Identification of immunomodulatory mechanisms during glioblastoma treatment and progression - toward the development of novel treatment strategies

Glioblastomas employ mechanisms that protect them from recognition by the immune system and actively suppress immune responses. These mechanisms act both locally within the tumor as well as systemically. This project aimed to analyze immunological changes in glioblastoma patients in the tumor and in peripheral blood during the course of the disease and treatment, in the context of tumor–host interactions. To this end, we investigated the clonal evolution of the T-cell repertoire in primary glioblastomas and tumor recurrences, analyzed the mechanisms underlying insufficient tumor antigen presentation, and determined circulating cellular immune profiles as well as soluble immunological biomarkers in patient blood.

We demonstrated that high T-cell clonality (lower clonal diversity) within the tumor is associated with significantly prolonged survival. This supports the notion of an expansion of T-cell clones that specifically recognize and attack tumors. In contrast, the clonality of circulating T cells in the blood is not prognostically relevant, although older patients generally exhibit reduced clonal diversity of peripheral blood T cells. In addition, we identified T-cell clones in different glioblastoma patients that can recognize the same antigens and are therefore likely tumor-relevant. These include not only viral antigens with which tumor-relevant T cells can potentially cross-react, but also human tumor-associated antigens whose relevance to glioblastoma had not previously been known.

Our analysis of peripheral immune cells in the blood of patients with primary glioblastomas and recurrences showed that cytotoxic T cells were activated, in particular with an increased prevalence of clonally expanded memory T cells. However, this immune activation is obviously insufficient to eliminate the tumor. In parallel, we observed a quantitative shift in the blood of patients from immunostimulatory helper cells toward immunosuppressive regulatory T cells (Tregs), and a marked dysfunction of both cytotoxic T cells and T helper cells, with reduced production of pro-inflammatory cytokines and increased production of immunosuppressive cytokines.

Analysis of soluble immunological biomarkers in the blood of glioblastoma patients revealed that BDNF (brain-derived neurotrophic factor) levels are elevated compared with healthy controls. High BDNF concentrations are prognostically unfavorable and associated with shorter overall survival. Moreover, numerous other pro-inflammatory proteins (e.g. chemokines), as well as proteins involved in neuronal interactions are associated with increased BDNF levels. Experimentally, BDNF inhibits T-cell activation, indicating that elevated levels of this factor are systemically relevant for immunosuppresssion.

To investigate a potentially insufficient antigen presentation by glioblastomas, we performed mutation analyses of genes involved in cellular antigen processing and presentation. Such mutations were found in approximately 5% of recurrent tumors, but only in approximately 1% of primary tumors. The presence of mutations was associated with reduced T-cell infiltration in the affected tumors. These results suggest that antigen-presentation–affecting mutations are not a primary mechanism of immune escape at initial diagnosis, but rather arise during therapy (e.g., radiotherapy and chemotherapy) and are therefore relevant for potential immunotherapies against recurrent tumors.

In summary, this study contributes to a deeper correlative understanding of the complex local and systemic immune modulation in glioblastoma patients and highlights starting points for the development of improved immunotherapeutic strategies tailored to the immunological characteristics of individual patients.