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Editorial

Immunotherapy for Brain Cancer and Other Neurological Disorders

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Glioblastoma Multiforme is the most malignant form of primary brain cancer with poor prognosis. Malignant gliomas are typically invasive and the dissemination results in frequent recurrence after surgical resection, conventional chemotherapy and/or radiation therapy. Brain is also a major target site for a variety of metastatic cancer, making brain metastases the most common type of brain tumors. Treatment of brain cancer is particularly challenging due to its unique anatomy features, the segregated immunological environment, the blood-brain barrier in drug delivery, etc. However, recent progress in novel experimental therapy is encouraging and brings hope for brain cancer patients. Specifically, cancer stem cell theory and its clinical application, genomics and next generation sequencing, and immunotherapy are among the key progress in treatment of brain tumors and other neurological disorders.

Brain tumor stem cells (BTSCs) were discovered a decade ago, which brought about wide-spread impact on brain tumor research and clinical practice. We and others isolated brain tumor stem cells and characterized their molecular features. The new concept provided a theoretical framework in understanding tumor heterogeneity, clinical diversity, and treatment resistance. For example, BTSCs were detected with high frequency in recurrent brain tumors after standard treatment. Importantly, existence of BTSCs per se does not dictate malignancy, as benign tumors were found to contain BTSCs. The molecule features and key signaling pathways in BTSCs would provide useful targets for future therapy. For example, CD133, as a BTSCs marker, is one of the tumor antigens of ongoing immunotherapy clinical trials.

A significant technology developed in the study of BTSCs is the application of neural stem cells as a delivery vehicle for brain tumor experimental therapy. Based on their highly-tractable tumor tropism, neural stem cells have been used to deliver therapeutic and immune modulatory proteins to the tumor local sites. We also demonstrated that adult stem cells may be used for this purpose.

Another field of major progress is the application of genome-wide analysis to the brain tumor classification for precise treatment regimen. For example, IDH1/2 mutation, chromosome 1p/19q deletion, and a number of oncogene-tumor suppressor gene expression levels, were used in low grade glioma classification into three types for differential treatment. Precise classification of lower grade brain tumors brought about individual-tailored treatment and significantly improved patient survival.

By far the most significant progress lies in the brain cancer immunotherapy. We worked on dendritic cells (DC)-based brain tumor vaccine targeting cancer stem cells about a decade ago, but the field has seen rapid progress almost every year. DC-vaccination targeting BTSCs is still an important goal, but improved tumor antigen selection and immunization technology is under development. The variety of immunotherapy may be divided into two categories: therapy to improve tumor recognition by immune system and therapy to inhibit tumor immune suppression/evasion. The former includes mainly DC vaccination, adoptive T cell transfer (ACT), while the latter includes the recent year cancer research breakthrough- checkpoint inhibitors. The PD-1 inhibitor Nivolumab (Opdiva, marketed in 2014) was approved by FDA to treat metastatic melanoma and now non-small cell lung cancer. Recently, it also demonstrated positive early signs in treating glioma patients. Clinical trials using other checkpoint inhibitors (Pembrolizumab/Keytruda and Durvalumab) are also under way. Another type of potential novel immune suppression treatment involves targeting FGL2.

ACT technology includes primarily chimeric antigen receptor (CAR) T cell therapy and T cell receptor (TCR) T cell therapy. CAR T cell therapy involves designer T cells targeting selected antigens on the surface of tumor cells independent of HLA restriction. CAR T cell therapies targeting CD19 had achieved phenomenal success in treating hematologic malignancies, especially in those patients with recurrence and resistance to standard treatment. As a pilot study applying this technology to treating solid tumors, CAR T cells targeting EGFRvIII-positive glioblastomas led to elimination of positive tumor cells in most patients, although considerable side effects were observed and the therapy could not eliminate entire tumors. Along a similar line, EGFRvIII-targeted tumor vaccine Rintega (rindopepimut) was tested in combination with Avastin in the ReACT phase 2 trial and achieved significant advantage in overall survival, including a quarter of patients having survived over two years. However, the therapy failed subsequently in phase 3 trial and was discontinued by Celldex Therapeutics, highlighting the complex nature in immunotherapy.

It is now generally believed that the ACT therapy should be combined with treatments overcoming immunosuppression mechanisms. Besides the well-studied checkpoint proteins (CTLA-4, PD-1/PD-L1, etc.), FGL2 emerged as one of the important immunosuppressive factors, with a role particularly in brain tumors. Combination immunotherapy may indeed hold the hope for future brain cancer therapy. Other progress in brain cancer treatment includes IDH1-targeted therapy, as well as the successful application of low intensity, intermediate-frequency alternating electric fields (tumor treating fields, TTF) to treating glioblastoma patients.

Other neurological disorders may also benefit from novel immunological tools-based therapy. Recently, an antibody targeting amyloid plaque (Aducanumab) developed by Biogen and Neurimmune significant reduced plaque pathology and slowed cognitive decline in early stage studies. Similarly, amyloid-targeting drug solanezumab by Lilly had brought promising results in early tests. These examples are especially encouraging, for a devastating disease with no good treatment available. In the frontline battling, multiple sclerosis (MS), Scientist Rebecca Coll won the 2016 Research Australia Discover Award for her contribution in identifying potential drugs targeting inflammasome protein NLRP3. As another example, study led by Gavin Giovannoni discovered that Alemtuzumab could prevent immune cells from entering brain and spinal cord, with the hope of alleviating relapsing-remitting MS.

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