Antibody Fragments Offer Possible New Therapy for Serious Viral Respiratory Illnesses

Antibody fragments introduced directly to the lungs have cleared a serious viral respiratory infection in mice, suggesting that a similar therapy may prove useful for such diseases in humans, report scientists from the National Institute of Allergy and Infectious Diseases (NIAID) and The Scripps Research Institute (TSRI) in the Feb. 15 Proceedings of the National Academy of Sciences.

"The therapy’s success may signal the beginning of an era of immunotherapy for infections by viruses that attack and grow in the linings of airways and lungs, such as respiratory syncytial virus (RSV) as well as influenza and parainfluenza viruses," says James E. Crowe, Jr., M.D., lead author of the study and a fellow in the NIAID Laboratory of Infectious Diseases.

In the study, the scientists cured RSV infection in mice using tailor-made pieces of human antibody, known as antibody binding fragments (Fabs), derived and produced using recombinant DNA technology in bacteria. The investigators delivered the Fabs directly into the lower respiratory tracts of the RSV-infected mice.

"This is the first time that a study has demonstrated the successful use of recombinant Fabs in a therapy for a viral infection in an animal," says coauthor Dennis R. Burton, Ph.D., professor at TSRI’s Departments of Molecular Biology and of Immunology. "This is particularly important because Fabs are inexpensive and easy to produce in bacteria."

"Our study suggests that Fabs may prove effective for treating serious RSV disease in the lower respiratory tracts of normal infants or the elderly as well as individuals of any age at high risk," adds Dr. Crowe.

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RSV is the leading cause of early childhood viral pneumonia and bronchiolitis--wheezy bronchitis--in the United States. Moreover, RSV-related illnesses are responsible for 90,000 U.S. hospitalizations annually. Worldwide each year, RSV causes about 1 million deaths among infants and young children, primarily in developing countries.

At greatest risk for death or long-term illness associated with RSV and similar respiratory viral infections are infants with congenital heart disease or bronchopulmonary dysplasia, a chronic disease frequently seen in premature infants who require support from a ventilator to breathe at the time of birth.

In addition, older children and adults with respiratory or cardiac anomalies have a high risk of developing serious RSV disease. Individuals with suppressed immune systems resulting from HIV infection or from receiving therapy for cancer or organ transplantation are at great risk as well.

The most recently developed experimental therapy for RSV disease relies on intravenous delivery of one type of whole antibody, a protein known as immunoglobulin G (IgG). This type of therapy contains only a small proportion of RSV-specific antibodies. However, the amount of IgG needed in the therapy can be reduced by a substantial amount by using human monoclonal IgG antibodies that are directed solely at RSV. Furthermore, IgG therapy can be made 80 to 160 times more effective, previous studies have shown, when delivered by aerosol, which carries the antibodies directly to the lung tissue that RSV infects.

However, only limited amounts of IgG can be safely and efficiently introduced into the lungs by an aerosol. By substituting the human monoclonal Fabs, fragments of IgG, the NIAID and TSRI scientists have reduced the quantity of protein needed to fight RSV by 2,000 to 8,000-fold.

"The success of the Fabs in mice has shown that RSV therapy can be improved using these fragments," says Dr. Burton. "If proven safe and effective for use in humans, Fab therapy could become important in the clinic in the management of respiratory viral infections in general."

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Fab therapy for RSV offers several advantages over using whole IgG, notes Dr. Crowe. Fabs can be made cheaply and easily in large amounts using bacteria, such as *Escherichia coli*, whereas IgG must be made by more complicated methods using animal cells.

In addition, Fabs lack structures common to IgG. IgG is shaped like a Y, with a Fab occupying the tip of each arm of the fork. An individual Fab has only one binding site that joins to RSV. In contrast, IgGs have two binding sites, permitting the antibodies to link up with several viruses into a chain-like immune complex. Such complexes can accumulate and cause damaging inflammation. Also, individual Fabs lack the IgG’s tail that is capable of triggering a cascade of harmful inflammatory reactions.

"Because of their simplicity, Fabs may be safer to use than whole IgG antibodies when treating RSV infections," says coauthor Robert M. Chanock, M.D., chief of NIAID’s Laboratory of Infectious Diseases. "The use of Fabs precludes a number of adverse effects whole antibody molecules can cause."

For the study, scientists screened many Fabs and found that in tissue cultures Fab 19 could neutralize RSV very efficiently by binding to a region of the virus. The investigators placed droplets containing Fab 19 into the lungs of anesthetized mice three or four days after their infection with RSV, a time when the virus replicates most actively. In four separate experiments, the investigators found that very small doses, up to 50 micrograms per mouse, could reduce the amount of RSV in the lungs 5,000 to 12,000 fold.

Moreover, the researchers could sustain the reduction and clear RSV if they gave the mice a daily dose of Fab 19 for three days. In contrast, the scientists could detect active RSV from untreated mice infected for the same length of time.

Fab-resistant strains of RSV could not be detected in the treated mice. However, to prevent resistance to RSV Fab therapy from developing in humans, the investigators suggest therapy should include one or more additional Fabs that can bind to other parts of the virus distinct from the region targeted by Fab 19.

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Other coauthors on the study include Brian R. Murphy, M.D., at NIAID, R. Anthony Williamson, Ph.D., research fellow in TSRI’s Department of Immunology, and Carlos F. Barbas III, Ph.D., assistant professor in TSRI’s Department of Molecular Biology.

NIAID, a component of the National Institutes of Health, supports investigators and scientific studies at universities, medical schools, hospitals and research institutions in the United States and abroad aimed at preventing, diagnosing and treating such illnesses as AIDS, tuberculosis and asthma as well as allergies. NIH is an agency of the U.S. Department of Health and Human Services.

TSRI is the nation’s largest non-profit biomedical research facility not affiliated with a university. Since its establishment in 1961, the Institute has become internationally renowned for its basic research into immunology, autoimmune diseases, neurosciences, molecular biology, chemistry and synthetic vaccine development. TSRI is divided into eight departments: cell biology, chemistry, immunology, molecular biology, molecular and experimental medicine, neurobiology, neuropharmacology and vascular biology.

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