

Modeling of regulatory mechanisms of oncogenic viruses Micro-RNA action

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Abstract. The article is devoted to investigate the dynamics of the regulatory mechanisms of viral miRNA during oncogenesis at Hepatitis B virus infection. Studies show that mutually conjugated molecular-genetic systems of hepatocytes and micro-RNA of oncogenic viruses have the following domains: a stable functional activity, the possibility of oscillatory modes of functioning, irregular oscillations (it may occur the chaotic behavior of oncoviruses micro-RNA and their regulatory network connections, which leads to chaotic uncontrolled cellular reproduction and cancer) and black hole effect (sharp reduction in the number of cells, which corresponds to the metastasis of cancer cells). The results of computational experiments show that depending on the parameters of the cell and the cellular external environment, some miRNAs can both activate and inhibit tumor growth.

1. Introduction

Experts from the International Agency for Research on Cancer (IARC) consider the following viruses as oncogenic for humans: Hepatitis B virus and Hepatitis C virus (HBV/HCV), Human papillomavirus (HPV), Epstein-Barr virus (EBV), Human herpesvirus type 8 (HHV-8). The viruses with oncogenic potential modify the cellular genome. The human oncoviruses viral genome encode regulatory miRNAs (microRNAs, miRs). The action mechanism of regulatory miRNAs has not studied in detail. Although large-scale international studies on regulatory mechanisms of viral infection are being conducted [1, 2, 3, 4, 5, 6, 7, 8], the genome data has not yet been interpreted, there is no in-depth understanding of gene networks functioning patterns, and the regulatory mechanisms of miRNA during oncogenesis are not clarified. Systematic and narrative reviews show that there are very contradictory facts about the regulatory role of miRNA during the tumor process [2, 3, 4, 5, 6, 7, 8]. For miR-205, both its overexpression and hypoexpression during the tumor process are noted. So MicroRNA-155 can have both oncogenic and tumor-suppressing effects [2, 7]. The following reasons for such different results are indicated: a) different collections of clinical samples from patients; b) various oncological diseases; c) intratumoral heterogeneity, i.e. coexistence within the same tumor cells with different genetic, epigenetic properties. Effective methods for modeling the molecular-genetic mechanisms of the occurrence of pathological processes allow us to understand the patterns of functioning of gene networks and the role of miRNA in pathogenesis. The disclosure of the regulatory mechanisms of microRNA action will significantly help determine the mechanisms of formation and development of pathological conditions in cancer at the molecular genetic level and will



allow to find effective ways of targeted therapeutic and prophylactic effects on the human body. Mathematical and computer modelling has a predictive ability by allowing simulation the main modes of the considered process.

2. Methods and Results

Studies are carried out on the basis of the method of living systems regulatorics [9], which makes it possible to consider a wide range of phenomena combined with the presence of the regulatory system, the regulatory environment and combined feedback on the example HBV infection of human hepatocytes. Non-coding miRNAs are considered as a regulatory system with an oscillator- regulator that can freely circulate and regulate cellular functions, biosynthesis at norm and pathological conditions (figure 1).

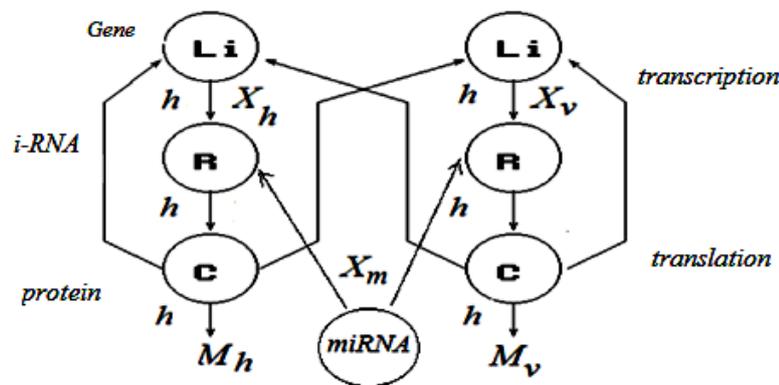


Figure 1. Gene regulation scheme taking into account the micro-RNA action.

The miRNAs of the hepatitis B virus do not encode proteins, but regulate protein synthesis. The same miRNA of the viral genetic system regulates the translation of many mRNA of the hepatocyte genetic system in nonlinearly, complex way. Viral miRNAs can be involved in suppressing the expression of their own viral genes. The activity of the molecular-genetic system of the hepatitis B virus depends on the hepatocyte functioning level. Taking into account these factors, the regulatory interrelated activity between the molecular-genetic systems of the hepatocyte and hepatitis B virus can be quantitatively described by the following system of functional-differential equations:

$$\begin{aligned}
 \frac{dX_h(t)}{dt} &= \gamma_h X_h(t-h) e^{-\delta_h M_h(t-h) - \delta_v M_v(t-h) - m X_m(t-h)} - b_h X_h(t); \\
 \frac{dX_v(t)}{dt} &= \gamma_v X_h(t-h) X_v(t-h) e^{-\delta_h M_h(t-h) - \delta_v M_v(t-h) - m X_m(t-h)} - b_v X_v(t); \\
 \frac{dX_m(t)}{dt} &= \gamma_v X_h(t-h) X_v(t-h) X_m(t-h) e^{-m X_m(t-h)} - b_m X_m(t); \\
 \frac{dM_h(t)}{dt} &= \mu_h X_h(t-h) - c_h M_h(t); \\
 \frac{dM_v(t)}{dt} &= \mu_v X_v(t-h) - c_v M_v(t); \\
 X_m(t) &= \varphi_m(t); X_h(t) = \varphi_h(t); X_v(t) = \varphi_v(t); M_h(t) = \eta_h(t); M_v(t) = \eta_v(t) \\
 &\text{at } t_0 - h \leq t \leq t_0 \quad (t_0 > h),
 \end{aligned}
 \tag{1}$$

where $\varphi_m(t), \varphi_h(t), \varphi_v(t), \eta_h(t), \eta_v(t)$ are continuous functions on $[t_0 - h, t_0]$; t_0 is the initial time at beginning of model studies (if necessary, in analytical studies, we can take $t_0 = 0$); $X_h(t)$ expresses the mRNA concentration of the hepatocyte genetic system; $X_v(t)$ expresses the activity level of the transcription system of the HBV genetic system; $X_m(t)$ is the miRNA concentration of the hepatitis virus genetic system; $M_h(t), M_v(t)$ are activity levels of the hepatocyte and virus translation systems (concentration of protein products). All parameters are non-negative. The first three equations of system (1) take into account the repressive effect of the molecular-genetic system of viruses on the functioning of hepatocytes.

The analysis of characteristic solutions of functional-differential equations of living system's regulatory mechanisms is usually difficult and cumbersome. Therefore, the following methods are used to determine the behavior of their solutions: simplifying equations, obtaining approximate solutions, visualizing, determining the presence and dynamics of critical points, studying their stability, determining the existence of regular and irregular oscillations, constructing characteristic phase patterns and determining the main parametric regions, using a Lamerey diagram and organizing the vector with a delayed identifiers. The methods for qualitative study of functional-differential equations are very important for obtaining the main characteristic features of the model's behavior. In many cases, it is useful to construct the corresponding reduced equations (the so-called model systems) on the basis of biological, biophysical considerations and mathematical techniques. It allows us to more effectively apply computer methods for analyzing the general patterns of solutions behavior.

3. Qualitative analysis of model systems

By taking into account that the hepatitis B virus encoded miRNA acts in infected cell, which regulates hepatocyte activity and controls HBV viral replication, we have the following reduced equations for the minimal mathematical model of interrelated functioning between the hepatocyte and viral miRNA molecular-genetic systems:

$$\begin{aligned}\theta_1/h \frac{dX_1(t)}{dt} &= a_1 X_1(t-1) X_2(t-1) e^{-X_1(t-1) - X_2(t-1)} - X_1(t-1); \\ \theta_2/h \frac{dX_2(t)}{dt} &= a_2 X_1(t-1) X_2(t-1) e^{-X_1(t-1) - X_2(t-1)} - X_2(t-1);\end{aligned}\quad (2)$$

where $X_1(t)$ is the hepatocyte mRNA concentration; $X_2(t)$ is the concentration of the hepatitis B virus microRNA; θ_1, θ_2 are the corresponding average durations of the activity of the molecular genetic systems of the hepatocyte and hepatitis B virus, respectively; h is the temporal radius of the cell (the time required for the feedback of molecular genetic systems); a_1, a_2 are non-negative constants expressing the resource availability of the systems and products for the considered genes.

The condition for the existence of non-trivial equilibrium positions based on (2) has the following form:

$$a_1 a_2 / (a_1 + a_2) \geq e.$$

Let us consider a qualitative analysis of the system of equations without delay

$$\begin{aligned}\theta_1/h \frac{dX_1(t)}{dt} &= a_1 X_1(t) X_2(t) e^{-X_1(t) - X_2(t)} - X_1(t); \\ \theta_2/h \frac{dX_2(t)}{dt} &= a_2 X_1(t) X_2(t) e^{-X_1(t) - X_2(t)} - X_2(t);\end{aligned}\quad (3)$$

The main isoclines are determined by the equations

$$\begin{aligned}a_1 X_2 e^{-X_1 - X_2} &= 1; \\ a_2 X_1 e^{-X_1 - X_2} &= 1.\end{aligned}$$

Depending on the a_1 and a_2 values, there are two types of characteristic phase portraits can be observed: with one attractor (at the origin of coordinates) and with two attractors (at the origin of coordinates and at point A_2) (figure 2).

Point A_1 is an unstable saddle-node equilibrium. For a detailed analysis of the solutions behavior nature near the critical points, we construct linearized equations for (3). Let $Z_1(t), Z_2(t)$ be a small and

$$Z_1(t) = \xi_1 + X_1(t);$$

$$Z_2(t) = \xi_2 + X_2(t)$$

and, neglecting nonlinear terms in the decomposition of the right-hand parts (3) in a Taylor series, we have

$$\begin{aligned} \theta_1/h \frac{dZ_1(t)}{dt} &= -\xi_1 Z_1(t) + \frac{\xi_1}{\xi_2} (1 - \xi_2) Z_2(t); \\ \theta_2/h \frac{dZ_2(t)}{dt} &= \frac{\xi_2}{\xi_1} (1 - \xi_1) Z_1(t) - \xi_2 Z_2(t). \end{aligned} \tag{4}$$

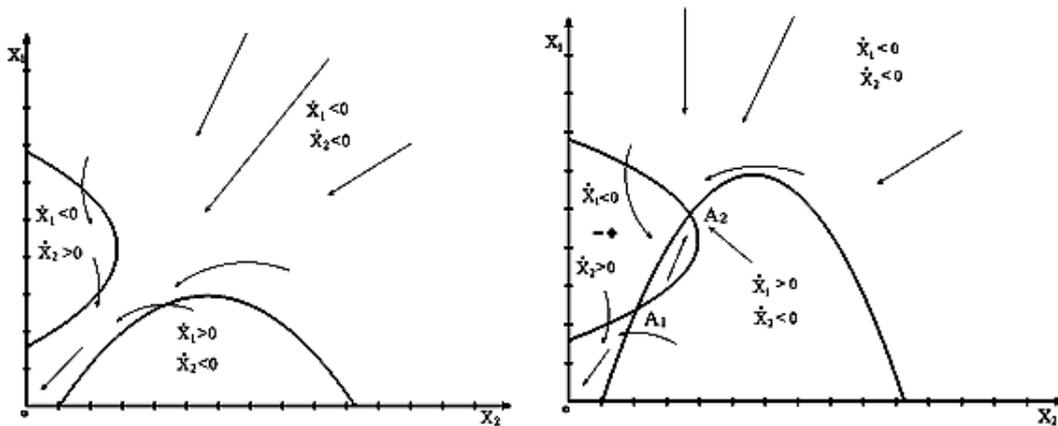


Figure 2. Characteristic phase portraits (3).

Characteristic equation has the following form

$$(\theta_1 \lambda + \xi_1)(\theta_2 \lambda + \xi_2) = (1 - \xi_1)(1 - \xi_2).$$

Here we have that there are negative roots only when

$$(\xi_1 + \xi_2) \geq 1.$$

In this case, since the bifurcation point for nontrivial roots has the following coordinates

$$\xi_1 = (n - 1) / b = 1 / b = a_1 / (a_1 + a_2);$$

$$\xi_2 = (a_2 / a_1) \xi_1 = a_2 / (a_1 + a_2),$$

then for coordinates of points A_0, A_1 we have

$$\xi_1 + \xi_2 < 1,$$

and for coordinates of point A_2 we obtain

$$\xi_1 + \xi_2 > 1.$$

Therefore, the equilibrium positions A_0, A_1 are unstable, and the bifurcation points A and A_2 are stable.

We return to the problem of qualitative analysis of functional-differential equations (2) with delay. Linearizing the equations around equilibrium positions we have

$$\begin{aligned} \theta_1/h \frac{dZ_1(t)}{dt} &= -(1 - \xi_1)Z_1(t - 1) + \xi_1/\xi_2(1 - \xi_2)Z_2(t - 1) - Z_1(t); \\ \theta_2/h \frac{dZ_2(t)}{dt} &= \xi_2/\xi_1(1 - \xi_1)Z_1(t - 1) + (1 - \xi_2)Z_2(t - 1) - Z_2(t); \end{aligned} \tag{5}$$

where $Z_1(t) = -\xi_1 + X_1(t)$; $Z_2(t) = -\xi_2 + X_2(t)$ are small. The characteristic equation for (5) has the following form:

$$\begin{vmatrix} -\theta_1/h\lambda - 1 - (\xi_1 - 1)e^{-\lambda} & \xi_1/\xi_2(1 - \xi_2)e^{-\lambda} \\ \xi_2/\xi_1(1 - \xi_1)e^{-\lambda} & -\theta_2/h\lambda - 1 - (\xi_2 - 1)e^{-\lambda} \end{vmatrix} = 0$$

or

$$(\theta_1/h\lambda - 1 - (\xi_1 - 1)e^{-\lambda})(\theta_2/h\lambda - 1 - (\xi_2 - 1)e^{-\lambda}) - (1 - \xi_1)(1 - \xi_2)e^{-2\lambda} = 0.$$

For simplicity, let $\theta_1 = \theta_2 = \theta$. Then we have one negative root

$$\lambda_1 = -h/\theta_2,$$

and for the second root we get the equation

$$\theta/h\lambda_2 + 1 + (\xi_1 + \xi_2 - 2)e^{-2\lambda} = 0. \tag{6}$$

or

$$(\lambda_2 + \theta/he^{-2}) + h/\theta(\xi_1 + \xi_2 - 2) = 0.$$

Let us apply Hayse criteria to investigate roots of the given transcendental equation

$$h/\theta > -1;$$

$$\xi_1 + \xi_2 - 1 > 0;$$

$$(h/\theta)(\xi_1 + \xi_2 - 2) < \eta \sin \eta - (h/\theta) \cos \eta$$

where η is root of the following equation

$$\eta = (h/\theta)t g \eta \quad 0 < (h/\theta), \quad 0 < \pi.$$

The analysis shows that for A_1 and the bifurcation points A , the second condition is not satisfied and, therefore, A_1 is unstable. For A_2 , the first two conditions are fulfilled, and the third condition is satisfied for certain values of h, θ and ξ_1, ξ_2 . For stability in the case $\theta = h$ we get

$$\xi_1 + \xi_2 - 2 < 2.24$$

or

$$\xi_1 + \xi_2 < 4.24.$$

Therefore, for sufficiently distant from the origin of coordinates, A_2 stability is lost.

It should be noted that the bifurcation point A (with growth of a_1, a_2 the equilibrium position of A splits into A_1, A_2) is stable for the generating equation (3), and unstable for (2). Qualitative analysis shows one-sided stability A of the generating equation (3). Thus, temporal relationships with the mutually conjugated molecular-genetic system of oncoviruses can lead to an oscillatory mode of functioning around one of the non-trivial equilibrium positions. Qualitative analysis shows that large values of h lead to rapid loss of stability of A_2 (figure 3) with an increase in ξ_1, ξ_2 . The domain G expresses the instability A_1 ; F is the range of parameter values at which A_2 is stable, and H is the loss of local stability of A_2 . We can estimate the change in the values of equilibrium positions depending on the values of the coefficients of resource supply of the molecular-genetic system (a_1, a_2).

Conducted qualitative studies of equations (2) show that mutually conjugated molecular-genetic systems of hepatocytes and micro-RNA of oncogenic viruses have a steady rest mode and, at certain values of parameters, can have a stable mode of functional activity, the possibility of oscillatory modes of functioning, irregular oscillations and black hole effect.

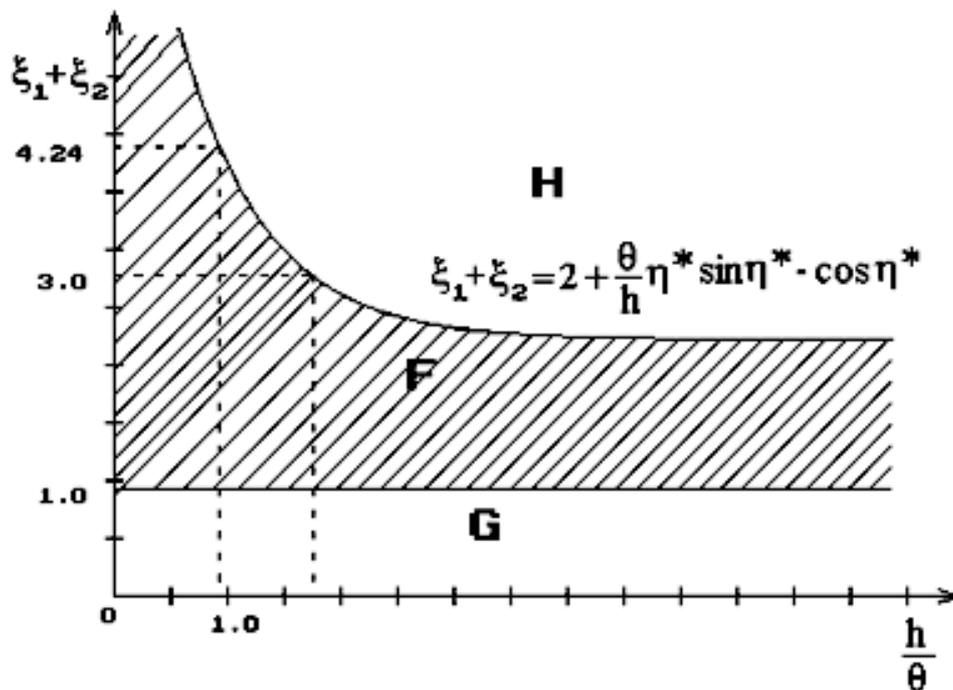


Figure 3. Dependence of stability (shaded F) solutions (2) from the parameter values.

Based on the results of qualitative research and quantitative calculations, a parametric portrait for model systems of a biosystem regulatorika was constructed with specific areas of the same type of behavior: trivial attractor, stationary mode, Poincare-type limit cycles, dynamic chaos, destructive changes - black hole. As a regions with normal behavior we accept a region with stable equilibrium - B and the area of regular oscillations - C (steady periodic mode). It can be assumed that region B is the region of functional activity of the cells, and region C is the region of the mitotic activity of the cells. The areas of anomalies are the area of dynamic chaos - D and the black hole area - E . The area of dynamic chaos is characterized by irregular fluctuations in the dynamic systems activity and can be identified as regulation loss in the

considered system and the onset of the tumor process. On the one hand it borders 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 - the black hole. The extinction region can be identified as the region with programmed cell death (apoptosis), and the black hole region as cancer metastasis. In most cases, the parameters of molecular-genetic system is located in regions B and C. If external influences are harmful to cells or to internal media and gene regulatory mechanisms are uncontrolled, then the cell moves to area A, where abnormal apoptosis occurs. Therefore, there occurs a genetically determined, evolutionarily fixed sequence of intracellular processes of dismantling nuclear and cytoplasmic structures to the elementary blocks, which are suitable for plastic and functional systems of neighboring normal cells. At certain values of internal and external conditions, it may occur the chaotic behavior of oncoviruses micro-RNA and their regulatory network connections, which leads to an abnormal state and death. Increasing the viral load on the hepatocyte regulatory system can take the system out of the rhythmic and stationary dynamics to the area of chaotic uncontrolled reproduction (which corresponds to abnormal cell division during the cancer) and further to the area of sharp reduction in the number of cells, which corresponds to the metastasis of cancer cells.

4. Conclusions

Thus, an extremely important role in the functioning of the human body at norm and at diseases belongs to the molecular-genetic regulatory mechanisms that ensure the performance of vital organ functions: maintain stable states in the body, characterized by a constant concentration of substances; provide periodic persistent fluctuations in the concentrations of certain groups of substances; control irreversible processes: development, growth, differentiation, apoptosis. Computational experiments show that there are the following main regimes of gene activity: stationary state, self-oscillatory behavior, irregular mode and a sharp decline in gene activity. The results of computational experiments show that various states of internal and external cellular environments can also provoke chaotic microRNA regulation, which leads to unregulated cell proliferation and reduction of apoptosis (cells do not die in time), depending on the parameters of the cell and the external environment, some miRNAs can both activate and inhibit tumor growth.

Acknowledgments

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