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TITLE

PROTECTION AGAINST SEASONAL AND AVIAN INFLUENZA VIRUS INFECTIONS USING NUCLEIC ACID-BASED ANTIVIRAL AGENTS

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Due to the enormous diversity of influenza viruses and their ability to mutate and/or develop resistance to antiviral drugs and vaccines, there is a compelling requirement to develop potential approaches which offer broad-spectrum protection against all influenza strains. This paper describes nucleic acid-based antiviral agents for the activation of toll-like receptor (TLR) signaling pathways, and their protective antiviral effects against various deadly influenza virus strains. TLR-3 is transmembrane protein expressed on dendritic cells, respiratory epithelium, and macrophages, and it plays a central role in mediating both the antiviral and inflammatory responses of the innate immunity in combating viral infections. Influenza viruses can effectively inhibit the host's ability to produce interferons, and thereby suppress the immune system's antiviral defence mechanisms. Poly ICLC is a synthetic double stranded RNA comprising of polyriboinosinic-poly ribocytidylic acid (Poly IC) stabilized with L-lysine (L) and carboxymethylcellulose (C). Poly ICLC and liposome-encapsulated Poly ICLC (LE Poly ICLC) are TLR-3 agonists and are potent inducer of interferons and activator of natural killer cells. Intranasal pre-treatment of mice with Poly ICLC and LE Poly ICLC provided high level of protection against lethal challenge with a highly lethal avian H5N1 influenza (HPAI) strain (A/H5N1/chicken/Henan clade 2), and against lethal seasonal influenza A/PR/8/34 [H1N1] and A/Aichi/2 [H3N2] virus strains. The duration of protective antiviral immunity to multiple lethal doses of influenza virus A/PR/8/34 virus had been previously found to persist for up to 3 weeks in mice for LE Poly ICLC and two weeks for Poly ICLC. RT-PCR analysis of lung tissues of mice treated with Poly ICLC and LE Poly ICLC revealed upregulation of TLR-3 mRNAs gene expression. Taken together, these results do support the potential role of TLR-3 agonists such as Poly ICLC and LE Poly ICLC in protection against lethal seasonal and HPAI virus infection.
(up to 250 words)