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# Oncovirotherapy of Glioblastoma: A Kind of Immunotherapy?

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## Description

Every year, approximately 3 to 5 of 100.000 people are newly diagnosed with a glioblastoma (GBM). The current standard of care is the surgical resection, radiotherapy and chemotherapy. However, despite this aggressive treatment, the median survival time is only 12 to 15 months after initial diagnosis [1,2]. Patients with recurrent disease normally have a life expectancy of only a few weeks. The ineffective treatment of GBM is based on its characteristics: GBM grow highly invasively making completely surgical resection impossible, show massive neoangiogenesis, generate a immunosuppressive tumor micro-milieu, and a subpopulation of extremely resistant glioma cells, named brain tumor initiating cells (BTICs) or glioma stem like cells (GSCs) remain stem cell characteristics. Beside this, physical barriers hamper the effective distribution of anticancer drugs. In this regard there is no defined treatment standard in case of disease progression during or after standard radiochemotherapy. Thus, the development of new concepts in the treatment of GBM is of particular importance. A variety of preclinical as well as clinical trials have shown that viruses can be used as potent agents in the treatment of cancer, also for the treatment of glioma. These either wildtype or genetically engineered viruses of different origin such as adeno-, parvo-, herpes-, reo-, measles, semliki-forest, coxsackie or vaccinia virus can replicate in and subsequently kill tumor cells, but not non-neoplastic cells. Due to these skills, those viruses are named oncolytic viruses (OVs). Additionally, OVs can contain therapeutic genes triggering either the patient´s anti-tumor immune response or modulating the GBM microenvironment, or coding for prodrug suicide genes [3-6]. In many clinical trials it has also been demonstrated that the use of OVs is safe related to toxicity and adverse side effects [7-9]. However, the clinical efficacy of GBM oncovirotherapy has not yet achieved the promising preclinical laboratory results. To address this mismatch, one should mentioned the complex interaction between cancer cells, OV infection and replication, the adjacent tumor microenvironment, chemotherapy as well the patient´s immune system, indicating that not only OVs play a role in the efficient (onco)lysis of GBM cells.

Recent reports have presented strong evidence for a significant role of oncolytic virotherapy in the activation of anti-tumor immune responses [10,11]. Virus-mediated induction of immune responses can tilt the suppressive effects of immune evasion mechanisms induced by GBM cells by several mechanisms. Viruses can influence the (immune suppressive) micro-milieu of the tumor. Oncolysis can lead to the secretion of danger molecules from the lysed tumor cells such as *high mobility group B1* (HMGB1), *heat shock proteins* (HSP) or *Y-box protein 1* (YB-1). HMGB1, as a consequence of immunogenic cell death, is released, binds to and activates *toll like receptors* on dendritic cells (DC), thus controlling the initiation of immune responses through processing and presentation of tumor-derived antigens [12,13] as well as inducing GBM regression [14]. Extracellular HSP70 acts as a danger signal and regulates immune function, including antigen cross presentation, DC maturation and natural killer (NK) cell activities [15,16]. YB-1 is a potent tumor antigen that could induce host immune responses against the tumor [17,18] and is involved in inflammatory responses through up-regulation of the chemokines CCL-2 and CCL-5 [19], both showing chemotactic properties for T cells and activation of NK cells. Beside the induction of danger protein secretion, therapeutic administration of OVs can enhance the expression of *major histocompatibility complexes* (MHC) on the surface of tumor and immune cells, facilitate the presentation of otherwise inaccessible tumor-specific immunogenic peptides on antigen presenting cells (APC) and push, via inflammatory processes, the production of inflammatory cytokines. It has been shown recently that OVs also attack and lyse GSCs/BTICs [20], cells that are mainly responsible for the propagation of GBM [21,22] and an important source for the presentation of tumor antigens [23]. In this regard, OVs might potentiate the immune attack also against these highly resistant cells. Overall, OVs might drive anti-GBM immune responses and can initiate anti-GBM immunity.

Regarding to the immunosuppressive character of GBM, oncovirotherapy of this tumor entity might have not yet achieved its full potential. *Programmed cell death protein* 1 (PD-1), expressed on lymphocytes, is an immune checkpoint surface receptor and mediator of immune suppression whereas its ligand PD-L1 is expressed on antigen presenting, and also on tumor cells [24]. Engagement of PD-1 inhibits T cell function and promotes apoptosis [25,26]. In GBM, the common loss of tumor suppressor *phosphatase and tensin homolog* (PTEN) function increases PD-L1 expression on the surface of GBM cells and subsequently induces immunoresistance. Blocking this interaction has been shown to enhance anti-GBM immune cell activity and to prolongate the survival of GBM bearing mice [27,28]. Another important immunosuppressive checkpoint molecule is the *cytotoxic T-lymphocyte-associated protein* (CTLA)-4, that is expressed on the surface of T helper cells and transmits an inhibitory signal. The combination of cancer vaccination with a CTLA-4 blockade has been a preclinical strategy for now several years. In this context, it has been demonstrated that glioma cell vaccination and CTLA-4 blockade is an effective strategy to treat intracranial gliomas in immunocompetent mice [29]. The ability of OVs to locally stimulate inflammation and direct tumor lysis positions them well as therapeutic partners in combination (immune)therapies. In this regard Zamarin et al. showed that blocking immune-repressive proteins in combination with virotherapy markedly increases the infiltration of activated immune effector cells into the tumor mass and leads to rejection of pre-established distant tumors and protection from tumor rechallenge in poorly immunogenic tumor models [30,31]. In other studies using melanoma mouse models, Quetglas et al. have demonstrated synergism of oncolytic virotherapy using IL-12 expressing Semliki

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forest viruses and blockade of PD-L1 [32]. Additionally, Engeland et al. have demonstrated that the blockade of PD-L1 and CTLA-4 enhances the therapeutic effect of oncolytic measles viruses [33]. Started end of 2014, a first clinical trial is testing the therapeutic effects of Ipilimumab, a humanized IgG monoclonal antibody that blocks CTLA-4, in combination with CAVATAK™ (Coxsackievirus A21), in the treatment of advanced melanoma (https://clinicaltrials.gov; NCT02307149) and it remains exciting to see the benefit of this combined treatment in the outcome of melanoma patients. To further enhance the immune-stimulatory effect of an oncovirotherapy approach anlongside with the blockade of immune-repressive molecules such as PD-L1 or CTLA-4, one could think about using tumor vaccination strategies such as the use of bispecific antibodies targeting death receptors and GBM specific antigens [34] or of the hybridoma/stem cell fusion technique [23,35]. In addition to OV-based tumor cell lysis and immune stimulation and to the reversal of the immunosuppressive GBM micro-milieu by blocking PD-L1 or CTLA-4, vaccination techniques allow the patient´s immune system to further recognize and destroy tumor cells.

In conclusion it is clear that immune responses induced by oncovirotherapy dedicate the benefit of this treatment. In future studies, combination of OVs with approaches to further overcome the immunosuppressive effect of GBM such as the use of checkpoint inhibitors as well as regulating the balance between anti-tumor and anti-virus immune responses and the use of tumor vaccination provide a strong rationale for the clinical exploration of these oncoviro-immunotherapy strategies and will hopefully assure maximum benefits for GBM patients.

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