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

N. Khatiashvili, 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 bone marrow to produce endothelial progenitor cells. As a result new network of capillaries surrounding the cancer 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

$$V_t = 4\pi \left( R_0 + th_0 \right)^3 - 4\pi \left( R_0 + (t - 1)h_0 \right)^3,$$

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 $s_1V_t$ nutrients, simultaneously the volume $V_{t-1}$ produces $s_1V_{t-1}$ 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
Hence \( U_0 \) consumes \( s_i U_0 \) nutrients per minute. Let \( p_1 + p_2 \) be a death rate of NC in 1 time unit, \( p_1 \) 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,

\[
p_2 = d_2 s_i V_{t-1},
\]

\( d_2 \) 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

\[
s_i (V_t - p_t t) + s_i (U_0 - (p_2 + p_3) t) = S_t.
\]

(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

\[
\frac{n_0}{U_0 + V_0} = \text{const}.
\]

Until some critical moment \( t^* \) TC and NC has only shared capillaries. The volume \( U_0 \) consumes \( \beta n_0 s_i \) oxygen, consequently \( V_t - p_t t \) consumes

\[
\alpha s_i n_0 (V_t - p_t t).
\]

For this case from (3) we obtain

\[
\alpha s_i n_0 (V_t - p_t t) + \beta s_i n_0 (U_0 - (p_2 + p_3) t) = S_{\max},
\]

(4)

where the constants \( \alpha \) and \( \beta \) means high consumption rate of TC and law 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

\[
\alpha (V_t - p_t t) + \beta (U_0 - (p_2 + p_3) t) = 1.
\]

(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 \( n_i \) capillaries. In this case (3) implies

\[
\alpha s_i n_i (V_t - p_t t) + \alpha s_i n_0 (V_t - p_t t) + \beta s_i n_0 (U_0 - (p_2 + p_3) t) = S_{\max}
\]

Consequently

\[
n_i = \frac{n_0}{U_0 + V_0} (V_t - p_t t).
\]

(6)

From (6) we obtain

\[
(n_i + \alpha n_0) (V_t - p_t t) + \beta n_0 (U_0 - (p_2 + p_3) t) = S_{\max} / s_0.
\]

(8)

Putting (7) into (8)

\[
(V_t - p_t t)^2 + \alpha (V_t - p_t t) (U_0 + V_0) + \beta (U_0 + V_0) \cdot (U_0 - (p_2 + p_3) t) = (U_0 + V_0) S_{\max} / s_0 n_0.
\]

(9)

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

\[
(V_t - p_t t)(\alpha + 2) \frac{n_i}{n_0} = \beta (p_2 + p_3).
\]

(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

\[
4 \pi h_0^2 (2R_0 + 2h_0 - h_0 - p_t) (\alpha + 2) \frac{n_i}{n_0} = \beta (p_2 + p_3)
\]

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

\[
\alpha = \frac{2}{3}; \beta = \frac{3}{8}; p_1 = \frac{1}{100}; p_2 + p_3 = \frac{1}{100};
\]

\[
V_0 = U_0 = 1mm^3
\]

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.
For NC we have (Fig. 2)

\[ U_t = 1 - \frac{t}{100}, \]

REFERENCES