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Stem Cells and Malignant Tumor Cells – Friends or Enemies

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INTRODUCTION

Glioblastoma cells express on their surface CD29, CD44, CD73, CD90 and CD105 antigens, which are also positive immunophenotypic signs for mesenchymal stem cells (MSCs) [1,2]. It is also known that expression of CD90 on the surface of rat C6 glioma cells is associated with identical Raman spectra in C6 glioma cell culture and in MSCs culture [1,3]. Such identity or peculiar immunophenotypic signs in undifferentiated cells can be explained. But in one case we are talking about malignant undifferentiated cells (glioma and glioblastoma cells) [1,3]. In another case, identical fingerprints are present on the membrane of non-tumor MSCs [2,3]. So, in one case we are talking about undifferentiated stem cells (SCs), a pool of which evolved in brain to increase efficiency of information storage in neural networks. In addition, SCs are necessary for implementation of reparative processes in brain injuries and diseases, that is, recovery of normal brain activity. In another case, we are talking about malignant cells (Cancer Stem Cells, CSCs) and their proliferation is associated with threat to human life. By the way, scientifically based data on the ratio of body weight at birth with the number of fetal SCs have been published [4].

Such associations in manifestation of identical immunophenotypes of tumor and non-tumor cells raise questions in any person who encounters the problem [5,6]. But after all, the same questions "arise" in immunocompetent cells, which, when in contact with undifferentiated cells, must decide on the correct behavior in each case. For example, aggressive tactics of interaction with tumor cells following the decision of immunocompetent cells ends with initiation of suspicious cells' destruction programs. And then the population of tumor cells is destroyed [7-9]. And what if there was a mistake in "recognition" of suspicious cells and non-tumor neuronal stem cells have been affected? In this case, destruction of endogenous brain stem cells will weaken brain reparative potential. One can only assume the implementation of such an erroneous mechanism, for example, in pathogenesis of such diseases as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and other neurodegenerative diseases.

The question on the interaction of SCs with tumor cells remains unresolved, since there is *in vivo* evidence MSCs activity does not contribute to death, but to proliferation of cells of malignant gliomas [10]. The authors [10,11] believe that MSCs secrete exosomes, which form conditions in tumor cells for activation of proliferative processes. Therefore, it is advisable to be wary of publications about the effectiveness of MSCs against tumor cells. The result depends on methodological features, for example, on the method of MSCs application *in vivo*. If MSCs are injected into bloodstream to treat brain injuries and receive signals from many of the body's cells through which blood vessels pass, then, ultimately, a small number of cells reach the intended site. Remaining MSCs scatter along the way to the brain. It is difficult for MSCs to cross the blood-brain barrier. And finally, MSCs enter the brain via unnatural way (with blood flow), and not by natural ways of transmitting information to the brain, for example, through the cranial nerves. MSCs from the blood stream enter the neuropil of brain and end up in unusual conditions like Frank Sinatra's

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"Strangers in the Night". MSCs' behavior begins to resemble the behavior of CSCs under these conditions.

Considering such fatal situations, researchers are trying to use the tropism of SCs in relation to tumor cells and place various antitumor substances and viruses into SCs in special migratory containers [8,12]. For this purpose, combinations of human MSCs with encapsulated antitumor drugs are used, which ensures active delivery of drugs to the tumor and opens up new strategies in chemotherapy [12-14]. The prospects of antitumor efficacy of MSCs loaded with human oncolytic viruses are analyzed [15].

The emerging optimism regarding participation and contribution of MSCs to antitumor processes in patient's body has faded significantly after becoming acquainted with the results of studies of an international group of scientists [16]. The authors of this study evaluated the effect of tumor-associated and normal MSCs in lung tissue on growth and spread of primary tumor cells of human lung carcinoma. It was found that tumor microenvironment (matrix) transforms expression of certain genes of MSCs, after which MSCs are involved in the development of tumor metastasis [16].

Our team adheres to a somewhat paradoxical hypothesis, which can be expressed concisely. In addition to undifferentiated non-tumor stem cells (for example, mesenchymal, hematopoietic, neuronal, etc.), from the very birth, tiny pools of undifferentiated tumor stem cells (CSCs) are present in the human body. Why should a healthy body in the process of evolution form a community of tissues and organs, including pools of SCs, MSCs with CSCs? It turns out to be a kind of combination of incompatible contradictions like in Friedrich Schiller's "Intrigue and Love." Let's try to answer the expediency of "incompatibility". A small pool of CSCs in a healthy body is needed to "train" immunocompetent cells to effectively prevent the migration of CSCs to other parts of the body. At all stages of phylogenesis and ontogenesis, a regularity is realized, which manifests itself in the fact that if the relationship between cells and intercellular matrix is violated, for example, when cells colonize the body's spaces intended for other cells, conditions are made for specific mutations leading to uncontrolled proliferation of tumor cells including CSCs. Thus, the presence of miniature pools of CSCs allows immunocompetent cells to taking a kind of training courses from the very birth to prevent activation of malignancy processes.

The observation of life cycle of a naked mole-rat (*Heterocephalus glaber*), in population of which oncological diseases are extremely rare, is an aid to development of such hypothesis [17]. Mole-rats are resistant to high levels of carbon dioxide. Hypercapnia leads to increase of hydrogen ions concentration in tissues and change of conditions familiar to tumor cells. It is known that within tumor cells the pH ranges from 7.12 to 7.70 and in the intercellular space of the tumor tissue it is 6.20-6.90 [18,19]. A shift in this ratio is the reason for violation of optimal aerobic glycolysis conditions for the tumor.

CONCLUSION

A deeper understanding of mechanisms governing the functioning of *Heterocephalus glaber*'s systems will make it possible to advance in solving the fatal problem of oncological pathology. To summarize the above, it is advisable to emphasize the well-known truth about the attractiveness of scientific discussions and disputes, and, on the other hand, the responsibility for constant advancement in joint resolution of key issues of life and death.

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