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Mathematical Modeling of Vitiligo Origin and Development with Taking Into Account the Regulatory MicroRNAs

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ABSTRACT

The paper presents the results of mathematical modeling of the regulatory mechanisms of melanocytes and keratinocytes cell communities dynamics at vitiligo origin and development with taking into account regulatory microRNAs. The results of computational experiments have shown that the developed functional-differential equations of the regulatory mechanisms of vitiligo development allow us to consider the main regimes of functioning depending on various external and internal influences: stationary state, self-oscillations (normally cyclic renewal of the skin epidermis), dynamic chaos (disturbances in normal renewal, onset of vitiligo) and a sharp destructive change – the "black hole" effect (irreversible stage of melanocytes destruction).

Key words : Mathematical modeling, vitiligo, microRNA, chaos, self-oscillation, delay-differential equations.

1. INTRODUCTION

Vitiligo affects around 8% of the global population, regardless of gender, skin type and age [1-3]. The exact cause of vitiligo is unknown and is most commonly associated with autoimmune processes, oxidative stress, and neurogenic disorders. Epidemiological surveys have shown that 20% of vitiligo patients have one or more first-degree relatives affected by vitiligo. Also, the regulatory mechanisms of vitiligo development are not fully understood. Insufficient knowledge of the etiology and pathogenesis of vitiligo is the reason for the unreliability and ineffectiveness of existing treatment methods. The overall effectiveness of vitiligo treatment does not exceed 80%, and the possibility of relapse reaches 90% [4]. Mathematical and computer modeling has a predictive ability, allows to simulate the main modes of the process under consideration [5].

Most researchers assume that the origin and development of vitiligo is due to many factors and gene interactions, in which noncoding RNAs contribute to a person's susceptibility to vitiligo [6-7]. Mathematical modeling of the regulatory mechanisms of the interrelated functioning of molecular genetic systems microRNA, melanocytes and keratinocytes is carried out on the basis of the method of regulation of living systems [8], which makes it possible to consider from a single point of view a wide range of phenomena combined by the presence of a regulatory system, a regulatory environment and a combined feedback [9-10].

2. MATHEMATICAL MODEL

Studies suggest that vitiligo occurence and development is due to a variety of factors and gene interactions in which noncoding RNAs contribute to a person's susceptibility to vitiligo. MicroRNAs circulating in blood plasma are regulators of protein synthesis. On the way from DNA to protein, they regulate the translation procedure, affect the information reading from mRNA. One and the same microRNA affects the translation of not one mRNA, but many. Moreover, the micro-RNA regulation is complex and uneven.

Let's consider the effect of micro-RNA on the cellular processes of the skin epidermis. As it is known, the molecular genetic system in the course of its functioning encompasses the transcription processes (copying of the necessary genetic programs from the hereditary apparatus in the form of a nucleic sequence) with the messenger RNA (mRNA) formation, translation (translation of the nucleic sequence into a chain of amino acids - elements of protein-enzymes) with the formation of polypeptides and the formation of enzyme proteins (the main building and functional elements of biosystems).

The type of synthesized protein is determined by the information recorded on the mRNA. Genetic variants of polymorphisms usually differ in the amino acid sequence of the protein gene product or the level of gene expression, i.e. transfer of genetic information and mRNA to proteins. The melanocytes expression plays an important role in vitiligo origin. The melanocytes number in relation to the keratinocytes of the basal layer is normally in a ratio of 1:30 and if the basal layer of epidermis is affected by vitiligo, then in the lesion layer there are only keratinocytes. MicroRNAs

are highly activated in vitiligo-affected skin, which for the greater part consists of keratinocytes.

We use the concept of ORASTA, consisting of an oscillator-regulator (OR) capable of receiving, processing and transmitting signals of a certain nature, and active system with time average (ASTA), which to allow a feedback loop in the system for a finite time [5]. Thus, non-coding circulating microRNAs can be considered as an oscillator-regulator that can freely circulate and regulate cellular functions, biosynthesis. The developed functional-differential equations of the mathematical model of the regulatory mechanisms of the interconnected functioning of the molecular genetic systems of microRNA, melanocytes and keratinocytes have the following form:

$$\begin{aligned}\frac{dX(t)}{dt} &= a_1 Y(t-h)Z(t-h)e^{-Y(t-h)-Z(t-h)} - b_1 X(t);\\ \frac{dY(t)}{dt} &= a_2 X(t) + a_3 Y(t-h) - b_2 Y(t);\\ \frac{dZ(t)}{dt} &= a_4 X(t) + a_5 Z(t-h) - b_3 Z(t)\end{aligned} \quad (1)$$

with initial conditions

$$\begin{cases} X(t) = \vartheta_1(t);\ t \in [0;\ h],\\ Y(t) = \vartheta_2(t);\ t \in [0;\ h],\\ Z(t) = \vartheta_3(t);\ t \in [0;\ h]. \end{cases}$$

Here $X(t), Y(t), Z(t)$ are the variables denoting concentrations of microRNA, the number of cells of melanocytes and keranocytes, respectively; h is feedback time; b_1, b_2, b_3 are rates of activity decline; a_i are the activity rates of the considered systems (i = 1, .., 4).

A qualitative analysis of the equations system (1) shows that the system has a stable trivial equilibrium position (attracting solutions) and can have nontrivial equilibrium positions. Let X_0, Y_0, Z_0 be the equilibrium positions of system (1). Then we have

$$\begin{aligned} a_1 Y_0 Z_0 e^{-Y_0 - Z_0} - b_1 X_0 &= 0;\\ a_2 X_0 + Y_0 (a_3 - b_2) &= 0;\\ a_4 X_0 + Z_0 (a_5 - b_3) &= 0. \end{aligned}$$

Determining Y_0, Z_0 from the last two equations and substituting into the first equation, we obtain

$$a_1 k_1 k_2 X_0^2 e^{-(k_1+k_2)X_0} - X_0 = 0;$$

$$k_1 = -\frac{a_2}{a_3 - b_2};$$

$$k_2 = -\frac{a_4}{a_5 - b_3}.$$

This shows that a trivial equilibrium position always exists. To find conditions for the existence of non-trivial equilibria, we assume that X_0 is nonzero. We have

$$a_1 k_1 k_2 X_0 e^{-(k_1+k_2)X_0} = 1.$$

We denote

$$F_1(X_0) = F_2(X_0),$$

where

$$F_1(X_0) = a_1 k_1 k_2 X_0 e^{-(k_1+k_2)X_0};$$
$$F_2(X_0) = 1.$$

For the presence of non-trivial equilibrium positions, it is necessary (Figure 1), that

$$max\ F_1(X_0) > F_2(X_0) = 1.$$

Calculations show that for

$$a_1 = \frac{e(k_1+k_2)}{k_1 k_2},$$

a nontrivial equilibrium position arises at the point

$$X_0 = \frac{1}{k_1 + k_2}$$

and, if

$$a_1 > \frac{e(k_1+k_2)}{k_1 k_2}, \quad (2)$$

there are two non-trivial equilibrium positions.

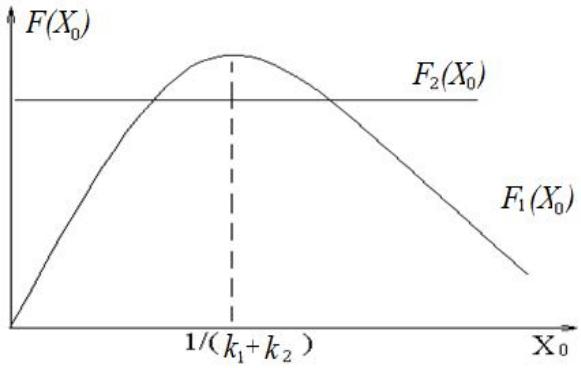

Figure 1: Geometric representation of the presence condition of nontrivial equilibria

Let (2) be fulfilled in such a way that we have two isolated nontrivial equilibria. The results of a qualitative study of the equations system (1) show that there are trivial equilibrium position and two nontrivial equilibrium positions α, β $(0 < \alpha \le 1/(k_1+k_2) \le \beta < \infty)$. Bifurcation occurs at a point $1/(k_1+k_2)$. The trivial equilibrium position is stable. If we disregard the time delay ($h=0$), then the first non-trivial

equilibrium position α is unstable, and the second β is stable. If we take into account the time delay then the attractor β can lose own stability with the occurrence of Poincare type limit cycles, chaotic regimes and “black hole” effect.

3. RESULTS AND DISCUSSION

A program was developed for obtaining approximate solutions of functional differential equations for a mathematical model of regulatory mechanisms of the interconnected functioning of molecular genetic systems of microRNA, melanocytes and keratinocytes. The results of quantitative studies of the mathematical model for the regulatory mechanisms of the interrelated functioning between keratinocytes and melanocytes, taking into account the microRNA circulating in the blood plasma, based on the system of functional differential equations (1), show that the models, taking into account temporal relationships, make it possible to effectively study the main regularities of the vitiligo occurrence, which have arisen in the normal oscillatory processes disurbance in skin epidermis renewal.

The values of the parameters a_1, a_2, a_3 can be used to control the activity of microRNA, melanocytes and keratinocytes. The values of the parameters b_1, b_2, b_3 make it possible to take into account the decay rates of the considered biosystems. These parameters make it possible to estimate the rate and degree of melanocytes destruction under different internal characteristics, as well as to predict the development of the melanocytes cell community at pathological conditions and changes in external regulatory signals. Analysis of the characteristic behaviors of solutions (1) using methods for obtaining approximate solutions of functional-differential equations shows the presence in the regulatory model of the system "microRNA-melanocytes-keratinocytes" modes of a stable stationary state, stable self-oscillatory behavior, irregular functioning and the effect of sharp destructive changes – the "black hole ”(Figures 2-5). Computational experiments have shown that microRNAs are highly activated in the skin epidermis affected by vitiligo. The model results are in good agreement with experimental data [11]. The area of irregular fluctuations is characterized by regulatory system infraction with a consecutive impairment in skin functional activity. The research results allow us to determine the state of the norm, the range of regular and irregular fluctuations and the critical level of microRNA, to develop effective measures to improve the skin condition in vitiligo.

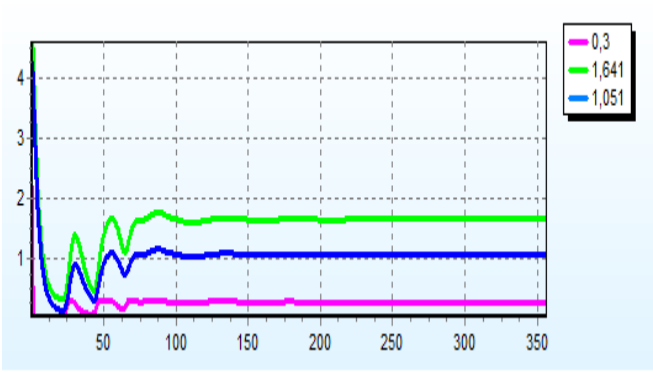

Figure 2: Steady state condition in the model for "microRNA-melanocytes-keratinocytes" regulatory system. Green line indicates keranocytes activity. Red line indicates microRNA activity and blue line indicates melanocytes activity

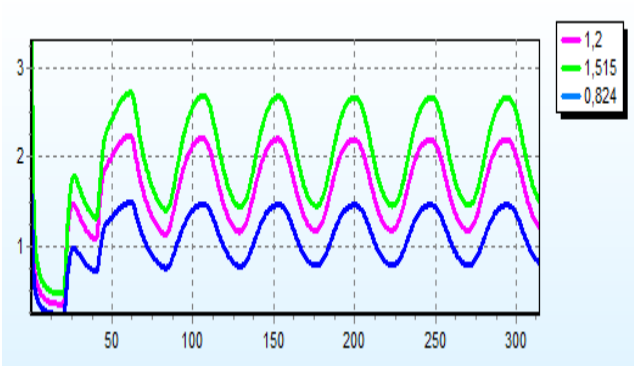

Figure 3: Stable oscillatory behavior of the regulatory model for "microRNA-melanocytes-keratinocytes" system. Red line indicates microRNA activity and blue line indicates melanocytes activity

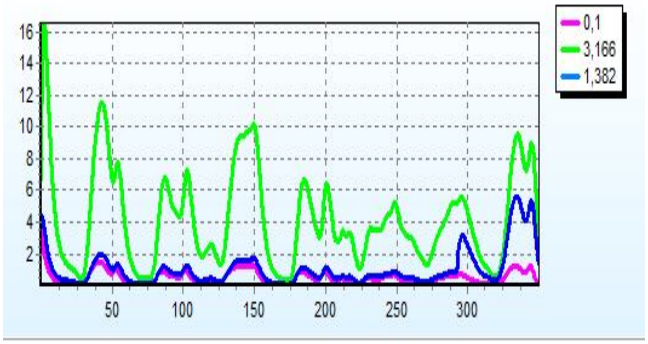

Figure 4: Chaotic behavior in the regulatory model for "microRNA-melanocytes-keratinocytes" system

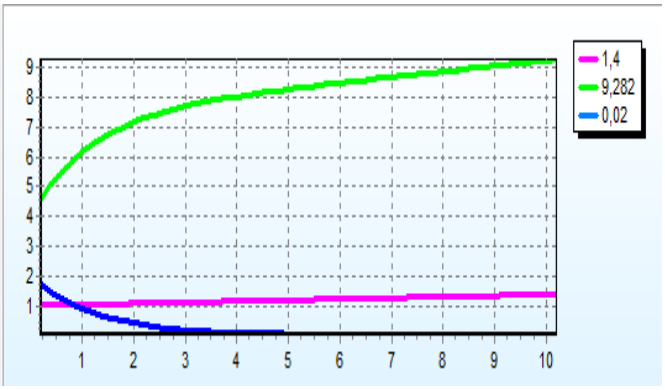

Figure 5: The "black hole" effect in the "microRNA-melanocytes-keratinocytes" regulators model system. Irreversible stage of melanocytes destruction

To identify the most general regularities in the occurrence of skin epidermal anomalies in vitiligo, we consider the simplified equations for the melanocytes dynamics ($M(t)$):

$$\frac{dM(t)}{dt} = (p_0 + pM^n(t-1))e^{-M(t-1)} - bM(t)$$
$$M_{k+1} = (p_0 + pM_k^n)e^{-M_k} \quad (3)$$

where p_0, p are values characterizing the constant rates of formation of micro-RNA and melanocytes; n is the parameter of melanocytes self-conjugation. For $p_0 > 0$, in the considered systems, the trivial attractor is replaced by a small attractor A (Figures 6) and (3) can have three nontrivial attractors – A, B, C. Analysis of the solution gradients (Figures 6) shows that A and C are attractors, and B is an anti-attractor. Consequently, this form of systems has two functional attractors, i.e. two possible modes of functioning with relatively low and relatively high activities.

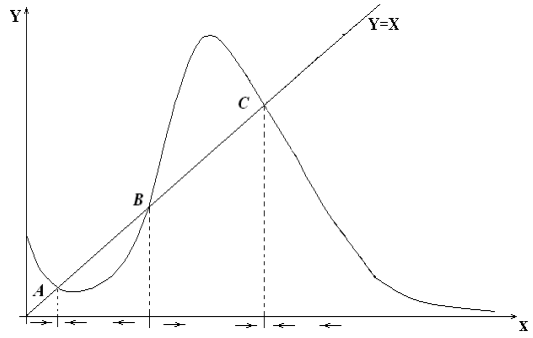

Figure 6: Equilibrium positions and solutions gradients for (3)

A qualitative study of the attractors A and C properties shows the possibility of steady state regimes and violation of its stability. In this case, in the neighborhood A and C there are limit cycles of Poincaré type. As expected (by analogy with control systems with a passive regulatory environment), attractor C can turn into a strange attractor with irregular solutions behavior in its pool. Under certain conditions, the "black hole" effect occurs. Regular stable oscillatory solutions describe the normal healthy renewal of the skin epidermis. Stability and irregular fluctuations disturbances can be an early sign of vitiligo. It is customary to distinguish the following stages of the vitiligo progression [4]:

- Preclinical. This stage is characterized by a deficiency in the melanocytes growth.
- The initial stage (possibly a reversible stage), there is a decrease in the melanin amount in melanocytes.
- Late stage (almost irreversible stage) melanocytes are destroyed.

Chaotic behavior in the melanocytes functioning can be attributed to the preclinical stage with a deficit in the melanocytes growth. We discovered two forms of "black hole" effect. The first, when chaotic oscillatory solutions break down to a trivial attractor, and the second - small (but not trivial) attractor. Apparently, the first form of a "black hole" can be called a "zero black hole", and the second - a "non-zero black hole". In the second case, when a "non-zero black hole" effect appears, the system does not "die", but is mainly in a state of relatively low activity (Figures 7). Qualitative research shows, in this case, the ambiguous behavior of the regulatory system. The nature of its functioning depends on the properties of the small attractor A. It can lose stability, turn into a strange attractor and exhibit the effect of a "non-zero black hole". Then a control system with two strange attractors with the properties of "nonzero black holes" appears. The behavior of such system with an active medium has an irregular character with an alternate "transfer" of the system to the pools of attractors A and C with the breakdown of oscillatory solutions. A "non-zero black hole" can be identified with an initial reversible stage with a decrease in the amount of melanin in melanocytes, and "zero black hole" with a late, almost irreversible stage, when melanocytes are completely destroyed.

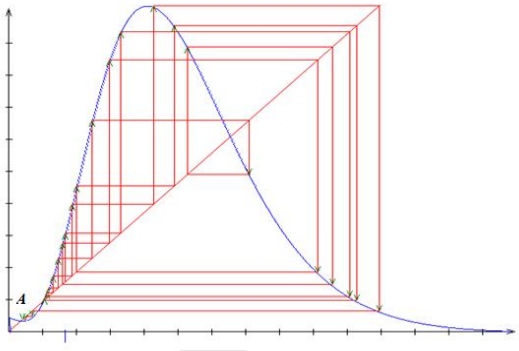

Figure 7: "Non-zero black hole" effect in (3)

Thus, computer aided investigations play vital role in the disease diagnosis and health care field [13-14]. An extremely important role in the functioning of the human organism at the norm and disease belongs to molecular-genetic regulatory mechanisms that ensure the fulfillment of vital functions of the skin epidermis: to maintain stable states, characterized by constant concentrations of circulating microRNA, the melanocytes and keranocytes cells number; to provide periodic continuous fluctuations in the numbers of

melanocytes and keranocytes, ensuring normal skin renewal; control irreversible processes: development, growth, differentiation, apoptosis. Computational experiments made it possible to determine the main modes in the model of the system "microRNA-melanocytes-keratinocytes": stationary state, self-oscillatory mode, irregular oscillation mode and a sharp decline in the activity of genetic systems.

5. CONCLUSION

The results of qualitative studies and quantitative calculations have shown that there are specific behavior areas in the "microRNA-melanocytes-keratinocytes" system: a trivial attractor, a stationary regime, Poincaré type limit cycles, dynamic chaos, "black hole" effect. The areas of normal behavior are generally considered to be the area of stable equilibrium and the area of regular fluctuations (stable periodic renewal of the skin epidermis). The regions of anomalies are the region of dynamic chaos and the region with "black hole" effect. The area of dynamic chaos is characterized by irregular fluctuations in the skin epidermis renewal and can be identified as a regulation loss in the functioning and pathological process of vitiligo. It borders, on the one hand, with the region of Poincaré type limit cycles (where the behavior of the system is characterized by bilateral bi-stable periodic oscillations), and on the other hand, with the region of sharp destructive changes – "black hole" effect, which characterizes the late, almost irreversible stage of melanocytes destruction. MicroRNA is an important regulator in vitiligo development, may activate keratinocyte proliferation and may be involved in melanocyte apoptosis.

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