TIM-3 BLOCKADE MODULATES THE TUMOR MICROENVIRONMENT IMPROVING THE OUTCOME OF PRECLINICAL PEDIATRIC DIFFUSE MIDLINE GLIOMA MODELS

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Background Diffuse Intrinsic Pontine Gliomas (DIPGs), encompassing Diffuse Intrinsic Pontine Gliomas (DIPGs), are the most aggressive pediatric brain tumors. Their meager survival has not changed despite the combination of radiotherapy with targeted therapies emphasizing the urgent need for effective treatments. Recent research suggested that the DIPG tumor microenvironment is neither highly immunosuppressive nor inflammatory. 1 These analyses showed the lack of infiltrating lymphocytes and the abundance of CD11b+ cells. TIM-3 is a member of the T-cell immunoglobulin and mucin domain protein family expressed on multiple immune cell types, including T cells, Treg, NK cells, monocytes, dendritic cells, and microglia, where it potently regulates not only adaptive immunity but also innate immunity. 2–3 Therefore, TIM-3 inhibitors could challenge several components in the tumor microenvironment, thereby providing potentially effective treatment for DIPGs.

Methods NP53 and XFM murine DIPG cell lines were used for animal experiments in immunocompetent orthotopic models. The tumors were processed by mechanical and enzymatic digestion and immune populations were analyzed by a flow cytometry panel. Antibodies against NK cells (NK1.1), CD4 (GK1.5), CD8 (CD8b) were used for animal depletion experiments alone or in combination.

Results In silico assessment of TIM-3 expression in DIPG datasets showed a robust expression of this gene. Moreover, single-cell sequencing analyses of DIPG biopsies uncover its expression in the myeloid compartment (especially in microglia). In vivo efficacy studies showed that treatment with anti-TIM-3 antibody significantly increased the overall survival in two DIPG immunocompetent orthotopic animal models (doubling the median), lead to long-term survivors free of disease (50%) and showed immune memory. Analyses of CD45+ populations in the tumor microenvironment showed a significant increase in microglia, granulocytes, NK and CD8+ cells corresponding with a NK and T-cell activate phenotypes in treated-mice. In addition, we have a substantial decrease in the Treg population, which causes an increase in the CD8/Treg ratio. CD4 and CD8 T-cell depletion led to a significant but not total loss of treatment efficacy. NK cells depletion also reduced the effectiveness of this therapy, albeit to a lesser extent than CD4-CD8 depletion. We are currently investigating the role of microglia in the outcome of the treatment.

Conclusions Our data uncovered TIM-3 as a potential target for the treatment of DIPG tumors. Inhibition of this molecule led to a potent antitumor effect mediated by a profound tumor microenvironment remodelling.

REFERENCES