Modulating P38 Kinase Activity

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Technology description

Protein kinases are involved in various cellular responses to extracellular signals. The protein kinase termed p38 is also known as cytokine suppressive anti-inflammatory drug binding protein (CSBP) and RK. It is believed that p38 has a role in mediating cellular response to inflammatory stimuli, such as leukocyte accumulation, macrophage/monocyte activation, tissue resorption, fever, acute phase responses and neutrophilia. In addition, p38 has been implicated in cancer, thrombin-induced platelet aggregation, immunodeficiency disorders, autoimmune diseases, cell death, allergies, osteoporosis and neurodegenerative disorders.
This invention includes compositions and methods for controlling the activity of p38 specifically in T cells through an alternate activation pathway.

Application area

By controlling p38 activity through interference with this alternate pathway, the T cells themselves can be controlled which in turn can be a treatment for conditions or diseases characterized by T cell activation such as autoimmune diseases, transplant rejection, graft-versus-host disease, systemic lupus erythematosus, and viral infections such as HIV infections.

Advantages

One major benefit for this invention is the development of small molecular inhibitors of the alternative p38 activation pathway (i.e. Gadd45a-mimetics). The inventors have found that Gadd45a specifically inhibits the activity of p38 phosphorylated on Tyr-323. p38 activated by MKK6 (which phosphorylates Thr-180/Tyr-182) is found not to be inhibited by Gadd45a. This emphasizes the specific nature of the activating modification and its regulation by Gadd45a, including its suitability as a tissue-specific molecular target.

Institution

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