



Tumor Microenvironment and Immunotherapy in Glioblastoma

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Editorial

Glioblastoma is the most malignant brain cancer which becomes fatal for almost all the patients within 2 years in spite of the tremendous efforts in surgery, radiotherapy, and chemotherapy. Immunotherapy including check-point inhibitors has been paid attentions more and more. Recently, Weller M, et al. [1] reported a surprising result in the ACT IV study, which assessed the efficacy of anti-EGFRvIII immunotherapy for glioblastoma, that a subset of patients with significant residual disease after surgery had a tendency to live longer than those with minimal residual disease. We had for a long time believed that minimal residual tumor is required for immunotherapy to be effective. Although further verification is necessary, this finding should have the essence for cure of this disease. One of the underlying mechanisms may be that a lot of antigens are necessary for the efficient induction of anti-tumor immunity. However, post-operative residual tumors usually pass through the antigen presentation process. How can we make the residual tumor cells to participate in the efficient antigen presentation system? Tumor mass usually contains both tumor cells and the reactive host myeloid cells [2]. The interaction between these cells mutually supports each other to survive, especially in terms of the secreted factors [2]. The soluble factors secreted from myeloid cells such as transforming growth factor- β (TGF- β) is the main player of the mutual interaction to develop an immune suppressive environments contributing to the development of tumor mass. This is called the M2 type cells compared with the pro-inflammatory M1 type macrophages. The important point here is the tumor cells with a lot of surrounding myeloid cells should have developed the support dependency. A switch to M1 type of myeloid cells may be a breakthrough for the subset of patients. Hypoxia accompanying glioblastoma further increases the recruitment of myeloid cells into the tumor. We showed that TGF- β highly expressed in the peri-necrotic areas and CD11b-positive myeloid cell accumulation was significantly associated with a shorter survival [3]. These features could affect the efficacies of immunological therapy such as vaccine therapy. We have been trying a Dendritic Cell (DC)-based vaccine therapy for newly-diagnosed glioblastoma using monocytes obtained with pre-chemoradiotherapy apheresis [4]. For the patients having tumors with the high infiltration of CD11b-positive myeloid cells, the DC vaccine therapy brought a significantly better survival than those without the vaccine therapy (unpublished data). Tumor-infiltrated myeloid cells are mainly the immune-suppressive M2 type, with high production of TGF- β , and under those conditions, immune stimulation by vaccine therapy would be highly effective. The immune suppression caused by myeloid cells can be restored by active immunization using vaccination.

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