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The unique role of TLR3 agonists and its induced products of innate immunity as pharmaceutical agents efficacious against highly lethal emerging viruses

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The Toll-Like Receptors (TLRs) represent a family of class I transmembrane receptors that are elements of an ancient system of immune response to pathogen associated molecular patterns (PAMPs). TLR3 uses a unique non-MyD88 intracellular signaling pathway to induce innate immune responses including Type 1 interferons (IFN) with reduced inflammatory responses compared to the MyD88 pathway used by the other nine TLRs. The PAMP for TLR3 is dsRNA. Mis-matched base pairing configuration of the two RNA strands (rintatolimod) restricted binding to TLR3. Homologous dsRNA strand base pairing activates TLR3 and cytosolic helicases using the pro-inflammatory MyD88 pathway.

Emerging human viral pathogens represent major potential hazards to human populations in which innate immune defenses of the host are compromised. Recent emerging viruses with high lethality in humans include the avian influenza viruses and the human coronoviruses. As example there are six known human coronoviruses (Hu-CoV), four of which are responsible for mild "cold-like" symptoms. Two (MERS-CoV and SARS-CoV), however, have evolved an infectious advantage over the four mildly pathogenic human coronoviral species by inhibition of innate immune responses. Multiple components of MERS-CoV (M, ORF 4a/b, and ORF 5) inhibit the de novo production of a key component of innate immunity, interferon (IFN),that is an induction product of TLR3 activation. Data demonstrate that natural IFN (Alferon) as well as restricted activation of TLR3 by rintatolimod protect cells and/or animals from infection by emerging viral pathogens or cytokine storm associated pathology.

Biography

William Mitchell completed his MD from Vanderbilt University, was a house officer on Osler Medicine at Johns Hopkins Medical Center, and received his PhD in Biochemistry from Johns Hopkins University. He is Board certified in Clinical Pathology and serves as Professor of Pathology, Microbiology, and Immunology at Vanderbilt School of Medicine. He is an independent member of the Board of Directors for Hemispherx Biopharma (Philadelphia, PA) and Chronix Biomedical (San Jose, CA/ Göttingen, Germany).

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