Immunosuppression

Immunosuppression is a reduction of the activation or efficacy of the immune system. Some portions of the immune system itself have immunosuppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions.

In general, deliberately induced immunosuppression is performed to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, or Crohn's disease. This is typically done using medications, but may involve surgery (spleen removal), plasmapharesis, or radiation.

A person who is undergoing immunosuppression, or whose immune system is weak for other reasons (for example, chemotherapy or HIV), is said to be immunocompromised. An immunosuppressant is any agent that weakens the immune system, including immunosuppressive drugs and some environmental toxins.

High grade gliomas (HGG) exert systemic immunosuppression, which is of particular importance as immunotherapeutic strategies such as therapeutic vaccines are increasingly used to treat HGGs. In a first cohort of 61 HGG patients Löhr et al., from the University of Würzburg, Germany, evaluated a panel of 30 hematological and 34 plasma biomarkers. Then, they investigated in a second cohort of 11 relapsed HGG patients receiving immunomodulation with metronomic cyclophosphamide upfront to a DC-based vaccine whether immune abnormalities persisted and whether they hampered induction of IFNγ+ T-cell responses. HGG patients from the first cohort showed increased numbers of leukocytes, neutrophils and MDSCs and in parallel reduced numbers of CD4+/CD8+ T-cells, plasmacytoid and conventional DC2s. MDSCs and T-cell alterations were more profound in WHO IV° glioma patients. Moreover, levels of MDSCs and epidermal growth factor were negatively associated with survival. Serum levels of IL-2, IL-4, IL-5 and IL-10 were altered in HGG patients, however, without any impact on clinical outcome. In the immunotherapy cohort, 6-month overall survival was 100%. Metronomic cyclophosphamide led to > 40% reduction of regulatory T cells (Treg). In parallel to Treg-depletion, MDSCs and DC subsets became indistinguishable from healthy controls, whereas T-lymphopenia persisted. Despite low T-cells, IFNγ-responses could be induced in 9/10 analyzed cases. Importantly, frequency of CD8+VLA-4+ T-cells with CNS-homing properties, but not of CD4+ VLA-4+ T-cells, increased during vaccination. Our study identifies several features of systemic immunosuppression in HGGs. Metronomic cyclophosphamide in combination with an active immunization alleviates the latter and the combined treatment allows induction of a high rate of anti-glioma immune responses [1)].

Glioblastoma, one of the most aggressive primary brain tumors, is characterized by highly immunosuppressive microenvironment. This contributes to glioblastoma resistance to standard treatment modalities and allows tumor growth and recurrence. Several immune-targeted approaches have been recently developed and are currently under preclinical and clinical investigation [2)].

1)

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2)
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