Immune Response Regulation for the Treatment of Cancer

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Technology description

Summary

Diacyl glycerol kinase (DGK) is upregulated in anergic T cells. To avoid being cleared by the immune system, cancer cells induce a state of anergy, or a lack of a normal immune response, in the host. Conversely, a wide variety of auto-immune disorders stem from an inappropriate immune response. DGK is a key protein in the determination of the strength of an immune response, and regulation of this protein may be an effective remedy for either stimulation of anergic cells for the treatment of cancer, or induction of anergy for the treatment of autoimmune disorders.

Description

It has long been thought that a highly effective strategy for the treatment of cancer would involve the natural defenses of the body i.e., the immune system. However, while cancer cells do express antigens that can be recognized by T cells of the host immune system, spontaneous immune-mediated rejection of cancer is rare. To avoid being cleared by the immune system, cancer cells induce a state of anergy, or a lack of a normal immune response, in the host. Overcoming cancer-mediated anergy would significantly enhance a wide variety of cancer therapeutics, including conventional chemotherapy, radiation, and surgery, using the native defense mechanisms of a patients own body. Conversely, a wide variety of disorders stem from the overactivity of the immune system, including allergies, rheumatoid arthritis, multiple sclerosis, Hashimotos thyroiditis, Crohns disease, Graves disease, transplant rejection and graft-versus-host disease. In these cases, it would be of great benefit to be able to specifically down-regulate the immune system. Dr. Gajewski and colleagues have identified a key element in the regulation of the immune response in mammals. Diacylglycerol kinase (DGK) alpha or zeta sits in the middle of a complex series of interactions that determine the strength of the immune response to an immunogen. They have determined that down-regulation of DGK can alleviate anergy, allowing the immune system to mount a defense against cancer cells. Using the small molecule inhibitors R59022 and R59449, as well as dominant-negative mutants to inhibit diacylglycerol kinase (DGK) alpha or zeta , the inventors have reversed T-cell anergy and induced an immune response in a mouse model. The inventors have also determined that up-regulation of DGK can induce anergy. The

identification of DGK activators could be used for the treatment of a wide range of autoimmune disorders.

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