Novel Lumican-Binding Peptides Acting on the Toll-Like Receptor Pathway in Inflammation and Related Conditions

Novel peptides for treating conditions or diseases resulting from dysregulation in the immune system, such as septic shock, wound healing and autoimmune diseases.

Technology

The Chakravarti Lab at NYU Langone Health has designed a series of synthetic peptide antagonists of lumican (an ECM proteoglycan that is secreted by activated fibroblasts), which block CD14 binding and suppress inflammatory signals. The lab discovered that lumican modulates cellular uptake by caveolae-mediated endocytosis, promotes Toll-like receptor 4 (TLR4) response to bacterial lipopolysaccharides (LPS), and restricts nucleic acid–specific TLR9 in macrophages and dendritic cells. Lumican binds the TLR co-receptor CD14 and Caveolin 1 (Cav1) in lipid rafts, leading to enriched TLR4, CD14 and Cav1 on immune cell surfaces. On the other hand, endosomal lumican delays TLR9 trafficking and competes with CD14 to bind and sequester pathogenic DNA mimics, thus dampening TLR9 responses (Maiti et al., 2021).

Background

The extracellular matrix (ECM) is a network of proteoglycans and fibrous proteins that provides support and regulates cellular signaling and dynamics. Dysregulation of ECM-cell interactions is the basis of chronic inflammatory diseases and autoimmunity. The inventors have shown lumican plays a dual protective role in barrier tissues, one of promoting bacterial defense and another of limiting antiviral and autoimmune inflammatory responses. Both these activities may be effectively harnessed in therapeutics. While the crosstalk between ECM and immune cells was known to exist, the inventors discovered molecular intermediates that regulate the host's response to infections and inflammation. These findings provide the basis for improved compositions and methods for modulating ECM-cell interactions to resolve inflammation.

Applications

- Prevention and treatment of inflammatory, autoimmune (e.g., lupus, rheumatoid arthritis), and infectious diseases (e.g., sepsis), wound healing, ocular diseases and cancer.
- Potential use as combination therapy with other agents to increase their efficacy.

Advantages

Technology ID
CHA10-02

Category
Life Sciences/Biologics
Autoimmune Disease
Life Sciences/Therapeutics/Inflammat
Disease
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- Promising drug candidate for multiple disease indications TLRs have been implicated in various disease indications, such as bacterial infections, inflammation and autoimmunity.
- Broader applications These peptides may modulate Cav1-mediated cellular internalization and increase the efficacy of other agents.
- Peptides as therapeutic agentsPeptides are small, easy to synthesize and have other advantages over other drug modalities, such as high specificity and affinity.

IP Status

Provisional patent application pending

References

1. Maiti G, Frikeche J, Lam CY, et al. , Matrix lumican endocytosed by immune cells controls receptor ligand trafficking to promote TLR4 and restrict TLR9 in sepsis