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Review Article

Mechanisms of Signal Transduction in Cells Facts and Hypotheses

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ABSTRACT

Our main assumption is that interaction between inductor and target molecules in cells is based on laws of quantum physics. An inductor molecule emits a specific monochromatic radiation which is captured by the appropriate target molecule according to the bio resonance absorption principle triggering the emission of its own radiation and thus turning it from target into inductor. This is a chain process that creates a signal path, along which the activated molecules move and interact with each other through contact as described by molecular biology. As part of this process, all impact (information) is mediated through electro-magnetic particles (biophotons) that interact with each other in the electromagnetic field according to laws of constructive and destructive interference. Increase or decrease in the target's response depends on type of interference predominance. Due to this effect, weak signals are sometimes able to produce stronger response than strong ones as the increase in their number leads to expansion of the area of destructive interference. This principle was confirmed in our pilot study using 3 experimental cell models: formation of colonies of granulocyte-macrophage precursors in soft agar under different concentrations of G-CSF; formation of colonies of erythrocyte precursors in methyl-cellulose under different concentrations of erythropoietin; apoptosis of mice melanoma cells (cell line B16) under different concentrations of vincristine. Further development of the biphotonic paradigm of information transduction in cell systems may contribute to better understanding of many normal and pathological processes in human body as well to improvement in some types of drug therapies.

Keywords: Signal transduction; Biophotons; Activation of cell programs

INTRODUCTION

The life and functional activity of all eucariotic cells is provided by the main programmes of vital activity: apoptosis, proliferation, differentiation. At the same time apoptosis (genetically determined cell death), the basic programme, is switched on by the variety of internal and external factors, the carrying out of other programmes is possible only when it is blockaded. The modern achievements of biochemistry, of molecular biology and of molecular genetics have made it possible to define the basic stages of each of these programmes, molecules, responsible for the induction and propagation of a signal, and also transcriptional factors, providing the expression of certain genes and the link between matrix DNA and the RNA-polymerase. The internal cellular proteins, expressed by genes as a result of carrying out such a signal cascade, are critical for the carrying out of one or another cellular programme, and determine the further fate of the cell. The cell itself plays a decisive part in the choice and execution of the programme of vital functions. This is linked to the fact that the ways of activating of signal molecules in a cell are of many kinds, depend on the presence and activity of certain intracellular signal molecules and transcriptional factors, and also, apparently, on the particular character of the signal received. In addition, there exist certain cross-links between the different ways of signaling, the way of choosing which is unclear until the end. For the perception of the external signals, initiating these ways, the cell uses its receptor apparatus. What is common to all the programmes is the fact that the inclusion of signal pathways when the receptor is activated takes place by means of phosphorylation with highly specialized intracellular enzyme-phosphokinases. However, the mechanism of linking the ligand molecule with the receptor, as well as the mechanism of

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attracting and activating intracellular phosphokinases, remains unclear until the end [1].

Many phenomena which are well-known in biology and medicine also have no explanation from the classical stance of modern biochemistry and molecular biology.

We will provide several examples from biology. Salmon fish determine the direction of movement to the spawn by smell at a distance of 100 km from the place of birth, even if they are released at a location above the spawning ground. Male saturn butterflies can find a female at a distance of up to 11 km. It has been established that 1 cubic meter of air at such a distance contains 1 molecule of female sexual attractant [2].

It is well known that the dose-response effect of drugs does not always follow a linear relationship in the therapeutic dose range. For instance, small doses of caffeine and adrenalin cause a stimulating effect while the large doses have a depressive effect. The same pattern is observed in many other drugs [3,4].

Signal molecules, the ways of their interaction and the mechanisms of their movement inside the cells (using cytoskeleton elements and protein-transporters) has been studied comprehensively by modern types of biochemical and molecular-genetic analysis with several types of intravital visualization techniques [5,6]. Critical importance of signal molecules is supported by the fact that significant fraction of the human genome (about 40% of the known 26.383 genes) is devoted to signal transduction (signal molecules, receptors, kinases, proto-oncogenes and ion channels) [7].

Meanwhile many mechanisms of the initiation and transduction of intracellular signals do not lend themselves to interpretation from the point of view of molecular biology. It becomes obvious from some figures: from 10 to 100,000 molecule-receptors may be expressed at the cell surface; 4,000 protein molecules take part in signal transduction; signal molecules have to cover great distance during their movement inside a cell (molecule diameter is about 2-10 nm while cell diameter is about 10,000 nm).

Following questions arise:

1. How do signal molecules find their targets?
2. How their movement is directed?

In 2013, the Nobel Prize in Physiology and Medicine was awarded to Randy Shekman, James Rothman and Thomas Sudhof for their work on deciphering the mechanism of transporting and introducing signal molecules into target cells. However, these works did not provide an answer to the above-mentioned questions. A different paradigm is required.

The purpose of this article is to present a concept according to which the formation of signal pathways, the search for the target and the strength of ultimate effect on it obeys the physical laws of biophoton emission of signal molecules.

RESULTS OF OUR PILOT STUDY

We conducted pilot studies of dependence of the nature and magnitude of cell-mediated response on the concentration of inducing substances in in-vitro experiments. The following assumptions were made: the response strength depends on the quantity of target cells involved in the reaction; the concentration of inducer substance reflects the number of molecules involved in the process. Three cellular models were applied:

- Colony-formation in the soft agar of granulocyte-macrophage precursors (CFU-GM) under the effect of various concentrations of granulocyte colony-stimulating factor (G-CSF);
- Colony formation in the methyl cellulose of erythroid precursors (CFU-E) under the effect of various concentrations of erythropoietin (EPO);
- Apoptosis of murine melanoma cells (cell line B16) under the effect of various concentrations of vincristine.

The effect of G-CSF on CFU-GM in the soft agar

A granulocyte colony-stimulating factor (G-CSF) was used - Granocyte (Aventis) in dilutions of 2 μg/ml; 0.2 μg/ml; 0.02 μg/ml and 0.002 μg/ml (G-CSFf). In order to obtain ultra-low concentrations of Granocyte (G-CSFp), a homeopathic dilution technique potentiation was applied (lab. Boiron, Paris). Homeopathic potentiated drug of Granocyte was obtained in concentrations of 2 x 10-12 и 2 x 10-60 (6CH and 30CH, respectively, according to the homeopathic nomenclature).

The effect of various concentrations of this drug on the proliferation program was studied in the cell culture. Precursor cells extracted from the umbilical blood of new-born infants at 35-36 weeks of gestation were used as target cells.

Cultivation was carried out in the "agar drop-fluid medium" system [8]. The method of cultivation, the course of experiment and results were described earlier [9].

Three indicators were considered during the analysis of results: cloning efficiency (CE) - the sum of colonies and clusters per 105 explanted cells; proliferated potential (PP) - the ratio of the number of colonies to clusters; % of large colonies. The data are summarized in Table 1.

Notes: G-CSFF - pharmacological form of G-CSF; G-KSFp - homeopathic form of G-CSF; 6CH – 2 x 10-12 mcg/ml; 30CH -2 x 10-60 mcg/ml; CE - cloning efficiency; PP proliferative potential.

The data presented show that CE under the effect of G-CSFf increases slightly with ten-fold decrease of concentration (statistically insignificant) in the absence of any change in the proliferative capacity of precursors.

Subsequent dilution of G-CSF within the indicated limits did not change the results of cultivation.

Table 1: Deviation from the control of CFU-GM cultivation indicators with the addition of homeopathic and pharmacological forms of G-CSF.

Parameter	Experiment number	Concentration, mcg / ml	Deviation from control, % (M ± m)		
			CE	PP	* of large colonies
G-CSFf	1	2.00	+46,6 ± 0,3	None	None
	2	0.2	+80,0 ± 18,3	None	None
	3	0.02	+80,0 ± 10,2	None	None
	4	0.002	+78 ± 13,4	None	
G-CSFp	5	6 C H	+235.2 ± 90,4	+119.2 ± 24,1	+181.2 ± 40
	6	30 C H	+70.3 ± 16.5	+127,9 ± 39,2	+216,5 ± 14,3

Therefore, this model revealed unexpected data not supporting the presence of any direct relationship between the concentration of inducer and the magnitude of target-cells response. Conversely, the decrease of concentration by 10, 100 and even 1000 times had no significant effect on the cloning of precursors while the use of ultra-low doses stimulated a response.

The use of potentiated forms of G-CSFp in concentrations of 2 x 10-12 (6 C H) caused a considerable increase of CE; the increase of precursors proliferation (PP and % of large colonies) was observed during the use of G-CSFp in concentrations of 2 x 10-12 (6 C H) и 2 x 10-60 (30 C H) and Figure 1.

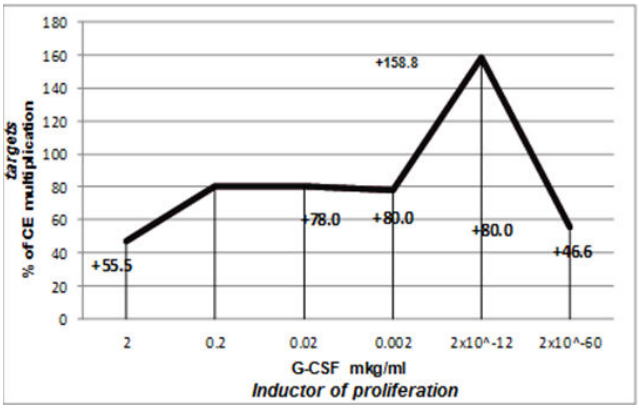

Figure 1: The dependence of GM-CFU colony efficiency (CE) from G-CSF concentration.

The effect of erythropoietin on the colony formation of erythroid precursors in methylcellulose

Target cells in this experiment were CD-34+ cells obtained by magnetic selection from the mononuclear fraction of donor's bone marrow extracted on ficoll. As we know, CD-34+ cells have receptors on their surface only for early hematopoietic growth factors, such as IL-3 and GM-CSF. The expression of late growth factors on their surface, in particular, erythropoietin, requires preincubation with early growth factors for 16–48 hours [10]. The design of the experiment is presented in Figure 2.

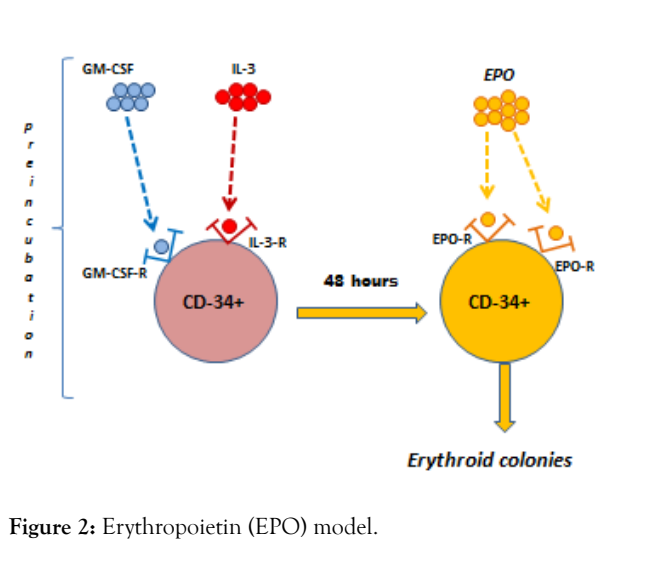

Figure 2: Erythropoietin (EPO) model.

Colony formation of erythroid precursors was carried out in methylcellulose using the following concentrations of erythropoietin (unit/ml) 30; 3,0; 0,3; 0,03; 0,003; 0,0003. Cultivation with each concentration of erythropoietin was carried out in 2 versions: preincubation with early growth factors and without preincubation. Negative control - the same conditions of cultivation, but without erythropoietin.

There was no growth of erythroid colonies in the negative control, as well as in all cultures with erythropoietin, but without preincubation. The dynamics of cloning efficiency of erythroid precursors depending on the concentration of erythropoietin is presented in Figure 3.

The following facts should be noted:

- no correlation between the decrease of erythropoietin concentration and the level of cloning efficiency of erythroid precursors;
- With low concentration of erythropoietin (1000 times in one series and 10,000 times less than initial in another), a surge of colony formation was observed, despite the fact that much higher concentrations of erythropoietin in these experimental series did not cause stronger proliferation of precursors.

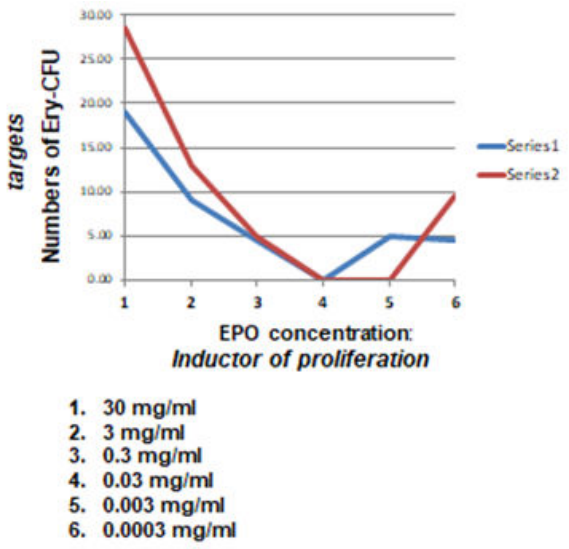

Figure 3: The dependence of cloning efficiency of Ery-CFU from EPO concentration.

Apoptosis of murine melanoma cells (cell line B16) under the effect of various concentrations of vincristine

The cell line of murine melanoma (B16) was used as a target for the proapoptotic effect of various concentrations of vincristine. The level of apoptosis was taken into account by flow cytofluorometry method when cells are stained with Annexin V (AnV) and Propidium iodide (PI), after 24-hour incubation of cells with cytostatic. The dynamics of changes in the proapoptotic activity of various concentrations of vincristine is shown in Fig.4. Apoptosis evaluation was performed by the absolute number of apoptotic cells in 1 μl of culture. As shown in Figure 4, this cellular model demonstrated the absence of a linear relationship between the concentration of cytostatic agent and efficiency of its impact on the cells of the culture. Moreover, when the concentration of vincristine decreased 10,000 times, as compared with the initial concentration, there was a significant increase in its pro-apoptotic activity in both series of the experiment.

DISCUSSION

The data obtained from various cellular models are of the same type. They can be summarized as follows: the connection between the concentration of the inducer substance and intensity of cell-mediated response does not obey the law of linear correlation. Moreover, in some instances, it turned out that a small number of inducer molecules (low concentration of a substance) causes a more intense response of target cells than high concentrations of the same substance.

We tried to explain this seemingly paradoxical situation using the paradigm of biophoton energy field. In accordance with this hypothesis formulated by F. Popp и J. Chung in 1998 [11], all living objects are open dynamic systems exchanging information and energy at all levels; information is a form of energy exchange.

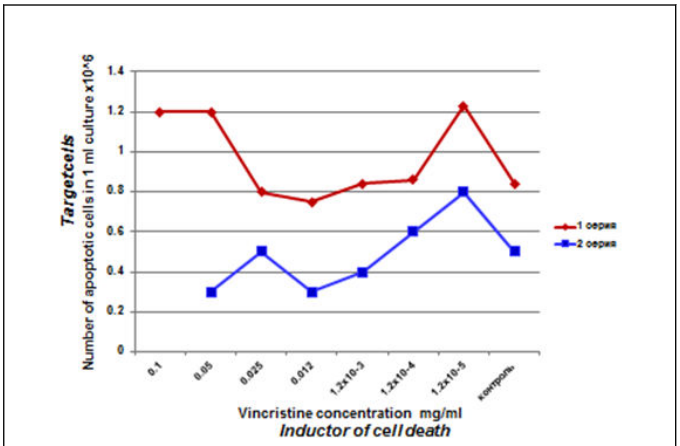

Figure 4: Number of apoptotic cells in 1 ml of B 16 culture (mice melanoma cells) after 24-hour incubation with Vincristine.

The study of bioenergy dates back to almost a century ago. It is strongly associated with the name of A. G. Gurvich [12], who in 1923 described the "mitogenetic rays" emitted by the dividing cells of onion roots. Multiple experiments have demonstrated that these rays, when spread horizontally and when in action for 1–2 hours at a distance of 1.5–2.0 mm from the dividing onion roots of another specimen absorbing such rays, cause a 20-25% increase of mitotic activity in the latter. The rays were later attributed to UV spectrum with a wavelength between 190 and 300 nm. The "golden age" of mitogenetic rays lasted for about two decades. Thousands of articles and several books were published on these studies. Interest towards these works gradually faded and resurfaced again in the 50s after the development of photomultipliers (photomultiplier – PM tubes) which were able to capture and measure very weak light (cited in [13]).

The use of photomultipliers in subsequent years has demonstrated that all plant and animal objects emit energy in a very wide range (180-1000 nm), covering the ultraviolet which is visible and close to the infrared spectrum, with a frequency of 3 x 1014 - 1.6 x 1015 Hz [14]. It was also demonstrated that living organisms can utilize various forms of energy, partially transforming it into their own energy reserves [15].

The study of the "informative nature" of ultra-weak photon emission of living systems was stimulated by the studies of F. Popp in the 1970s [16]. He also introduced the concept of "biophotons" and formulated the idea that electromagnetic interactions are used to transduce the necessary signals, acting as regulators of biological systems. In addition, each intracellular molecule is characterized by its own spectrum of biophoton

emission (electromagnetic radiation) and the same spectrum of resonance absorption. An example of this were studies conducted by T. Karu [17] the intracellular Cyt-C molecule goes through 4 forms in the process of metabolism: 2 oxidized (CuA and CuB) and 2 restored (CuA and CuB). Each of them emits photons with a wavelength of 820 nm, 760 nm, 680 nm and 620, respectively, absorbing photons of the same type.

In support of this concept, data obtained at the end of the last century demonstrated the possibility of exchanging bioinformation between cells without chemical mediators and special transducing molecules such as hormones, growth factors and neurotransmitters. Back in the 60s of the last century, V.P. Kaznacheyev conducted a series of experiments demonstrating that a monolayer of fibroblasts grown in a hermetically sealed vessel on a quartz plate which is placed at the bottom of the vessel can repeat the unique pattern of the same culture grown in another vessel when the bottoms of these chambers are pressed to each other [18]. In 1988, G. Albrecht-Buehler published data confirming this and indicating that fibroblasts in tissue culture can determine the orientation of others by signals that penetrate glass but not a metal plate, i.e. transmitted by electromagnetic radiation [19]. Golantsev V et al. [20] showed that a mouse mammary explant, stimulated by the administration of hormones that cause secretion, can stimulate the secretion of protein in another mouse mammary explant, separated from the former by quartz glass. Shen X et al. [21] have demonstrated that stimulation of a "respiratory blast" in neutrophils can cause a similar reaction in another population of neutrophils, chemically separated, but optically bound to the former one.

These and other data suggesting possible bio-photon activation of cell programs are indirectly confirmed by the presence of high energy potential inside the cell. Nanovoltmeter with a diameter of 30 nm, revealed the presence of high voltage electric field in the cytosol of cells: 15 million volts per meter, that is 150 volts per 1 cell with a diameter of 10 microns. For comparison: in an ordinary house - 5-10 volts per meter, under a high-voltage line - 10,000 volts per meter [22]. It was later demonstrated that the voltage of electric field inside the cells is significantly higher than in the intercellular space [23].

HYPOTHESIS

The reference data provided above and the results of experiments lead us to the following hypothesis about the mechanisms of signal transduction in a cell. Cells and individual molecules emit certain monochromatic waves, while the cell receptors perceive them in accordance with the principle of bioresonance absorption. The signaling pathway appears to be structured in the same way: an inducer molecule emits a specific monochromatic beam, which, based on the principle of bioresonance absorption, is perceived only by the corresponding target molecule. This causes activation of its own radiation turning it from a target molecule into an inducer molecule. This process goes through the chain, forming a corresponding signalling pathway, along which the movement and contact interaction of activated molecules occurs in accordance with the laws decoded and described by molecular biology. Sometimes, as demonstrated by the works of Gurvich and his followers, biophoton activation alone is sufficient, and signal can be realized without contact.

Our data suggest that there is an interaction between monochromatic beams emitted by inducer molecules, even before they reach the target receptor, which affects the perception and activation of the receptor. In accordance with the laws of wave physics, there is a constructive (amplification of radiation with unidirectional waves) and destructive (annihilation of rays with different directions of their waves) interference between monochromatic beams in a coherent field (coordinated flow of wave processes). It is schematically presented in Figure 5.

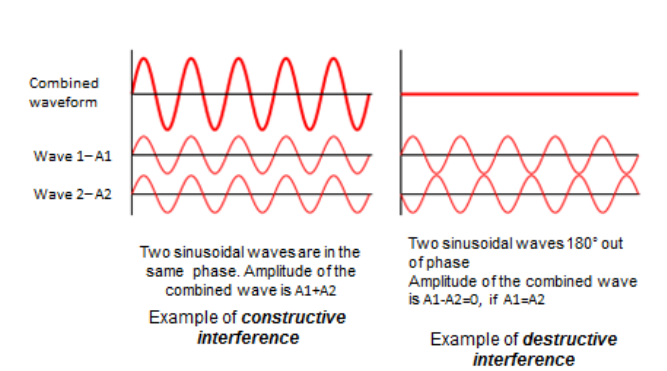

Figure 5: Interference between two monochromatic waves.

With an increase in the number of radiation sources (in our case, the number of G-CSF, erythropoietin and vincristine molecules, i.e. increase of their concentration), the area of destructive interference increases. This interferes with the signal and reduces its effect on the target. Conversely, a smaller number of inducer molecules can produce a greater effect than their high number, as the likelihood of destructive interference decreases and the signal strength increases. This seemed to occur naturally in our experiments with a significant decrease in the concentration of inducers. It can be assumed that the "critical" level of concentration of the inducing substance, at which the constructive interference prevails, and, consequently, the signal amplification is very unique, depending on the properties of the inducer's biophoton radiation, susceptibility of targets and the distance between them.

CONCLUSION

Therefore, this paper formulated the concept of the role of biophoton connections in the transmission of information to implement many programs that ensure cell life in the whole organism. It was demonstrated how the use of a new, biphotonic paradigm of information communication in living systems helps decipher many obscure phenomena. However, many things remains unresolved and require additional research, in particular, the development of a methodology for determining the concentrations of active substance, providing optimal "understanding" of biophoton signals by target molecules and / or cell receptors. In the future it will provide a better

understanding of many physiological and pathological processes of the human body. We think that the most important and interesting area of such studies is immunology, and in particular, the development of immune tolerance; preventing the development of resistance to chemotherapy; cytokine therapy; targeted anticancer therapy and many other processes.

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