillatory processes and the establishment of rhythms which respond optimally to the new conditions of existence of the tumor and arising in the course of its development in the host. In fact, an ultradian rhythm with periods of 8 and 18 h is observed in a transplanted tumor in the early stages of its growth, when it is still probably not very securely under the influence of the regulatory systems of the host, is comparatively autonomous, and behaves more like a tissue culture than as part of the organism. With the course of progression, a shift to a stable circadian rhythm takes place, which evidently reflects the more active connection between the transplanted neoplasm and the host. This connection, against the background of elimination of unadapted populations, imposes a residual rhythm in the region of the circadian oscillations so characteristic of DNA synthesis, proliferation, and other processes in which phosphorus actively participates.

From the standpoint of these discussions we can probably explain why, in some investigations, a circadian rhythm of mitosis was not found or changes in the rhythm were observed [6, 8, 9]. This phenomenon is evidently connected with the fact that the investigations were conducted at times when, in the course of natural development of the tumor, a 24-hourly rhythm had not yet appeared or it had already disappeared. Our attention is thus redirected once again to the fact that in all investigations of neoplasms, information relating to any one time cannot by any means reflect the true situation in such an actively changing biosystem.

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PRODUCTION OF ANTITUMOR CYTOSTATIC FACTORS BY INACTIVATED RESIDENT PERITONEAL MACROPHAGES OF SYRIAN HAMSTERS

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Cells of the monocytic series (Mc) are an important component of the antitumor defensive system of the body and can exert both cytolytic and cytostatic action (CSA) on tumor cells (TC). A CSA is effected by both activated [1-4] and inactivated Mc [5-7]. According to previous communications, the mechanisms of CSA of inactivated and activated Mc are different: in the case of CSA of inactivated Mc contact between effectors and targets is essential; activated Mc can exert their CSA with the aid of soluble cytostatic factors (CSF), secreted by Mc into the medium Ability to detect CSF evidently depends not only on the level of their production, but also on sensitivity of the target cells used to detect them. We previously showed that spontaneously transformed hamster epithelial cells (STHE), with a low level of malignancy, are

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