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ANALYSIS AND MATHEMATICAL MODELLING OF DYNAMICS OF TWO TUMOURS SYSTEM

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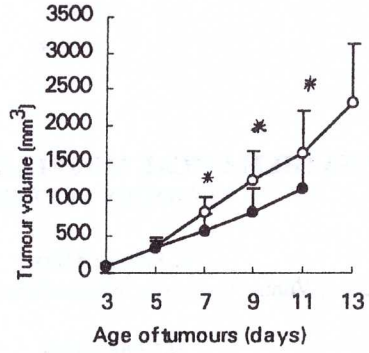
Mathematical characteristics of two tumours cell subpopulations during their interaction are studied. The role of immune system and the hypothesis concerning soluble factors are included into the mathematical model of the system. Considerable evidence is available that growth of normal organs, tissues and malignant tumours is regulated by endogenous biochemical growth inhibiting substances.

One-dimensional Gompertz, logistic, etc., nonlinear, ordinary differential equations may be used to model dynamics of various cell populations. Their growth curves are exponential followed by decline in growth rate with resultant plateau phase. It is not clear, however, what mechanisms predetermine the plateau size of malignant tomour. The premise can be made that the theoretical plateau size of tumour may depend on 1) interaction between tumour cells within the tumour, 2) interaction with normal organs, immune system and other tumours (metastases) within the organism.

The mechanisms of these interactions are not sufficiently clear. Various immunological effects have been proposed, but it seems that direct interaction between tumour cells also may take place. It can be suggested that the serum factor may have different effects on tumour cells during different cell cycle phases and in different growth environment and it can be hypothesized that the serum factor may be involved in the interaction among two tumour cell subpopulations and the immunological system.

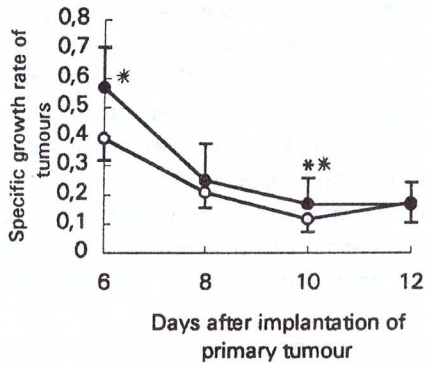
Preliminary experimental results obtained in Lithuanian Oncology Centre indicate the existence of the mutual interaction between two solid SL2 tumours implanted in the same DBA/2 mouse with the interval of two days. Five simultaneous measurements of the tumour volume were carried out during the period of 15 days for every tumour pair with and without immunotherapy. Statistical analysis indicates that during the experiment exponential tumours growth took place.

The primary tumours were induced by subcutaneous injection of 10^7 SL2 cells on the left side of the chest into naive mice on day 0, and the secondary tumours were induced by subcutaneous injection of 10^7 SL2 cells on the right side of the chest on day 2 into the mice that already had the primary tumour. Specific growth rate of tumors v'/v, $v = v(t)$ (v – tumor volume) was estimated on days 6, 8, 10 and 12.



Statistical analysis of primary and secondary tumors volumes and specific growth rates is performed. Mathematical model is based upon the results and ideas due to statistical analysis performed.

Correlation between specific growth rates of primary and secondary tumors was either absent or weak on days 6, 8, and 10 (r = 0. 22, p = 0.35; r = 0.45, p = 0.047; and r = 0.18, p = 0.44, respectively). Interestingly, the strong correlation between specific growth rates of primary and secondary tumors was found on day 12 (r = 0.87, p = 0.0001). Furthermore, specific growth rates of primary and secondary tumors in each mouse reached almost identical values on day 12 despite significantly different volumes of primary and secondary tumors.

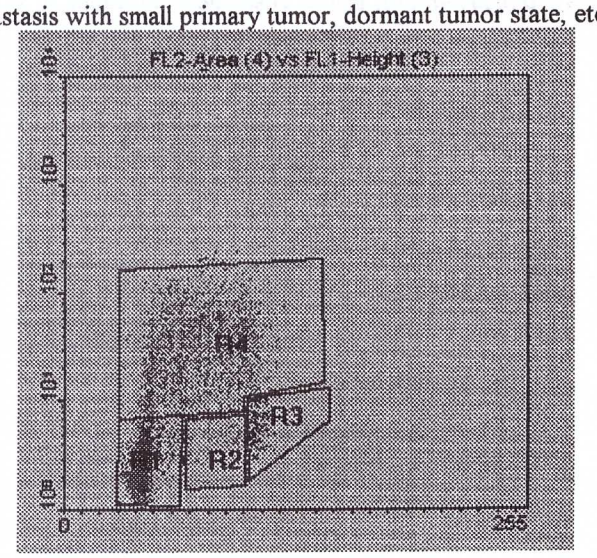


This result suggests that growth regulation on day 12 in these tumors is probably influenced by the same systemic growth regulatory factor. If this growth regulatory factor is produced by tumor cells, negative correlation between specific growth rates of tumors and combined volumes of tumors should exist. However, our results show that specific growth rates of primary or secondary tumors on day 12 do not correlate with the combined volumes of both tumors on day 11 (r = –0.11, p = 0.65; r = –0.20, p = 0.41) or day 13 (r = 0.32, p = 0.17; r = 0.22, p = 0.36). The absence of correlation between specific growth rate of tumors and their combined volumes suggests that growth regulatory factor is produced by the host.

Various mathematical methods are used to describe dynamics of one population or evolution of a system of interacting populations: dynamical systems with discrete or continuous time, deterministic or stochastic. We use systems of ordinary differential equations and their qualitative analysis. Our attempts to model growth of two tumors based upon the hypothesis of "integrated organ" were not successful. Classical models of interaction between 2 populations (predator and pray, symbiosis, competition) do not conform to our experimental results also. The most appropriate is more complex model (*) involving 4 equations for the number of two solid tumor cells $x_1(t)$, $x_2(t)$ and the number of lymfocytes in corresponding tumor $y_1(t)$, $y_2(t)$ with cytotoxic cell migration between two tumors (nondimensional form):

$$\begin{aligned} \dot{x}_i &= j_i + \frac{\alpha_i x_i y_i}{1+y_i} - \beta_i x_i y_i - \gamma_i x_i - c_i x_i + c_k x_k \\ \dot{y}_i &= y_i(1 - x_i - \frac{\mu_i}{1+\nu_i y_i}), \; i,k = 1,2, \; i \neq k, \end{aligned} \qquad (*)$$

where α_i, β_i, γ_i, μ_i, ϑ_i, c_i, j_i are positive constants, i.e. parameters of i'th tumor (i = 1,2), that we suppose to be equal in both tumors. A lot of known results of two tumor growth may be interpreted by these equations, i.e. completely inhibited growth of the secondary tumor in case the time interval between implementations is sufficiently long, growth of metastasis with small primary tumor, dormant tumor state, etc.



Analysis of this model and the results of our experiments invokes the series of new experiments based on flow cytometry technique aiming to extend the knowledge in the cell cycle characteristics of both tumors. To measure the distribution of cell DNA content a fluorescent dye the propodium iodide (PI) specific for DNA is added into the cell suspension medium. To measure kinetics of cell population the bromodeoxyuridine (BrdUrd) is added into a medium, too. The cells during the active DNA synthesis incorporate BrdUrd into the newly synthesized DNA. The amount of

BrdUrd incorporated by a cell depends on the rate of DNA synthesis of that cell, duration of incorporation and, finally, on BrdUrd concentration.

Here we present a plot, where the horizontal axis (FL2-A) corresponds to the amount of DNA, vertical axis (FL1-Height) is the amount of incorporated BrdUrd. It is possible to estimate the cell cycle parameters of cell population. The cells in phase G0/G1 are located in region R1, during the active synthesis in R4, during the nonactive synthesis they are in R2, during G2M they are in R3.

The results of statistical analysis of new experiments will be presented soon together with the results of mathematical modeling.

REFERENCES

1. Gorelik, E. 1983. *Concomitant tumor immunity and the resistance to a secondary tumor challenge*. Adv. Cancer Res. **39:** 71.
2. Characiejus, D., H.F.J. Dullens, and W. Den Otter. 1990. *Mechanisms of tumour rejection in the murine DBA/2-SL2 concomitant immunity system*. Cancer Immunol. Immunother. **32:** 179.
3. Alekseeva, E.I., Kuznetsov, V.A. *Effect of migration cells on the stability of multicentrical immune-dependent tumors.* Биофизика, 36: 509 (in Russian).
4. Bertuzzi A., Gandolfi A., Sinisgalli C., Starace G. 1993. *Cell cycle analysis from DNA-BrdUrd distributions*, Eur. J. Histochem. 37/Suppl. 4, 7-14.