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Small Molecule Inhibitors of Toll-Like Receptor 3 for Treatment of Inflammatory and Infectious Diseases

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Background

Toll-like receptors (TLRs) are highly conserved trans-membrane proteins that detect pathogen-associated molecular patterns and elicit pathogen-specific immune responses. TLR3 signaling is activated by dsRNA released from necrotic cells during inflammation or viral infection. TLR3 activation induces secretion of type I interferons and pro-inflammatory cytokines, such as TNF-R, IL-1, and IL-6, triggering immune cell activation and recruitment that are protective during certain microbial infections. TLR3 signaling has also been associated with increased susceptibility to herpes simplex encephalitis, and has been shown to contribute to morbidity and mortality in certain viral infection models, including West Nile, phlebovirus, vaccinia, and influenza. Therefore, modulation of TLR3 pathways offers an attractive strategy to fight a variety of diseases.

Despite the significant potential, the discovery of small molecule inhibitors of TLR3 has been slow due to the complexity associated with disrupting the protein-RNA contact: immense effort is required to design individual compounds that target specific RNA-binding domains with high binding affinity and selectivity.

Technology

A University of Colorado research group led by Hang (Hubert) Yin has developed a series of small-molecule probes that were shown to be competitive inhibitors of dsRNA binding to TLR3 with high affinity and specificity. In a multitude of assays, one compound (4a, see publication below) was profiled as a potent antagonist to TLR3 signaling and also repressed the expression of downstream signaling pathways mediated by the TLR3/dsRNA complex, including TNF-R and IL-1β.

A challenge in the development of inhibitors to target TLRs is to engineer specificity, there being at least 12 homologous TLRs present in murine macrophages, all sharing a ligand-binding domain. Dr. Yin's group tested their lead compound against a panel of homologous TLRs and found that compound 4a inhibited TLR3 signaling without affecting other TLRs, showing it is highly selective in intact cells. This compound also showed low cytotoxicity.

Key Documents

"Modulators of TLR3/dsRNA Complex and Uses Thereof." Patent application filed January 20, 2011; available under CDA.

Small-Molecule Inhibitors of the TLR3/dsRNA Complex. J Am Chem Soc. 2011 Mar 23;133(11):3764-7. *PDF available upon request.*