ACTIVATING THE ANTIGEN PRESENTING CELLS TO IMPROVE VIROTHERAPY EFFICACY IN DIFFUSE MIDLINE GLIOMAS


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Background Within Diffuse Midline Gliomas, Diffuse Intrinsic Pontine Glioma (DIPG) is the principal cause of non-accidental pediatric deaths. Although gold-standard treatments have improved, the outcome for children with DIPGs remains poor pointing to the need for alternative therapies. In this sense, we have previously demonstrated that the oncolytic adenovirus Delta-24-RGD (which has already shown safety and feasibility in DIPG patients) is able to recruit T cells into the tumor. However, such as T-lymphocyte infiltration rapidly acquires an exhausted phenotype that prevents from achieving long-term anti-tumor responses. Therefore, we decided to improve this therapy by combining the Delta-24-RGD with the activation of the costimulatory receptor CD40, which is known to increase antigen presentation and enable T-cell priming.

Methods To determine anti-tumor efficacy, we treated immunocompetent and immunodeficient mice bearing orthotopic DIPG tumors with an intratumoral injection including the Delta-24-RGD and a CD40 agonistic monoclonal antibody. Survival and toxicity were monitored after treatment and the changes in the tumor immune microenvironment were analyzed by flow cytometry, immunofluorescence, and RNA sequencing. Long-term survivors were rechallenged with primary tumor cells to study the development of anti-tumor immunological memory.

Results The combination therapy is safe and extends survival of immunocompetent treated mice as compared to single treatments or non-treated mice, resulting in 40% of complete responses. In addition, mice that rejected the tumor were able to control the growth of a rechallenge with the primary cells indicating the development of long-term anti-tumor immunity. This, together with the lack of effect observed in immunodeficient mice evidences a key role of the adaptive immune system in the anti-tumor response. We found that the combination remodels the tumor context towards a proinflammatory scenario with an increase of proinflammatory chemokines, proliferating T lymphocytes and activated dendritic cells, which express high levels of the CD40 receptor. In addition, the blocking of CSF1R (mainly expressed by microglia/macrophages) avoids the recruitment of dendritic cells into the tumor and abrogates the anti-tumor effect observed upon the combination of Delta-24-RGD and anti-CD40.

Conclusions Our results show that the combination of Delta-24-RGD with the stimulation of CD40 is safe, has a potent and long-term anti-tumor effect and promotes a proinflammatory tumor microenvironment. We believe that these results can be translational and open the door for a future innovative clinical trial.

Ethics Approval The study was approved by the University of Navarra’s Ethics Committee for Animal Experimentation (CEEA), approval number 068-20