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Biomedical Prospects for The Use of Stem Cells for The Treatment of Gliomas

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Abbreviations: MiRs: MicroRNAs; SCs: Stem Cells; TNF-α: Tumor Necrosis Factor

Introduction

Low efficiency of classic antitumor therapy initiates search for new ways of early diagnostics, prophylaxis and treatment of tumors. Specialists sometimes pay attention to extraordinary strategies based, for example, on the use of stem cells (SC) as specific biological agents aimed at destruction of malignant gliomas [1-3]. These technologies are the result of stem cells fundamental ability to migrate to brain tumors penetrating through blood-brain barrier [1]. Malignant gliomas have been chosen for analysis of effectiveness of cell technologies in oncology because they are one of the most fatal and do not respond to existing methods of antitumor treatment. It is quite often when deep tumor invasion into vital brain regions complicates total surgical elimination of gliomas.

Therefore, new additional treatment methods are important, for example, SCs which are comparatively easy modified in order to transfer therapeutic genes [2] and weaken immunoreactivity to SCs of patient's organism after their implantation [4]. It is considered that weakened immunoreactivity contributes to preservation of antitumor viruses in tumor tissue [5]. From this perspective, microRNAs (miRs) seem promising therapeutic agents in glioblastoma cells destruction [3]. Unfortunately, the question "which miRs are the most effective against glioblastoma?" still remains unanswered. On the other hand, separate retrospective studies in patients with recurrent high-grade glioma who received neural SC-mediated enzyme/prodrug gene therapy showed positive effects of such cell therapy [6].

Stem cells and malignant glioma cells

There is another one paradox in oncology: detection of identical Raman spectra of mesenchymal rat's SC and tumor cells of rat's C6 glioma [7]. It is quite unusual that the spectra of two types of undifferentiated cells – tumor (C6 glioma) and non-tumor ones (neural SC) match, and this unusualness enhances by evidences of identical biomarkers detection on their membranes, for example CD90 [8,9]. This evolutionary phenomenon requires explanation. Protective mechanisms of immune system are activated during formation of tumor tissue in the organism. It is known that antigen presentation is the main event in the development of immune response. Expression of CD28 antigen on T-cells is one of the key stages of the process. CD28 interacts with B7/BB1 ligands.

The process is modified by the plenty of signaling molecules, including heat shock proteins, cytokines, different subtypes of Toll-Like Receptors and mediators. Tumor-associated antigens also take part in anti-tumor reactions. SCs try to avoid immunological surveillance at each stage of these processes. Statistics demonstrates that tumor cells attained perfection in masking and phenotype changing in order to stand against protective immune reactions. Let us come with next situation. For example, protective elements of immune system detected CD90 on glioma cells. Dilemma arises for T-killers – to get rid of these suspicious elements or save them alive, because neural SCs also have the same biomarker. Let's assume that they decide to kill suspicious cells. But what of these cells were not tumor ones, but neural SCs? In this case reparative potential of nervous system decreases leading to progression of neurodestructive processes typical for, for example, Alzheimer's disease. But there is also positive effect – brain tumor does not develop. The opposite "decision" of immune system aimed at preservation of "unclear" cells similar to SCs may lead to manifestation of tumor process.

Contradictions in the technique of stem cells implantation in brain tumors

Neural and other type of SC show taxis to damaged tissues and tumor microenvironment. Various signaling substances including anti-inflammatory and angiogenic factors are expressed into these areas [10]. Activated astrocytes and microglial cells of peritumor edema zone initiate inflammatory process in glioma [11] that attracts mesenchymal SCs. Tumor necrosis factor (TNF-α) contributes to increase of chemokine receptor expression in order to ease chemotactic invasion of mesenchymal SC [12]. Interaction between mesenchymal SC and elements of intercellular matrix is the key factor in implementation of SC migration process [13]. As mentioned before, plenty of factors influence taxis of SCs to tumor tissue. Further investigations are needed to unite these factors into complex mechanism of SCs migration and develop improved clinical protocols for SCs use as therapeutic agents for glioma treatment [14].

It should be kept in mind that mesenchymal SCs contribute to tumor growth by suppression of immune system [15] and malignant transformation of implanted mesenchymal SCs [16]. Therefore, conditions for interactions between mesenchymal SCs and tumor cells as well as potential risk of transformation of mesenchymal SCs into malignant neoplasms still remain unknown. The good news is that mesenchymal SCs transplantation to more than 1000 patients did not lead to tumor development in none of the cases [17]. Authors note [17] that infiltration of macrophages and granulocytes was much higher in tumors subjected to injection of mesenchymal SCs compared to intact ones. This testifies that mesenchymal SCs possess pro-inflammatory effects in such model.

Conclusion

It should be reminded that malignant gliomas are one of the most fatal tumors, and all existing treatment methods remain ineffective due to invasive growth and high risk of relapse. The therapy based on neural and mesenchymal SCs is promising because of positive results both in experiments and clinic. Collected data say for the use of SCs potential in combination with traditional surgical, chemotherapeutical, radiological and especially those techniques which are aimed at activation of immune system [18], delivery of metabolizing genes and/or oncolytic viruses [19].

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