Beta-arrestin inhibition to prevent S1P1 internalization as a treatment for intracranial diseases

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Value Proposition

Glioblastomas (GBMs) are among the most common and deadly malignant brain tumors with a mean survival time of approximately 14-15 months following diagnosis. Current treatments for GBMs include surgery, radiation, and chemotherapy, however, survival remains low. Immunotherapy, which has proven successful for the treatment of other cancers, is an emerging field that may be a promising treatment for GBMs. However, treating GBMs remains challenging due to the immunosuppressive nature of GMBs. Treatment is further complicated by T-cell lymphopaenia (low number of circulating T-cells) in many patients. Previously, it has been shown that T-cell sequestration in the bone marrow of GBM patients is due do loss of the sphingosine 1-phosphate receptor 1 (S1P1), a G-protein coupled receptor, on the surface of T-cells. Introduction of a cell surface stable S1P1 leads to freeing of T-cells from bone marrow and licenses T-cell activating immunotherapies that were previously ineffective. However, there are currently no direct pharmacological methods available to increase S1P1 cell surface expression.

Technology

This invention is a method for increasing S1P1 cell surface expression on T-cells through genetic or pharmacologic inhibition of beta-arrestins. Beta-arrestins are required for internalization of G-protein coupled receptors including S1P1. The inventors showed that knockout (KO) of beta-arrestins stabilizes S1P1on the surface of T-cells and prevents immune sequestration similar to knockin of stabilized S1P1. This was shown by adoptive transfer of T-cells from beta-arrestin 1 or 2 KO mice. In addition, beta-arrestin 2 KO mice with an implanted glioma survived significantly longer than beta-arrestin 1KO or wild type mice. This invention could substantially aid in the development of new immunotherapies for GBMs by overcoming immunosuppression common in GBM patients.

Other Applications

T-cell bone marrow sequestration appears in conjunction with other intracranial tumors and inflammatory processes in the brain, including stoke.

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Advantages

- T-cells without beta-arrestin are not sequestered in the BM
- Beta-arrestin KO T-cells phenocopy S1P1 stabilized T-cells
- Pharmacologic inhibition of beta-arrestin increases S1P1 surface expression

Publications

- Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors (Nat Med, 2018)