

On the Mathematical Model of Vascular Endothelial Growth Connected with a Tumor Proliferation

N. Khatishvili, Ch. Pirumova, V. Akhobadze

Abstract—In the paper the mathematical model of tumor growth is considered. New capillary network formation, which supply cancer cells with the nutrients, is taken into the account. A formula estimating a tumor growth in connection with the number of capillaries is obtained.

Keywords—Differential Equations, Mathematical Models, Vascular Endothelial, Tumor

I. INTRODUCTION

At the normal conditions the cell circle at the human body is controlled by the Central Nerve System (CNS). Under abnormal conditions such as different stresses (for the example oxidative stress, free radicals, radiation, damage of the immune system, viruses), the degenerated cells are beginning to grow. A primary characteristic of Tumor Cells (TC) is their ability of rapid division, high oxygen consumption rate and production of necrotic proteins. At the beginning the immune system still has resources to fight them, but when the volume of TC reaches a critical size, its growth becomes uncontrolled [1]-[6]. CNS recognizes them as normal cells (NC).

Blood carries oxygen and other nutrients to different parts of the body. Capillaries play an important role at this process, but also they can play fatal role for the body, supplying TC with nutrients. When the tumor diameter reaches about 2mm, this part of the body will be under permanent lack of oxygen [1],[2],[3]. CNS signals to bones marrow to produce endothelial progenitor cells. As a result new network of capillaries surrounding the cancer sphere grows. So the primary stage of Vascular Endothelial Growth Factor (VEGF) is lack of oxygen. New capillaries supply TC with the nutrients, and by means of them the products of metabolism and necrotic substances are carried out to the blood. The

VEGF in tumor is more dangerous stage and leads to metastases [1]-[7].

Necrotic substances circulating in the blood poison normal cells and inhibits normal cell circle. As the human organism has restricted immune resources, apoptosis can occur at all cell phases [1]-[6].

We admit that tumor grows in the spherical form across the radius of the sphere. About half of the tumor volume may be malignant cells, 1% to 10 % blood vessels, and the remainder interstitium (a collagen rich matrix that surrounded TC) [1]-[6]. At the periphery of TC Interstitial pressure is low, whilst inside the tumor is high which inhibits delivery of agents from the bloodstream [1]-[7]. There is a chronic hypoxia in tumor periphery. Hypoxic regions exist between tumor vessels in the tumor center [1]-[7].

By means of our model rate of cancer growth and normal cells death is discussed.

II. THE MATHEMATICAL MODEL

Let us consider a part of the body where TC originated under some factors. We define this volume by $V_0 + U_0$. This part consists of TC (V_0) and NC (U_0) as well.

Let at the initial time t_0 tumor be represented by the sphere with the necrotic cells of radii R_0 and living tumor cells with layer h_0 . Here we consider the simplified model, when tumors grow along the radius of the sphere with a constant layer h_0 i.e. in every time unit the new layer h_0 is formed. Consequently in every moment t we have

$$V_t = \frac{4\pi}{3}(R_0 + th_0)^3 - \frac{4\pi}{3}(R_0 + (t-1)h_0)^3, \quad (1)$$

where V_t is the volume of tumor living cells at the time t .

Let $1mm^3$ of tumor cells consume s_1 nutrients per minute. Hence V_t volume consumes $s_1 V_t$ nutrients, simultaneously the volume V_{t-1} produces $s_1^v V_{t-1}$ of waste products, the poisoned proteins are among them. Part of this poisons is carried out of the body, but part of them circulates in the interstitial fluid and poisons normal cells (especially near the tumor) [1-6]. As the body is a complicated dynamical system we will take the average values.

Suppose, that initial volume of NC at the time t_0 is U_0 and the consumption rate of $1mm^3$ of NC is s_2 nutrients per

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minute. Hence U_0 consumes $s_2 U_0$ nutrients per minute. Let $p_2 + p_3$ be a death rate of NC in 1 time unit, p_2 be a cancer factor and p_3 be a drug factor. Let p_1 be a death rate of TC in 1 time unit, p_2 is proportional to the necrotic part of the tumor,

$$p_2 = d_2 s_1^v V_{t-1}, \quad (2)$$

d_2 is a definite constant.

By U_t we denote the NC volume at the moment t . Suppose that the volume $U_t + V_t$ consumes S_t nutrients.

Consequently the following equation is valid

$$s_1(V_t - p_1 t) + s_2(U_0 - (p_2 + p_3)t) = S_t. \quad (3)$$

Suppose, that the volume U_0 contains n_0 capillaries (this number is a constant for every healthy organ of the definite body). In average $1mm^2$ cross-section of the body contains 3000 open capillaries [11]. In 1 time unit S_0 mg oxygen is consumed by a single capillary (97% of it is carried by Red Blood Cells-RBC) [8]-[12]. Taking into the account the ability of the genetic system we admit

$$\frac{n_0}{U_0 + V_0} = const.$$

Until some critical moment t^* TC and NC has only shared capillaries. The volume U_0 consumes $\beta n_0 s_0$ oxygen, consequently $V_t - p_1 t$ consumes

$$\alpha s_0 n_0 (V_t - p_1 t).$$

For this case from (3) we obtain

$$\alpha s_0 n_0 (V_t - p_1 t) + \beta s_0 n_0 (U_0 - (p_2 + p_3)t) = S_{\max}, \quad (4)$$

where the constants α and β means high consumption rate of TC and low consumption rate of NC (as at this volume NC are hypoxic), $\alpha > \beta$, $\alpha + \beta = 1$, S_{\max} is a maximal ability of the body of nutrients consumption, as it has restricted capabilities. (4) implies

$$\alpha(V_t - p_1 t) + \beta(U_0 - (p_2 + p_3)t) = 1. \quad (5)$$

If at this time, the part U_0 is wholly replaced by TC we can estimate the rate of apoptosis

$$U_0 = (p_2 + p_3)t^*.$$

Now let us consider formation of new capillary network. Let for the moment $t > t^*$ V_t contains n_t capillaries. In this case (3) implies

$$\alpha s_0 n_t (V_t - p_1 t) + \alpha s_0 n_0 (V_t - p_1 t) + \beta s_0 n_0 (U_0 - (p_2 + p_3)t) = S_{\max} \quad (6)$$

Consequently

$$n_t = \frac{n_0}{U_0 + V_0} (V_t - p_1 t). \quad (7)$$

From (6) we obtain

$$(n_t + \alpha n_0)(V_t - p_1 t) + \beta n_0 (U_0 - (p_2 + p_3)t) = S_{\max} / s_0, \quad (8)$$

Putting (7) into (8)

$$(V_t - p_1 t)^2 + \alpha(V_t - p_1 t)(U_0 + V_0) + \beta(U_0 + V_0) \cdot (U_0 - (p_2 + p_3)t) = (U_0 + V_0)S_{\max} / s_0 n_0. \quad (9)$$

Taking second order derivative of (9) with respect to time t and assuming $S_{\max} = const$ we obtain

$$(V_t - p_1)(\alpha + 2)\frac{n_t}{n_0} = \beta(p_2 + p_3). \quad (10)$$

III. CONCLUSION

We obtain the relationship between new capillaries number and TC growth velocity.

In the case of sphere using (1) from (10) one obtains

$$4\pi h_0^2 (2R_0 + 2h_0 t - h_0 - p_1)(\alpha + 2\frac{n_t}{n_0}) = \beta(p_2 + p_3)$$

Hence, we obtain relationship between number of capillaries and apoptosis.

Note. All quantities given at this paper can be measured at the laboratory.

EXAMPLE

In the sequel we will focus at the oxygen consumption as the vital factor for the body.

Here we consider TC in the human brain. The brain is supplied with oxygen constantly. At the normal conditions $1mm^3$ of brain tissue consumes 0.036 mg oxygen per minute [9], [11], [12]. Let at some blood-brain unit TC originated.

Suppose

$$\alpha = \frac{2}{3}; \beta = \frac{1}{3}; p_1 = \frac{1}{100}; p_2 + p_3 = \frac{1}{100};$$

$$V_0 = U_0 = 1mm^3$$

than from (5) we obtain

$$V_t = \frac{1}{2} + \frac{t}{50}.$$

In this case $1mm^3$ of TC consumes 0.048 mg oxygen and NC consumes 0.024 mg oxygen. At the Fig. 1 the graph of growth rate of TC is given.

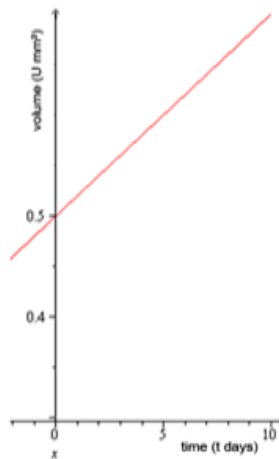


Fig. 1 Tumor Cells (TC)

For NC we have (Fig. 2)

$$U_t = 1 - \frac{t}{100}.$$

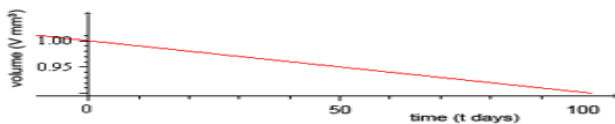


Fig. 2 Normal Cells (NC)

REFERENCES

- [1] R. K. Jain, Sci. Am., no. 271, pp.58-65, 1994.
- [2] K. Groebe, P. Vanpel, "Evaluation of oxygen diffusion distances in human breast cancer". *J.of Radiation Oncology*, vol .15, Issue 3. pp.691-697, 1988.
- [3] M.V. Denhirst , "Perivascular oxygen tensions in transplantable mammary tumor". *J. Radiation Research*, pp.17-182, 1992.
- [4] D.Goldman, Theoretical Models of Microvascular Oxygen Transport to Tissue, *J. Microvasculature*, vol. 15, Issue 8, pp. 795-811, 2008.
- [5] J. Clairambault, " A Step Toward Optimization of Cancer Therapeutics ". *IEEE Jan./Feb.*, pp. 10-16 2008.
- [6] M.B. Kastan, J. Bartek, "Cell-cycle check points and cancer". *Nature*, vol.432, no. 7015, pp.316-323, 2004.
- [7] T. Inai, M. Mansueto, Hashizume . *Am.J. Pathol.* ,no. 165,pp. 35-52, 2004.
- [8] A. Krogh, "The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue", *J. Physiol.*no.52,pp. 409-415.
- [9] G. Mchedlishvili, M. Varazashvili, A. Mamaladze, N. Momtselidze, "Blood flow structuring and its alterations in capillaries of the cerebral cortex". *Microvasc. Res.*no. 53, pp.201-210,1997.
- [10] M. Khizanishvili, M. Shakarashvili, "Correction of NO-inducible apoptosis with Plaféron LB in the Jurkat cells culture", http://www.kheladze.ge/journal_3_folder/Correction%20of%20NO-inducible%20apoptosis%20with%20Plaferon%20LB%20in%20the.pdf
- [11] Knut Smidt-Nielsen, *Animal Physiology*. Cambridge University Press (5th ed), 607 p.,1997.
- [12] J. T. Ottesen, M. S. Olufen, J.K. Larsen, *Applied Mathematical Models in Human Physiology*, SIAM, Philadelphia, 295 p. , 2004.