Extended Abstract

Nanomedicine 2017: Anti-fusion targeted nanomicellar theranostics: Novel antiviral strategies for respiratory syncytial virus infection-induced lung disease-Shyam S Mohapatra-University of South Florida, USA

Abstract

The respiratory syncytial virus (RSV), is an important pathogen that infects an estimated 64 million people and causes ~200,000 deaths globally every year. Despite progress in the biology of RSV, there is no effective treatment or vaccine against RSV infection. Currently, only high-risk infants receive antibody-based prophylaxis, which is expensive and moderately effective in reducing hospitalization. Therefore, a broadly applicable, effective and inexpensive approach to prevent or treat RSV-bronchiolitis or pneumonia remains an urgent unmet need. We have been investigating nanomedical approaches against RSV infection and have reported on a variety of different strategies including genome vaccine, and siRNA-based nanoparticles. More recently, we have developed a novel prophylaxis and/or therapy against RSV infection was inspired by the following discoveries: A platform of phospholipid micellar nanoparticles (PMN) was developed, which when given intranasally delivers payload predominantly to the lung, A decoy short heptad repeat (HR)2 peptide was identified, which effectively inhibits the RSV-cell fusion. iii) Human mesenchymal cells were found to be highly susceptible to RSV. The latter aided in establishing a novel 3D scaffold for anti-RSV drug screens, which consisted of creating a completely naked mouse lung scaffold (nMLS) by completely decellularizing and recellularizing the nMLS with desired human cells such as including hMSCs and epithelial cells and then infecting the cells in scaffold with RSV with or without drugs. A robust immunocompromised mouse model was created by combining cyclophosphamide treatment with infection by a highly mucogenic strain, RSV-L19F.

As a consequence, these advancements have led to the hypothesis that a RSV-targeted PMN (RTPMN), connecting HR2D anti-fusion peptide and plasmid encoded siENA s against RSV-NS1 can deliver a safe, effective and inexpensive anti- RSV prophylaxis and therapy. The accomplishment of preclinical formulation of anti-RSV PMN- based prophylactics and therapeutics is predicted to pave the way to IND-driven research and clinica Drugs that intervene with virus attachment, fusion or intracellular replication can inhibit infection. Anti-RSV antibodies intrude with the viral lifecycle by binding free virus (neutralizing antibody), attachment to host cell (antibodies to membrane-bound and secreted

vareties of attachment or G protein), virus-cell and cell-cell fusion (anti-RSV F Ab), inhibiting nucleoprotein (anti- RSV F Ab) or by inhibiting the organic feature of secreted surface glycoprotein G (anti-RSV G Ab). Two fundamental organizations of the virus, RSV-A and R.S.V-B, are 67% homologous at the level of necleotides and 53% homologous at the amino acid sequence of the G protein.

The Mechanism of RSV entry to a cell is not fully defined but it is explained that binding of fusion(F) protien to TLR4 receptor and that the G protein can act as a fractalkine receptor agonist mediating immune cell chemotaxis. The G protein is no longer required for viral entry as recombinant viruses Lacking the G protein stay infectious. The viral wall and cell membranes fuse, an impact mediated through F protein after they get bind and the nucleocapsid complex then enters the cytoplasm. The F protein is Largely conserved between stains (89% amino acid homology and 79% nucleotide) and anti-F antibody induced with the aid of important RSV infection is cross-reactive between group A and B virus. Antibodies against the G protein are largely group and even subgroup specifically. The finding of further receptors for RSV binding and uptake would be a prominent advancement.

Various microscopic molecules can intrude with the manner of fusion and several inhibitors of fusion (for instance, benzimidazole drugs such as BMS-433771 or TMC353121) are under advancement. At a higher level , interior a cell, small interfering RNAs (siRNAs) can target viral RNA that avid viral protein synthesis or molecules that inhibit function of key enzymes that may also dealing with replication and meeting of other viruses in addition to RSV. A good instance is VX-497, an inosine monophosphate dehydrogenase (IMPDH) inhibitor, developed originally and tested in clinical trials for the HBV treatment but with broad anti-viral activity. It is also proved that RSV might also cause persistent infection. Persistence has been verified in guinea pigs, cattle and mice. Persistent year-round RSV detection in patients with COPD is related with airway infection and accelerated decline in FEV1. Those with persistent RSV infections may, therefore, advantage from anti-viral drugs able to take away persistence, and, therefore, alter the natural history of COPD. In addition, tablets in a position to take away sources of RSV outbreaks in the neighborhood may want to probably make a contribution to limiting the incidence of RSV in young children.

Samples from RSV-infected infants display elevated IL-4/IFNγ ratios in infants during the first week of acute bronchiolitis compared with children with upper respiratory tract symptoms alone. regular with immoderate type 2 and/or deficient type 1 immune responses in RSV bronchiolitis. In mice, RSV contamination is associated with an increase in gamma-delta T cells that make a vary of cytokines, and depletion of these cells substantially attenuates disorder [30]. In man, RSV contamination has been reported to be related with reduced IFN-gamma production by using gamma-delta T cells, compared to a control group infected with rotavirus.

Studies of genetic polymorphisms point out that innate responses can also be especially important in explaining the variant in severity of RSV disease. In mice, macrophages play a key position in the early response to RSV infection. In human cells, they have been reported to upregulate Toll-like receptor three and four expression, consequently promotion sensitivity to bacterial endotoxin and other TLR4 ligands. The fact that common TLR4 polymorphisms exhibit a big affiliation with RSV bronchiolitis, and that TLR4 expression on

cells in the peripheral blood will increase all through bronchiolitis suggests that this effect may additionally be of widespread pathogenic significance.

The shut involvement of the host immune response in the pathogenesis of RSV disease suggests that it may be viable to regulate disease with anti-inflammatory or immunoinhibitory drugs. However, any attempt to restrict the immune response would have to be accompanied through therapy with especially fantastic antiviral drugs to forestall rebound of viral replication. Despite many trials of steroid therapy, there is no clear benefit. Inhibition of other inflammatory pathways ought to be tested as soon as robust antiviral pills are available trials.

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