Cytoregulatory Therapy in Neurooncology: from Cell Transplantation to Neurorestoration and Neuroregulation of Brain Glial Tumors

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Introduction. Modern neurooncology offers three methodological approaches to brain tumor (BT) therapy: 1) cytoreductive, i.e. removal of tumor cells (TC); 2) cytostatic, i.e. structural elimination of TC; 3) cytotoxic, i.e. TC poisoning. We attempted to develop the strategy of controlling TC by precursor cells (PC) with induced properties. Antitumor regulatory potential of neural stem cells (NSC) and neural PC is universally acknowledged but so far has not found clinical use. Regulatory potential of genetically engineered reprogrammed SC and PC for BT is hardly clinically applicable through high risk of genetic consequences. Our approach is therapy of BT by regenerative techniques and we name it cytoregulatory therapy (CRT) analogously to existing methods. CRT is based on fundamental principles of mathematical control system theory [1, 2] and biological principle of cell induction; it is aimed not to eliminate TC but to regulate and control their fate. Regulation is achieved by donor PC induced for proliferation and/or apoptosis. The object of regulation is transplanted induced multipotent (neural, hematopoietic, mesenchimal) SC (iMSC). The goal of this study is to demonstrate CRT potential for BT therapy using iMSC.

Materials and methods. In vivo study included 56 C6 glioma (C6Gl) Wistar rats. NSC were obtained from human olfactory nasal sheath and hematopoietic (CD34+) SC (HSC) were mobilized through standard 4 days stimulation of hematopoiesis by G-CSF followed by leukapheresis, separation and culturing of CD34+, CD45- HSC. iMSC were obtained by endocytosis of nanocontainers (NC) with apoptosis inducers (ricin or viscumin) in NSC and HSC cytoplasms when culturing. NC diameter varied from 100 to 200nm (Fig. 1).

0.5x10⁶ iMSC were stereotaxically implanted into tumor according to coordinates: Ap – 1; L 3,0; V 4,0 – 3,5 TBS – 2,4 mm by automatic injector on 7 day after C6Gl inoculation. Glioma sizes were calculated by ellipsoid formula \( V = \frac{4}{3}\pi abc \), where a, b, c — ellipsoid semi axes. Purposeful change of tumor volume and cell mass was considered CRT result. In vivo study had 8 groups of rats: 1 – 7-day C6Gl; 2 – 14-day C6Gl; 3 – 14-day C6Gl+NSC; 4 – 14-day C6Gl+HSC; 5 – 14-day C6Gl+neural iMSC; 6 – 14-day C6Gl+hematopoietic iMSC; 7 – 14-day C6Gl+ ricin intracerebrally; 8 – 14-day C6Gl+ viscumin intracerebrally.

Figure 1. Nanocapsules with ricin

Results. 1. After 2 weeks native NSC and HSC evenly distributed through tumor and homed to target cells in TC. NSC and HSC transplanted to C6Gl slowed BT growth almost twice. 2. iMSC (both of NSC and HSC) enhanced proliferative processes, and tumor increased almost twice (compared to control). 3. Intracerebral injection of ricin and viscumin lead to global toxic damage (Fig. 2).

Figure 2. A) 7-day C6Gl; B) 14-day C6Gl, volume – 220.3 ml. C) 14-day C6Gl after NSC (down) and HSC (up) implantation; volume – 170.4 ml, p<0.05. D) Glioma after implantation of iMSC of NSC (up) and iMSC of HSC (down), volume – 360ml; E) Intracerebral injection of ricin (up) and viscumin (down) in tumor and peritumoral space.

Discussion and Conclusions. The obtained results comply with CRT concept. Inhibition of C6Gl growth by transplanted NSC and HSC highlights their regulative antitumor potential that has to be used in clinic. Tumor growth after iMSC transplantation is associated with rapid apoptosis (5-7 days) resulted from degradation rate of NC. Local apoptosis of iMSC in their injection site led to acute damage or modeled surgical reduction of a tumor part, thus enhancing C6Gl proliferation. Even distribution of iMSC through the tumor happens by day 14, consequently NC with degradation rate of no less than 14 days are requisite. The approach requires further research but does not derogate from CRT prospective for BT and other tumors therapy. Controlled cell induction of SC and PC can provide a new tool for BT therapy.

References:

1. Grodins FS, Control Theory and Biological Systems, 1963
2. Neimark MN, Control System Theory, 1992

Disclosures. The authors have nothing to disclose.