

CD40

Cluster of differentiation 40, CD40 is a costimulatory protein found on antigen-presenting cells and is required for their activation. The binding of CD154 (CD40L) on TH cells to CD40 activates antigen-presenting cells and induces a variety of downstream effects.

Deficiency can cause Hyper-IgM syndrome type 3.

Immunostimulatory agonistic CD40 antibodies (α CD40) are in clinical development for solid tumors, but are yet to be evaluated for glioma. Here, we demonstrate that systemic delivery of α CD40 in preclinical glioma models induces the formation of **tertiary lymphoid structures** (TLS) in the proximity of meningeal tissue. In treatment-naïve glioma patients, the presence of TLS correlates with increased T cell infiltration. However, systemic delivery of α CD40 induces hypofunctional T cells and impairs the response to immune checkpoint inhibitors in pre-clinical glioma models. This is associated with a systemic induction of suppressive CD11b+ B cells post- α CD40 treatment, which accumulates in the tumor microenvironment. Our work unveils the pleiotropic effects of α CD40 therapy in glioma and reveals that immunotherapies can modulate TLS formation in the brain, opening up for future opportunities to regulate the immune response ¹⁾.

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