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The study of molecular signals and the immune system behavior in cancer cell metastasis: A literature review

Relevance: *This study's relevance is due to the lack among academia of a holistic picture of the processes that occur in the body in cancer cell metastasis. Particularly, a lot is unclear about the physical mechanism of molecular signaling and organizing immune responses, as well as registering the frequency and amplitude of ultra-weak electromagnetic signals with the development of a tumor process in the body.*

The purpose of this study was to review the literature sources regarding the physicochemical mechanisms of processes that occur in the body in cancer cell metastasis.

Results: *The analysis of the selected sources gives reason to believe that a medico-biological point of view is not enough to explain tumor metastasis. The mentioned sources highlight the issues related to the physical and chemical components of this process. The publications state the facts of the reorganization of cancer cells at receiving molecular signals. Hence, the authors do not explain what structures form molecular signals of a strictly defined frequency and how physically the cancer cell receives these signals and implements them into practical responses. It is evident that these molecular signals are ultra-weak electromagnetic waves. Methods of quantification of some parameters of the metastasis process are proposed, as well as the ways to register ultra-weak electromagnetic signals.*

Conclusion: *Data on the physicochemical mechanisms of various stages of metastasis of malignant tumors included in this review complements the picture of the process of cancer metastasis in the human body and defines a range of issues that require interdisciplinary research involving both physicians and biologists, and specialists in quantum physics, electronics, and chemistry. Only quantum electrodynamics can explain the mechanism of a cell cytoskeleton transformation (from a healthy to a tumor cell) under the influence of weak electromagnetic signals. The authors reveal priority directions for an interdisciplinary study of bioenergetic processes that occur in the body in cancer cell metastasis.*

Keywords: cancer, metastasis, IMB receptor, IMB effector, integral membrane proteins, cell membrane, electromagnetic radiation.

Introduction: Individual cells of the body are transitioned into tumor cells due to DNA damage that has hereditary information. Usually, if DNA is damaged, special cell structures repair the damage, or the cell dies. However, the DNA remains damaged in cancer cells while the cell continues to live, actively divide, and produce new cells with similar damaged DNA. A cancerous tumor produces toxins that poison the body, results in the physical exhaustion of the body and disruption of the immune system. Besides, the body does not need such mutated cells since they cannot perform the functions originally assigned to them. The cancer cells are disseminated throughout the body with further tumor growth with the help of lymphatic, hematogenous, implantation, or intracanalicular routes, forming secondary colonies of tumor cells - metastases. At that, modern ideas about the intravasation of cancer cells through the vessel wall are based on comparisons with the intravasation prototype when mature thymocytes and dendritic cells exit into regional lymph nodes [1]. The exchange of information and energy to implement these actions – “communication” between cells and the central nervous system (brain) - is performed using ultra-weak electromagnetic waves. It is known that a living cell used natural elec-

tromagnetic fields of the external environment in the evolution process as sources of information that ensure continuous adaptation (synchronization) of organisms to changes in various environmental factors. The questions about the interaction mechanisms of an ultra-weak electromagnetic signal with the structure of cells, as well as the problems of frequency-resonant energy supply of regulation of processes in a cell, remain unresolved in all the studies included in the review. Hence, the main research directions are to review research papers describing various aspects of cancer cells' metastatic spread and identify research problems from the physical perspective.

Objective: Review the literature data on the physicochemical mechanisms of the processes occurring in the body during the metastatic spread of cancer cells

Materials and methods: This review is mainly based on the presentation and analysis of published references describing the physical and chemical mechanisms of various metastatic spread stages of malignant tumors, as well as on the publications of the authors of this review [1-27] that specify previously obtained results related to the topic of the review. The references are fundamental works of scientists, articles in scientific

periodicals. The literature search in electronic databases was performed using the following keywords: "metastatic spread of malignant tumors," "IMB-receptor," "IMB-effector," "cell membrane," "integral membrane proteins," "electromagnetic radiation." This literature review includes 27 references that meet the selection criteria.

Results: The published data were analyzed concerning searching for the physical and chemical components of the metastatic spread of tumor cells in the body. As a result, we found seven abstracts which described the physical and chemical mechanisms of the process:

Thesis 1. A metastatic spread is a complex process that involves primary tumor cells, healthy immune cells, other body tissues [2, 3]. Under the works studied, a secondary cancerous tumor prepares a suitable environment in healthy tissue even before the primary tumor cell is disseminated to the appropriate place that meets its existence requirements *using systemic molecular signals* [3, 4].

The physical and chemical components of the process. What does a *molecular signaling system* mean? Molecular signals are weak electromagnetic waves that cause cancer cells to prepare a suitable environment in healthy tissue by exchanging energy and information.

Activation of the system of molecular signals in the corresponding areas of the autonomic nervous system, for example, through the surface of the body's skin, should cause a response from the genome of cell groups associated with this area of the autonomic nervous system [5]. Hence the problem arises: how to measure weak electromagnetic molecular signals and differentiate their role assignment. The study of electrical conductivity at acupuncture points [6] and other measuring methods [7] could solve the problem. Such studies could reveal some new antitumor treatment methods free of the side effects inherent to chemotherapy and radiation therapy [8].

Thesis 2. Premetastatic and metastatic niches promote the infiltration, survival, and formation of colonies of cancer cells in the target areas and are the nodal stages of metastatic cancer spread [9]. It is known that, depending on the type of tumor, exosomes from the inside can consist of various proteins and RNA and, accordingly, secrete various substances, as well as *run different molecular programs to create a premetastatic niche* [10-12], that is, an environment favorable for the growth of metastases. Some tumor cells change their shape and penetrate the surrounding tissues as soon as the metastatic niche is ready [4, 10, 13].

The physical and chemical components of the process. Disclosure of specific mechanisms associated with the environment transformation contributing to the metastatic spread of disseminating cancer cells is impossible without studies of the extracellular matrix role, premetastatic and metastatic niches in these changes. Many questions arise when explaining organ specificity about the effect of hypoxia and inflammation on the construction of the premetastatic niche, as

well as the interaction between cancer cells and the environment [9].

All molecular programs are embedded in cellular proteins and RNA. An in-depth analysis of these studies is given in the work of Bruce Lipton [14]. The cell membrane contains integral membrane proteins (IMBs) that enable nutrients to pass through the membrane into the cell and metabolites to exit the cell. IMBs are subdivided into two functional groups: IBM effectors and IBM receptors. The receptor proteins are equivalent to our senses. Their action is similar to molecular "nanoantennas" tuned to perceive certain signals from the internal and external environment. IMB receptors are activated when their electrical charge changes. The redistribution of the electric charge after the IMP receptor binding to the acting agent (signal) of the external environment "forces" the protein chain to fold differently, and it assumes an active conformation [14].

Different IMB receptors react differently but strictly specifically to chemical or physical nature signals. For example, the histamine receptor corresponds to the charge and configuration of the histamine molecule, the insulin receptor - to the insulin molecules, the estrogen receptor - to the estrogen protein molecules that provide them with one hundred percent "recognition" and adhesion to each other. IMB receptors can also recognize physical nature signals: sound, light, electromagnetic vibrations, vibrations of energy fields, radio waves, and others. In this case, if the wave energy vibrations fall into resonance with the vibrations of the antenna of the IMB-receptor, the "antennas" vibrate like a tuning fork, the charge is redistributed, and the IMB-receptor changes its configuration [15].

The effector protein is of particular interest - sodium-potassium ATPase present in every cell membrane in large quantities and is an essential energy consumer and the main source of energy in the body. In each cycle, sodium-potassium ATPase lets in 2 positively charged potassium ions into the cell and releases three positively charged sodium ions out of the cytoplasm.

Enzymes as one of the IMB effector types promote the breakdown and synthesis of a variety of molecules. Individual IMB effectors (enzymes and their derivatives, cytoskeletal, and channel proteins) can activate genes after activation, in their turn.

The meaning of membrane integral proteins has become clear only in recent decades, after the generalization of the results received during the studies of signal transduction in a cell. All scientists' efforts in this direction are focused mainly on the classification of many complex information pathways between the perception of signals by the cell membrane and the activation of proteins responsible for the cell's response.

Thus, genes cannot control their activity themselves. They only carry information; the rest is done by IMB receptors, IMB effectors, and their derivatives that determine chromosomal regulatory proteins' activity.

The ability of the membrane to "meaningfully" interact with the environment makes it a real cellular "brain"

[14]. The cell can demonstrate the “meaningful” behavior of the cellular “mind” only if there is a functioning membrane that has both IMB receptors (providing information perception) and IMB effectors (providing action). All these cell action mechanisms based on signal receipt determine the launch of a molecular program to create a premetastatic niche.

Thesis 3. *During the invasion process, cancer cells change their direction, starting from the cytoskeleton. It all starts with the reorganization of the cytoskeleton. The cell begins to change its shape; the meazin-2 protein is activated inside the cell that ensures its movement [10]. After this, the posterior end of the cell tears away from its surroundings and is pulled up to the anterior end. Then, the cell leaves the tumor and begins to travel in the bloodstream. It is not known whether this process is random or directed.*

The physical and chemical components of the process. It is known that cytoskeletal proteins (a kind of effector proteins) play the function to control the shape and mobility of the cell due to the mechanism of switching on the intercellular energy-information exchange. A very important task today is to measure and study the parameters of electromagnetic signals of effector proteins and, as a consequence, cytoskeletal proteins. Signal transduction studies require routine nanotechnology measurements.

Thesis 4. The tumor cell must survive in the bloodstream for the successful completion of metastatic spread since the cell is exposed to adverse physical conditions and attacks from the immune system. For example, large cancer cells can block blood vessels and trigger a local inflammatory response. In this case, *the mechanism of apfactose action is triggered, after which the cancer cell is attacked by the immune system cells that, in most cases, results in the cessation of the metastases development.* Larue and Bellacosa [16] specify that tumor cells launch a “coagulation cascade” program to survive in the bloodstream forming a protective sheath of platelets around themselves. This process is universal for many tumors since more than 90% of cancer patients have changes in blood clotting.

The physical and chemical components of the process. Many scientists have demonstrated the process of recognition and destruction of cancer cells by T-lymphocytes using polarized secretion. Moreover, T-lymphocytes continuously examine the environment and are practically never wrong in recognizing cancer cells [5, 7, 17-18, 21]. However, the following question arises - what are the mechanisms to obtain the information by killer T-cells about the environment and cancer cells?

T-lymphocytes analyze the information received and “make a decision” to attack cancer cells. If T-killers do not have a “thinking system,” then the central nervous system (CNS), the human brain, probably performs the analysis and decision-making for them. In this case, some questions arise again:

- How does the instantaneous exchange of information happen between the central nervous system and T-lymphocytes?

- What is the function of the “brain of the cell” - the cell membrane?

- How are the actions of T-lymphocytes controlled through the central nervous system?

Thesis 5. The epithelial-mesenchymal transition, where epithelial cells acquire fibroblast-like and mesenchymal properties with a decrease in intercellular adhesion, endow the emerging cancer cell with invasive and metastatic properties during malignant transformation and tumor progression. In this case, the suppression of E-cadherin cell adhesion molecule may be a critical molecular event [16]. The key molecules are considered to be blood coagulation factors, as well as membrane phospholipid and phosphatidylserine. Phosphatidylserine creates a favorable surface for platelet adhesion, and the *clotting factor activates platelets and creates a coagulation signaling cascade. As a result, the cancer cell is surrounded by a protective membrane of platelets that helps it travel through the bloodstream and form new tumors.* The question arises: why does the protective membrane of platelets protect the cancer cell from the attack of T-lymphocytes? T-lymphocytes consider a cancer cell with a platelet membrane as “their own”; that is, T-lymphocytes’ recognition function is “deceived.”

The physical and chemical components of the process. However, the following is not clear in this process: how does the information and energy exchange of tumor cells and lymphocytes occur? Thrombosis symptoms are directly related to tumor progression and metastatic spread, worsening cancer therapy, and decreasing the patient’s chances of recovery [11]. Due to the formation of a protective membrane in metastatic cells, 20-30% of cancer patients die directly from thrombosis. However, it is known that the reduction of disseminated intravascular coagulation syndrome (disseminated intravascular coagulation syndrome) and inhibition of the blood clotting factor reduce the metastatic potential of cancer cells and can help to fight against metastatic spread [22, 23]. It is believed that a cancer cell behaves like a leukocyte in the bloodstream penetrating through the walls of the vessel. Analysis of cancer cells’ behavior showed that 82% of the cells were successfully extravasated on the 3rd day, 2% of the cells began to replicate; 36% of the cells were alive on the 13th day, 0.07% formed micrometastases [11, 24].

A cell informed by IMB receptors about external signals must “take adequate responses” to maintain its vital activity. After that, the IMB-effectors begin to operate. The tandem of IMB receptors and IMB effectors is similar to the operation of a switch that functions in an irritation-response to irritation manner. Functionally, the cell membrane’s IMB receptors act as a sensory nerve, and the IMB effectors act like a motor nerve that induces a response. Hence, it becomes necessary not only to observe the information and energy exchange processes of receptor proteins and effector proteins but also to learn how to measure their activity parameters.

A sufficient number of biological studies have been performed with the current trend to model bone metastases in vitro and ex vivo to understand cancer cells' tropism during metastatic spread to certain organs and develop effective treatment methods against metastatic spread [25]. However, it is impossible to obtain an answer about the targeted selection of preferred tissues by tumor cells for their metastatic spread when performing studies with cultures of bone organs without analyzing the physical and chemical composition of the processes occurring in various involved body pathways that provide many targets for metastases.

The bone microenvironment homeostasis in a healthy organism is supported jointly by the bone matrix, osteoblasts, osteoclasts, and capillaries. When cancer develops, tumor origin factors impact the bone components, resulting in subsequent bone resorption or immense bone formation. At that, understanding the metastatic spread pathways enables identifying therapeutic targets in bone metastases [26].

Thesis 6. The tumor does not form with the accumulation of metastatic cells until the growth of blood vessels begins. For this purpose, *cells secrete blood vessel growth factor "alpha" and form endothelial cell precursors* [10, 11, 16].

The physical and chemical components of the process. The cell has IMB receptors appropriately tuned to pick up stimulating signals. However, the blood vessels formed under the influence of a tumor are often defective; they branch and have improper connectivity. There are also dead-end capillaries through which blood does not circulate. This deprives the tumors of nutrients and oxygen, causes stress, and often contributes to a subsequent multiple metastatic spread and generalization of the process. The issue requires a thorough study of the chemical and physical aspects of the release process of blood vessel growth factor "alpha" by cancer cells and the study of the role of IMB receptors and IMB effectors in this process. Besides, it is required to search for the possibility to select frequency influences from the outside to create a malfunction in forming additional capillaries to supply nutrients to the tumor.

Thesis 7. Usually, the metastatic spread process is aggressive and results in a high degree of probability of the patient's death in a short while. However, sometimes *the body comes to equilibrium with the tumor process, not completely suppressing it but also preventing it from fully progressing and destroying the body.*

The physical and chemical components of the process. There is the possibility to balance the metastasis of cancer cells and the destruction of cancer cells by the immune system by T-lymphocytes among the many possibilities. Nevertheless, it is a temporary balance. An encouraging result of this phenomenon is that the body adequately responds to the destructive effect of a developing tumor within its resources to ensure a sufficient level of energy resources, in most cases exposing the further risk of tumor spread throughout the body, on the one hand, by maintaining their control before changing the priority of the action direction concerning metastatic spread, on the other hand.

Conclusions: All the seven theses need relevant studies. They require consideration of different stages of a malignant tumor metastatic spread, taking into account the physical and chemical components of the process. In particular, it is required to:

- study and quantify the information and energy exchange processes of receptor proteins and effectors for creative activity;
- investigate signal transduction in normal cells and tumor cells, measure parameters of weak electromagnetic signals of molecules (DNA, RNA, cells, genomes, lymphocytes, cytoskeletal proteins, integral membrane proteins, and other protein complexes);
- investigate the role of receptor proteins and effectors in the release of blood vessel growth factor "alpha" by cancer cells and the malfunctioning mechanism in the formation of new blood vessels - the creation of dead-end capillaries;
- investigate the balance between metastases of cancer cells and the destruction of cancer cells by the immune system by T-lymphocytes, taking into account the energy supply of genomes, lymphocytes, protein complexes;
- choose the required frequency of energy fluctuations, for a possible impact on physical and biochemical processes during metastatic spread;

We should search for ways to register some parameters of informational and power exchange in the cell. The authors plan to use supersensitive detectors based on modern photomultiplier tubes (PMTs) [5, 19], as well as a device of their design for high-frequency probing of immunological reactions [21]. It is also proposed to use such devices as "AIS LIDO" and "EMIGRAPH" developed by specialists of the Kyiv National Technical University for analysis and screening in the range of mm-waves emitted by biologically active points of a person, a functional magnetic resonance imager, a portable MRI apparatus of Bernhard Blumich - MOUSE (Mobile Universal Surface Explorer) [27].

Conclusion: Priority areas of interdisciplinary research for bioenergetic processes occurring in the body during metastatic spread of tumor cells have been identified, such as the development of equipment and software algorithms to record the frequency and amplitude of ultra-weak electromagnetic signals from the membrane of cells, genomes, lymphocytes, etc.; development of methods to provide energy supply to immune systems, in particular, T-lymphocytes to increase their ability to fight against various diseases, according to the resonant frequency of electromagnetic signals of cell membranes, genomes, lymphocytes, etc.; development of new treatment methods based on the ability of organismic structures to assess their environment and interact with it through energy (electromagnetic, thermal and other) fields.

The successful solution of the problems posed in this work will enable developing new methods to prevent the formation of malignant tumors and treat cancer patients by influencing the mechanisms of cell metabolism based on the application of the quantum physics achievements.

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