STING PATHWAY MODULATORS FOR IMMUNOTHERAPY

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BRIEF DESCRIPTION

Using a genetic screen, the inventors identified ACBD3 as a gene involved in STING pathway activation via exogenously provided cyclic dinucleotides. ACBD3 recruits PI4KB to the Golgi, to stimulate PI4P accumulation in the Golgi. ACBD3 depletion in cells results in impaired STING activation in response to certain cyclic dinucleotides. A negative regulator of PI4KB recruitment to the Golgi is the protein OSBP.

The inventors propose that modulation of ACBD3 and OSBP functions can be used to modulate STING pathway function as a means to either enhance activation of the pathway in the context of immunotherapy, or inhibit pathway activation in the case of pathology resulting from inappropriate STING pathway activation. As a proof of principle, molecules that inhibit OSBP have been described (itraconazole and OSW-1), including one (itraconazole) that is FDA approved for treating fungal diseases albeit by a different mechanism. The inventors have shown that these inhibitors, which are predicted to increase PI4P accumulation in the Golgi, greatly enhance STING pathway activation induced by exogenously supplied cyclic dinucleotides. Conversely, the inventors find that genetic depletion of PI4KB depletes STING signaling in cells induced by STING agonists, indicating the potential of PI4KB inhibitors for treating inflammatory diseases that result from inappropriate STING pathway activation.

SUGGESTED USES

Possible applications include:

» Enhance the effects of STING agonists as cancer immunotherapies. This could include (i) co-injecting STING agonists and an OSBP inhibitor into tumors; (ii) injecting low doses of STING agonist systemically and OSBP inhibitors intratumorally; (iii) injecting STING agonists intratumorally and OSBP inhibitors systemically; (iv) injecting low doses of STING agonists and OSBP inhibitors systemically.

» Employ STING agonists combined with OSBP inhibitors for immunotherapy of viral infections.

» Enhance the immuno-therapeutic effects of chemo- and radiotherapies. In addition to killing tumor cells, chemo- and radiotherapies are known to activate the cGAS-STING pathway and can thereby promote anti-tumor immune responses. Combining OSBP inhibitors with chemo- or radiotherapy may therefore greatly amplify the anti-tumor immune responses that accompany chemo- and radiotherapy.

» Protecting specific tissues from STING pathway activation. STING pathway agonists such as CDNs, at high concentrations, can cause local tissue damage. In the context of systemic treatments with STING agonists (or systemic effects that result when STING agonists migrate out of a locally treated tumor), critical tissues may be protected if they are locally treated with a PI4KB inhibitor.

» Inhibit STING pathway activation in inflammatory diseases. Inappropriate activation of the STING pathway may underlie certain inflammatory diseases, including inflammatory bowel diseases, arthritis and possibly lupus. Inhibitors of PI4KB may be effective in ameliorating the pathological manifestations of such diseases.

ADVANTAGES

CATEGORIZED AS

» Biotechnology
» Health
» Medical
» Therapeutics

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2020-091-0

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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