Non-viral vector delivery systems of siRNA as a gene therapy strategy to target brain cancer

Xinai Shen

Glioblastoma (GBM) is the most common and high mortality rate primary brain tumor, in spite of surgical resection in conjunction with radiotherapy and chemotherapy, the medium survival period for glioblastoma patients is presently only 14.6 months [[1]](#endnote-1), only about 10% patients survived for more than 5 years.[[2]](#endnote-2) GBM is a blood-rich tumor, and have a variety of growth and pro-angiogenic factors. Research shows that vascular endothelial growth factor - A (VEGF-A) plays an important role in angiogenesis. VEGF-A isoform combine with VEGFR-1/2, and promote vascular endothelial cells division and growth[[3]](#endnote-3). Because VEGF-A is highly expressed in GBM, it can be used as the target of anti-angiogenesis therapy for GBM.

Bevacizumab could specifically bind to the VEGF-A and use in recent and newly diagnosed GBM. However, bevacizumab could reduce vascular permeability so that the transient vascular normalization restricts further drugs penetration into brain parenchyma and reduces therapy on glioma[[4]](#endnote-4). Bevacizumab also has short effect, so most patients’ tumor grow after 6 months.[[5]](#endnote-5) One of the reason is that GBM is a kind of highly infiltrating inflammatory tumor, hardly to be completely removed, so there are infiltrating stromal cells. The combination of temozolomide (TMZ) and bevacizumab in the treatment of gliomas can be active and safe.

In recent years, small interfering RNA (siRNA) has been found in malignant tumor, which is a powerful tool for gene therapy[[6]](#endnote-6) like controlling the occurrence and development of glioma. A variety of siRNA perhaps inhibit glioma, especially it can be designed to target specific genes involved in the proliferation, invasion, migration and angiogenesis. [[7]](#endnote-7) I learnt that siRNA can express RNA interference (RNAi), which is the process of sequenc-spacific, post-transcriptional gene silencing in animals and plants.[[8]](#endnote-8) SiRNA are powerful reagents for mediating gene silencing, and the concentration of siRNAs is effective when it is several orders of magnitude lower than that used in traditional antisense or ribozyme gene-targeting experiments.[[9]](#endnote-9)

A specific siRNA may be a promising target for treat GBM, so I would learn more about the effects of various siRNA.

Blood-brain barrier (BBB) is a major limitation to the use of drugs in the brain. Besides, the feeding capillaries in glioma reserve the characteristics of the BBB and form a blood-brain tumor barrier (BTB), which is similar to BBB. Though BTB is more permeable than BBB, the blood vessels of brain tumors often highly express receptors, thus facilitating ligand-dependent drug delivery, it still blocks drugs from entering the brain. Therefore, methods that can help pass the BTB and BBB could enable the use of many anti-tumor agents in glioma therapy.

Polypeptide Angiopep-2 can actively penetrate into the brain compartment by binding to specific receptor of low-density lipoprotein receptor-related protein 1 (LRP-1), which is highly expressed on the surface of the BBB. It is expressed in both cytoplasm and cell surface of gliomas. [[10]](#endnote-10) LRP-1 enters brain tissue by receptormediated transcytosis (RMT) transport mechanism. It can help drug cross the BBB, increase the drug concentration in brain tissue, and then improve the cure rate. For this reason, I think this is an immense method to increase the proposition of drug entering the brain. Angiopep-2 can be used to modify TMZ, bevacizumab and siRNA to promote crossing BBB. Then succeeding study need to investigate the targeting efficiency and pharmacodynamics.

Polylactic acid (PLA) has become one of the commonly used drug carriers because of its good biocompatibility and biodegradability, but its hydrophilicity is poor. Polyethyleneglycol (PEG) has attracted much attention as a common hydrophilic modified material. [[11]](#endnote-11) It can be considered that PLA-PEG polymeric materials carry bevacizumab, TMZ and siRNA and induce intracellular release to reduce dosage.

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