NEUTROPHILIC CXCR2 AND BLT1: THERAPEUTIC TARGETS FOR ACUTE ITCH AND ECZEMA

Tech ID: 27120 / UC Case 2017-050-0

PATENT STATUS

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BRIEF DESCRIPTION

The inventors have demonstrated that CXCL1, a neutrophil chemotactic and natural ligand for CXCR2, robustly induces itch when injected subcutaneously in mice.

CXCL1 is the mouse homologue for human Interleukin-8, which is increased in several inflammatory skin disorders, including psoriasis and atopic dermatitis. The inventors have demonstrated that IL8 is increased in primary human keratinocytes upon activation by multiple itch agonists.

Importantly, CXCL1-induced itch is entirely dependent on neutrophils. Further, mice lacking TRPA1 show reduced itch responses to CXCL1, and TRPA1 has previously been implicated in several forms of histamine-independent acute and chronic itch. In addition, loss of TRPA1 results in reduced CXCL1 expression in skin. Blocking/ablation of the high-affinity LT4 receptor, BLT1, also results in reduction of CXCL1-induced itch. Both LT4 and reactive oxygen species (ROS) are produced by neutrophils and have been proposed to directly activate neurons and induce itch.

The inventors show that neutrophils also play a key role in chronic itch. In a mouse model of atopic dermatitis, depletion of neutrophils during induction of itch dramatically reduces itch and inflammatory responses. The inventors also show that CXCL1 is increased in multiple mouse models of chronic itch, and LT4 is increased in skin of mice with atopic dermatitis. They propose that neutrophils activate sensory neurons through the ion channel TRPA1 in a CXCL1/BLT1/LTB4-dependent fashion.

SUGGESTED USES

Diagnostic applications for chronic itch or hyperalgesia, treatment for eczema, treatment for allergic itch, psoriasis, or other inflammatory pain and itch disorders involving neuroimmune interactions. Treatment for atopic disease, including asthma.

Topically applied CXCR2 or BLT1 antagonists, oral CXCR2 or BLT1 antagonists, intradermally or sub cutaneously injected CXCL2 or BLT1 antagonist at the site of pruritus or pain. Itch diagnostics using levels of CXCR2 and/or LT4 and/or neutrophils at site. Biomarkers for disease severity. Depleting antibodies against neutrophils to stop itch and inflammation.

ADVANTAGES

In contrast to current itch therapies, which broadly target the skin barrier (e.g. lotions and creams) or the immune system (e.g. antihistamines, steroids and other immunosuppressant drugs), this invention proposes to employ existing and future inhibitors of the C-X-C Motif Chemokine Receptor 2 (CXCR2) and/or the Leukotriene B4 Receptor 1 (BLT1) in order to block itch or inflammatory pain induction mediated by neutrophils. The invention also employs the use of neutrophil depleting antibodies to block itch and inflammation in eczema, psoriasis, asthma, and other chronic inflammatory diseases.

Currently, patents exist for antagonists to BLT1, particularly for respiratory diseases like asthma and chronic obstructive pulmonary disease. Patents also exist for inhibition of enzymes involved in the production of Leukotriene B4 (LTB4), including 5-Lipoxygenase Activating Protein (FLAP), Leukotriene A4 Hydrolase (LTA4H) 4-6, and 5-Lipoxygenase (5-LD) 7 for inflammatory and skin diseases. However, no causal link between neutrophils and itch has previously been shown.

Antagonists to BLT12 and CXCR219,20 currently exist, so many possible therapeutic options will be available in the near future. Further, previous studies have shown no increase in adverse effects with systemic CXCR2 blocker treatment20. While TRPA1 blockers exist, these have not yet been tested in humans for chronic itch.