Small molecular inhibitors of hedgehog protein signaling for treating or protecting against influenza infection

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Technology description

Researchers at UC San Diego, The University of Texas at Austin, and The Scripps Research Institute have demonstrated a new role for NS1 in modifying cell-cell signaling. This novel activity was identified by expressing NS1 in theDrosophilawing, which produced phenotypes similar to those caused by over-activation of a branch of the Hedgehog (Hh) signaling pathway. Genetic epistasis experiments indicate that NS1 carries out this function by acting at the level of Gli1/Ci, a key transcriptional mediator of the Hh pathway. They screened for NS1 mutants in which the Hh modulating activity was lost and identified a point mutation in NS1 that impairs this function and defines a novel interaction surface between NS1 and host factors. When this mutant was incorporated into a mouse-adapted viral strain, lethality of the virus increased and greater lung epithelial damage was observed, which could be partially rescued by treating the mice with an Hh antagonist. These results suggest that in addition to its multiple cell autonomous functions, NS1 also modifies communication between host cells, that paradoxically promotes host survival, perhaps thereby optimizing its likelihood for widespread propagation. This invention provides a novel intracellular target which is known to play an essential role in virulence of seasonal as well and highly virulent forms of influenza. Blocking essential host signaling systems such as the Hh pathways that are exploited by the pathogen may be more effective than vaccines and should complement or augment the efficacy of existing drugs acting on extracellular viral targets.

Influenza has been the cause of yearly epidemics and global pandemics throughout history. Due to the high degree of sequence conservation between disease genes in humans and flies,Drosophilahas been enlisted to serve as a powerful multicellular host model to identify novel interactions between viral proteins and host machinery. Among influenza's eleven viral genes, NS1 (nonstructural protein 1) is known to be indispensable for virulence. There are very few effective drugs to treat influenza infection and these drugs(e.g., Tamiflu) act on highly mutable extracellular proteins that function in the late phase of viral escape from the cell. Also, viral surface proteins which are the main targets for vaccines mutate rapidly to evade suppression. Knowledge of new host signaling responses to viral infection could lead to therapies targeted to these interactions. These treatments may be effective at suppressing the pathogenesis of many different strains of flu unlike vaccines which typically target only a few strains and require constant reformulation since the virus can evade host antibodies.

Additional Information

Additional Technologies by these Inventors

RNA Library from Drosophila Useful for Identification of Mammalian Signal Transduction Pathways

A Novel Genetic Method For Generating Gain-Of-Function Mutations

Application area

Small molecule inhibitors of Hh signaling could be supplied as pills, inhalers, or intravenously to 1) preventatively treat patients likely to have been exposed to influenza infection or 2) treat patients with infection who are suspected or known to be infected by the virus. This could provide a treatment that could be used either alone or in combination with existing drugs such as Tamiflu.

Institution

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