Tertiary lymphoid structures (TLSs) are ectopic lymphoid organs that develop in non-lymphoid tissues at sites of chronic inflammation including tumours. Key common characteristics between secondary lymphoid organogenesis and TLS neogenesis have been identified. TLSs exist under different maturation states in tumours, culminating in germinal centre formation. The mechanisms that underlie the role of TLSs in the adaptive antitumour immune response are being deciphered. The description of the correlation between TLS presence and clinical benefit in patients with cancer, suggesting that TLSs could be a prognostic and predictive factor, has drawn strong interest into investigating the role of TLSs in tumours. A current major challenge is to exploit TLSs to promote lymphocyte infiltration, activation by tumour antigens and differentiation to increase the antitumour immune response. Several approaches are being developed using chemokines, cytokines, antibodies, antigen-presenting cells or synthetic scaffolds to induce TLS formation. Strategies aiming to induce TLS neogenesis in immune-low tumours and in immune-high tumours, in this case, in combination with therapeutic agents dampening the inflammatory environment and/or with immune checkpoint inhibitors, represent promising avenues for cancer treatment.

Immunostimulatory agonistic CD40 antibodies (αCD40) are in clinical development for solid tumors, but are yet to be evaluated for glioma. Here, we demonstrate that systemic delivery of αCD40 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 αCD40 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-αCD40 treatment, which accumulates in the tumor microenvironment. Our work unveils the pleiotropic effects of αCD40 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)].

1)
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