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EDITORIAL

Multimodal therapy for brain tumors*

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Ting Lei. M.D., Professor of Neurosurgery, Doctoral Supervisor, Director of the Neurosurgery Department, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, China. He obtained his bachelor's and master's degree from Tongji Medical University, China, and became a neurosurgeon afterward. Then, he successfully obtained a German Academic Exchange Service scholarship to undertake his doctorate in medicine at the University of Erlangen-Nuernberg in Germany. Under the supervision of Profs. R. Fahlbusch and M. Buchfelder, he completed his doctoral degree in the same university and returned to Tongji Hospital to become the first postdoctoral fellow in the Department of Neurosurgery. Since 1998, he has been Chief of the Neurosurgical Department.

His scientific interest is basic research and clinical treatment of brain tumors, including pituitary adenoma and glioma. He introduced transsphenoidal surgery in the treatment of pituitary adenoma in Hubei Province, China. Currently, he performs more than 300 transsphenoidal surgeries annually. Over the past years, he also modified this surgical approach to make it less invasive and provide patients with fast postoperative recovery and better quality of life.

He has been an active researcher in the brain tumor research community for over 30 years now. He received several grants from the National Natural Science Foundation and published more than 500 peer-reviewed papers in national and international journals, including the *Journal of Neurosurgery*, *Epilepsy*, *European Journal of Cancer*, and *Cancer Letter*. Meanwhile, he is also an academic editor of several journals. Prof. Lei serves as the chairman of the neurosurgery branch of the Wuhan Medical Association and is a committee member of several academic associations.

Brain tumors are devastating diseases that occur when resident brain cells are transformed. As most other solid tumors, brain tumors are classified as either malignant or benign.

Gliomas are the most common malignant brain tumors in the central nervous system, accounting for around 70% of the newly diagnosed cases in adults. They constitute approximately 30% of all brain tumors, and approximately 60% of gliomas occur in the four lobes of the brain. Overall, brain tumors are relatively rare. The average annual age-adjusted incidence rates of all malignant brain tumors range from 4.95 to 8.97 per 100 000 people, whereas those of nonmalignant brain tumors range from 8.90 to 19.02 per 100 000 people. Males are more frequently affected with gliomas than females [1]. Like that of most malignant cancers, the etiology of gliomas is still unclear. However, occupations, lifestyles, and environmental carcinogens have been reported to be associated with a high risk of gliomas, but the only unequivocal factor identified so far is therapeutic X-irradiation [2].

Multimodal treatments of gliomas include surgery, radiotherapy, chemotherapy, and immunotherapy. However, despite all these possible strategies, most patients with malignant gliomas still have poor prognoses. One of the reasons is drug resistance. Over the last years, several theories have evolved about drug resistance in glioma treatment, such as the glioma stem cell hypothesis and epigenetic changes of the tumor cell genome. In our current issue, Dr. Cai and colleagues summarized the role of histone modifications in brain tumor drug resistance [*Xi GF, Mania-Farnell B, Lei T, et al. Histone modification as a drug resistance driver*

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in brain tumors]. Recent studies showed that posttranslational gene regulation such as histone modification provides a critical regulatory platform for chromosome condensation and segregation, gene transcription, and DNA replication and repair. For brain tumors, several studies reported differences in histone modification in adult and pediatric brain tumors compared with normal tissue, indicating that these changes are also characteristics of brain tumors. Histone modifications, including acetylation, methylation, ubiquitylation, or glycosylation on lysine; methylation on arginine; and phosphorylation on serine or threonine, could indirectly or directly influence the ABC transporter and DNA repair, which are both critical mechanisms of drug resistance. The review also included other possible mechanisms thereby histone modifications contribute to drug resistance in glioma treatments. Understanding and uncovering further mechanisms of histone modification that induce drug resistance by using sophisticated techniques will shed new light on glioma therapies.

Compared with traditional therapies, immunotherapies for gliomas have been subjected to in-depth investigations and have drawn a lot of attention. Dendritic cell (DC) vaccination is an active immunotherapy that trains the immune system of the body to create an antitumoral response. We have been working on basic research and clinical applications of DCs in glioma treatment for several years and have shown in a pilot clinical study that whole tumor extract-pulsed DC injection can significantly prolong the survival of patients with glioblastoma multiforme. However, we could not clearly see any survival benefit in some of the patients. Along with other groups, we realized that whole tumor extract is not really a specific antigen for pulsing DCs. Dr. Wang searched for new antigens for DC vaccination [*Wang Y, Xie RF, Niu HQ, et al. IL-13Ra2- and glioma stem cell-pulsed dendritic cells induce glioma cell death in vitro*]. In this article, she reported that IL-13Ra2 is significantly expressed in gliomas but not in normal brain tissue, and that it does stimulate DC activation. Moreover, she demonstrated that glioma stem cell (GSC) extract significantly triggered DC production, indicating that GSC could also be used as antigen for DC vaccinations. We will continue this work and try to optimize DC immunotherapy to contribute to the improvement of multimodal therapies for glioma in the future.

Malignant brain tumors such gliomas are lethal diseases due to their relapse and drug resistance. Benign tumors could also be fatal because of difficulties in surgeries and complications in the perioperative period. Craniopharyngiomas are epithelial tumors that arise from embryonic epithelial cells of the craniopharyngeal duct, which have a tendency to invade the critical neurovascular structures, particularly the visual pathways and hypothalamus, resulting in high morbidity and mortality. We have been using the transsphenoidal approach to treat infradiaphragmatic craniopharyngioma, and have shared some of our experiences in the current issue. We recommend the transsphenoidal approach because it could preserve pituitary function and avoid damages to the hypothalamic structures and optic nerve. Moreover, for tumors that could not be totally removed at one time, the transsphenoidal approach is an ideal technique for resecting infradiaphragmatic tumors.

Pituitary adenomas are also quite common brain tumors in the central nervous system, different subtypes of pituitary adenoma are identified according to their hormone secretion. Prolactinomas, which has the highest incidence rate in pituitary adenomas, are unique for its treatment with dopamine agonist. A few studies demonstrated that bromocripitne treatment could influence tumor consistency which is a very important factor for surgery. We summarized 238 patients of prolactinoma who underwent transphenoidal surgery in our center (Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China), and we found that female patients who took dopamine agonist before surgery have harder tumor consistency, however with male patients we did not see any difference [*Huang YM, Hu F, Wu K, et al. Sex-related changes in tumor consistency in prolactinoma patients after bromocriptine pretreatment*]. This information may give neurosurgeons suggestions before operations.

Brain tumors are complicated cancers because of their location and histology. Understanding their molecular mechanisms of tumorigenesis and drug resistance could help optimize treatments. The last decades have seen great advances in basic and clinical research on brain tumors, and sophisticated techniques such as high throughput sequencing accelerate the development of personalized medicine in brain tumor treatment. This issue presents some of the new findings and summaries of cases of brain tumors in basic and clinical research. Hopefully, this will inspire our colleagues in this field.

References

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