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Are the Respiratory Organs Repository for Viruses?

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ABSTRACT

The earth is brimming with viruses. Mouth and lungs are the depository and repository of nearly 20 viruses. Infections of the respiratory tract may be caused by viruses, bacteria and fungi. Viruses are frequently responsible for upper respiratory illness. Influenza is a specific acute illness caused by a group of myxoviruses. It occurs in epidemics and occasionally pandemics, often explosive in nature. Respiratory syncytial virus is the most important respiratory pathogen of early childhood, especially, in the first two months of life. This is because it causes bronchiolitis and pneumonia, and carries a risk of mortality. The infant has fever, and cough, wheezy respiration and occasionally erythematous rash are prominent features. The virus is not susceptible to any known therapy, and immunization is ineffective. Influenza, parainfluenza and measles viruses rarely produce specific pneumonia. Pneumonia caused by chickenpox virus however is usually characteristic. The radiograph shows numerous miliary nodular shadows which may eventually calcify. It occurs almost exclusively in adults. The adenovirus cause occasional mild pneumonia.

INTRODUCTION

Monocytes, make an appearance in lung tissue, will start to modify into larger cells (1).

CD14 has been used as a marker in man (2).

This parenchymal lung infection often manifests as interstitial lung infiltrates and lung edema early in the course of disease (3).

Macrophages sense and respond to pathogens and other environmental challenges and participate in tissue repair after injury (4).

Macrophages have several origins during ontogeny and display great diversity (5).

Macrophages of different phenotypes recruited from the monocyte reservoirs of blood, spleen and bone marrow (6).

Newly emerged highly pathogenic (HP) H7N9 influenza virus, causative agent of human pandemic infection (7).

Influenza viruses are the most common causes of human respiratory infections (8).

Common cytokines, like interleukins (IL–2, IL-6) and TNF–a, are associated with the common symptoms of HPIV infection (9).

Ribavirin is potential for the treatment of HPIV-3. Ribavirin is a broad-spectrum antiviral and is currently being administered to those who are severely immuno-compromised (10).

In the United States, 60% of infants are infected during their first HRSV season, and nearly all children will have been infected with the virus by 2–3 years of age (11).

The Centers for Disease Control consider HRSV to be the "most common cause of bronchiolitis, and pneumonia in children (12).

Over the last two decades, there have been major advances in the understanding of Varicella infections, management and prevention (13).

Patients with impaired immune status and patients with chronic lung disease who develop primary Varicella-Zoster infection have an increased risk of developing pneumonia (14).

Complications of rhinovirus infections, which include otitis media, sinusitis, exacerbations of asthma, and other pulmonary diseases, can be significant in certain populations (15).

The disease, Influenza, is mainly caused by influenza type A and type B viruses, although influenza type A virus causes a more severe disease and is the only type that has caused pandemics in the past (16).

Currently, influenza type A virus is further classified into 18 HA and 11 NA subtypes.

Of these identified type A subtypes, only H1N1 and H3N2 are the major circulating viruses causing human influenza. There are 16 H and 9 N subtypes that cause infections in aquatic birds, and recently discovered H17N10 and H18N11 are bat influenza-like viruses (17,18).

A new strain of H5N1 HPAI virus with higher virulence reemerged in late 2003.

The virus spread globally and infected humans in 16 countries with a mortality rate of about 53% (19).

Thailand reported a total of 25 human cases with 17 deaths between January 2004 and July 2006. The kinetics and longevity of the antibody response for some of these patients as determined by hemagglutination inhibition (HI), microneutralization (MN) (8), and indirect immunofluorescence (IF) assays (20).

Chronological record of significant events

Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century.

In 1875, Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. Chickenpox is a viral infection caused by the varicella zoster virus (VZV). While the origin of the term chickenpox is unknown, some believe that it was derived from chickpeas due to the blisters' resemblance to chickpeas.

Respiratory syncytial virus (RSV) was discovered in 1956 and has since been recognized as one of the most common causes of childhood illness. It causes annual outbreaks of respiratory illnesses in all age groups. Adenoviruses were first discovered in 1953 by Wallace Rowe and his colleagues. Human adenoviruses (HAdVs) include 52 recognized serotypes assigned to 7 species (A–G) on the basis of biophysical, biochemical, and genetic criteria. (21)

The serotypes of subspecies B1 (HAdV-3, HAdV-7, HAdV-16, HAdV-21, and HAdV-50) generally cause acute respiratory disease (ARD). (22)

In 1959, Sabin proposed the name reovirus to reflect the fact that viruses of this group had been isolated from the respiratory and enteric tracts and were orphan (reo) viruses without known associated disease. (23)

Recent studies suggest measles potentially first appeared as early as the 4th century BC. (24,25)

The first systematic description of measles, and its distinction from smallpox and chickenpox, is credited to the Persian physician Muhammad ibn Zakariya al-Razi (860–932), who published The Book of Smallpox and Measles. (26)

Parvovirus B19 (B19) was discovered in 1974 and is the only member of the family Parvoviridae known to be pathogenic in humans.

Hantavirus pulmonary syndrome was first recognized during the 1993 outbreak in the Four Corners region of the southwestern United States. It was identified by Dr. Bruce Tempest. It was originally called Four Corners disease, but the name was changed to Sin Nombre virus after complaints by Native Americans that the name "Four Corners" stigmatized the region. (27)

Lung macrophages challenged with respiratory viruses

Most of the cells of the immune system derived from the hematopoietic system. Phagocytic cells are found in the circulation (Monocytes and granulocytes) and reside in the tissues (macrophages). Each cell type expresses characteristic surface molecules (CD3, CD4, and CD8.) Alveolar or pulmonary macrophages present freely on the outer surface of lung. These cells scavenging the dust particles, microorganisms and other debris. The primary function of macrophage is phagocytosis.

The macrophages by their property of amoeboid movement put forth pseudopodia which help in engulfing any solid particle such as the invading microorganisms. The macrophages have lysosomal granules, containing acid hydrolases and degradative enzymes with which it destroys the phagocytosed substances. The attachment of antigens to macrophage is specific. All the macrophages have surface receptors for C3 component of complement as well as for Fc component of antibody. The macrophages are involved in processing of antigens before they are presented to the T and B cells. (28)

Lower respiratory tract infection due to RSV is a complicated process and several cell types are implicated in the disease progression. (29)

Disease severity due to extensive lung tissue damage correlates with enhanced pro-inflammatory cytokine secretion and inflammation.

RSV infection of macrophage cells in the lungs of severely infected patients has been demonstrated (30), and these immune cells are proposed to play an important role in the early response to RSV infection. (31)

Pulmonary macrophage cells may behave differently with respect to RSV infection. (32)

The sustained pro-inflammatory cytokine levels even in the absence of a productive infection may help explain the persistence of symptoms that are associated with LRTI. (33)

Virus infections induce a proinflammatory response including expression of cytokines and chemokines. (34)

Macrophages are large eaters. These are the long lived phagocytes.

Alveolar or pulmonary macrophages are unique cells because they roam about freely on the outer surface of lung, where they are exposed to a constant supply of inhaled phagocytized particles. These cells move over alveolar surface, scavenger dust particles, microorganisms and other debris. The attachment of antigens to macrophage is specific. All the macrophages have specific receptors for C3 component of complement as well as Fc component of antibody.

Cellular mechanism involved in viral infection The C3 receptor promotes the adherence of antigen to macrophage by way of opsonization antigen by the complement whereas the Fc

receptors help in binding within the antibody there by promoting the phagocytosis of antigen antibody complex. Macrophages are involved in the processing of antigens before they are presented to the T and B cells.

When the antigen adheres with lymphocyte processing, receptors for the antigen, recognition takes place and thus the lymphocytes are induced to produce immunity. The macrophages that present antigens to T-helper cells (Th) should have MHC determinant of class 11 on the surface whereas macrophage that present antigens to T-cytotoxic cells (Tc) cells should have the MHC determinant, it cannot cooperate and thus antigen presentation cannot occur, which is known as MHC restriction Macrophages are important secretory cells producing and secreting a number of substances such as components of complement system, hydrolytic enzymes, toxic forms of oxygen and the monokines. The monokines have regulatory effects on lymphocyte function.

In some types of primary and secondary pneumonia, prominent features are destruction of lung tissue by the inflammatory process, a high incidence of abscess formation and the subsequent growth of pulmonary fibrosis and bronchiectasis. Research on Natural defenses against virus infection Virus neutralizing properties can be found in human plasma and interestingly enough in nasal secretions. The mechanism of the latter is particularly relevant to viruses of influenza virus which appear to possess a special mechanism of attachment to, and specific pathogenicity for, cells of ciliated epithelium of nasal cavity and bronchial epithelium. In 1942 Hirst found that influenza virus causes agglutination of chicken and red blood cells. The virus is first adsorbed to the cells for the time and then, quite spontaneously, releases itself. The freed virus is infective but red cell is modified so that it no longer agglutinates with the virus. The same attachment and release can be obtained in isolated preparations of lungs by allowing contact of the virus suspensions with the bronchial lining cells. The mechanism of attachment is due to the combination of an enzyme with its substrate. Attachment is only the start of the process of infection since virus particles can be altered by agencies such as ultraviolet radiation so that they can still agglutinate red cells but lack the ability to cause infection. Haemagglutination is inhibited by a component of normal serum by mucoprotein in mucus.

Isaacs and Lindermann, working with chick embryos which had been exposed to large amounts of inactivated influenza virus, found that an agent, named as interferon, was released after a few

hours into the fluid of the embryos. When applied to the pieces of fresh chorio-allantoic membrane, of preventing the growth of live viruses applied subsequently.

In case of pulmonary infection of mice with influenza virus, the amount of virus in the lungs begins to decline at the time when the interferon concentration reaches its peak, and antibody only becomes detectable later. Furthermore, animals which have been irradiated with X-rays so as temporarily to block antibody formation can still recover from virus infections in the normal way. (35)

Viral infections Viruses of many different kinds are inhaled and often they are trapped in the layer of mucus that coats the surface of the ciliated epithelial lining the upper respiratory tract. Rhinovirus for instance inhaled through the nose are engulfed in the mucous of the nasal passages and provided they are not inactivated by specific antibody or inhibited by other protective mechanisms, enter and infect the ciliated columnar epithelial cells.

As they multiply, the inflammation and irritation they set up is followed by the copious exudation of fluid that is the familiar rhinorrhea of common cold. At a lower level "mucociliary blanket" similar to that of the nasal passages extended from beneath the larynx to cover the bronchial tree as far as the finer bronchioles. Viruses eg.myxoviruses, are caught in the mucous and are swept upwards by the action of the cilia to be expectorated or swallowed.

Some however manage to adhere to and enter the underlying ciliated epithelial cells; if they have not been inactivated by specific antibody or firmly combined to glycoprotein inhibitor in the mucus, they are able to enter the host and initiate infection.

Laboratory Diagnosis

Detection of measles and Rubella, specific IgM antibody in an approved or certified laboratory - EXCEPT if the case has received a measles, Rubella -containing vaccine eight days to six weeks before sample collection and there has been no evidence of measles transmission in the community and no history of travel, or • IgG seroconversion or a fourfold or greater rise in titre to measles virus (where the second serum sample is collected at least 10 days after the first, acute sample).

1. Direct Examination of Specimen

Electron Microscopy morphology / immune electron microscopy Light microscopy histological appearance - e.g. inclusion bodies Antigen detection immunofluorescence, ELISA etc. Molecular techniques for the direct detection of viral genomes.

2. Indirect Examination

Viruses multiply only in living cells. They can be grown in animals, fertilized eggs or in cell cultures under strictly controlled conditions Cell Culture - cytopathic effect, haemadsorption, confirmation by neutralization, interference, immunofluorescence etc.

Eggs pocks on CAM - haemagglutination, inclusion bodies Animals disease or death confirmation by neutralization

Serology

Detection of rising titres of antibody between acute and convalescent stages of infection, or the detection of IgM in primary infection. Classical Techniques:

1.Complementfixation tests (CFT)

2.Haemagglutination inhibition tests

3.Immunofluorescence techniques (IF)

4.Neutralization tests

5. Single Radial Hemolysis

Newer Techniques

1. Complement fixation tests (CFT)1. Radioimmunoassay (RIA)2. Haemagglutination inhibition tests2. Enzyme linked immunosorbent assay (EIA)3. Immunofluorescence techniques (IF)3. Particle agglutination4. Neutralization tests4. Western Blot (WB) 5. ELISA5. Single Radial Haemolysis, 6. Recombinant immunoblot assay (RIBA), line immunoassay (Liatek) etc.

High Complexity Multiplex Panel Assays

Detection of respiratory pathogens by newer, nucleic acid amplification tests (NAATs)such as PCR, nucleic acid sequence-based amplification (NASBA), transcription-mediated amplification (TMA), strand displacement amplification (SDA), loop-mediated isothermal amplification (LAMP), rolling circle amplification (RCA), etc., have gained immense popularity over the past decade. (36)

Research on viral infection of the lung: Host Response and Sequelae

The recognition of pathogen-associated molecular patterns by the pattern recognition receptors such as the stromal cells (CD45-) and cells in the lung (CD45+) is the key to initiate the host immune response to the microbial invasion.

As well as the recognition of damage-associated danger signals are important to activate the intracellular innate protein complex, the inflammasone, which are responsible in the organization of both the innate and adaptive immune responses. In response to a viral respiratory tract infection, interferon (type I and III) are produced by the recognition of the melanoma differentiation-associated protein 5 and the retinoids acid-inductively gene I, both cytotoxic receptors, will recognize the double-stranded RNA.

Unknown cytosolic DNA receptors or DAI will recognize the double-stranded DNA. Retinoids acid-inductively gene I is also triggered by 5'-pppRNA from the transcription of double-stranded DNA, using an RNA polymerase III. After the recognition has been made, the interferon regulatory transcription factors will be activated through the kinase TANK-binding kinase; which then lead to the production of interferon type I and III in the site of the viral infection.

Viral molecules arrive to their respective TLR3, TLR4, TLR7, and TLR9 which will then stimulate through the adaptor protein molecules for the production of interferon type I; leading to the transcription of interferon genes and pro-inflammatory cytokines. Type I interferons (IFN-a, IFN-ß) and type III (IFN-?) share many functions, including induction by viral infection, activation of shared signaling pathways, and transcriptional programs. Interferon type I binds to the receptor IFNAR2 with high-affinity, which then activates a low-affinity IFNAR1 to form a signaling complex.

Interferon type III binds to a high-affinity IFNLR1 receptor that then activates a low-affinity IL-10Rß to form a signaling complex. IFN type I has a faster, more potent and transient response, than the IFN type III, which is less potent and slower. A systemic response is due to the response of IFN type I in many cells; in contrast with IFN type III that is concentrated at the epithelial life and barrier surfaces.(37)

The viral infection also results from the injures or dying cells as with the healthy neighboring tissue.

Damage-associated signals are molecules leaked or actively release into the extracellular when there is damage or cellular stress. These molecules (nucleotides, heat shock proteins, nuclear proteins, mitochondrial DNA, cytokines, and reactive oxygen species) are recognized by neighboring cells, such as antigen-presenting cells, responding in the activation of caspase-1, which aids in the maturation and release of active IL-1ß and IL-18.(38)

Inflammasomes are large multiprotein complexes that are activated by respiratory tract viruses and as they sense the pathogen-associated pattern molecules using the pattern recognition receptors (PRPs), expressed in macrophages, monocytes, dendritic cells, neutrophils, epithelial cells, and cells of the adaptive immune system.

These cytoplasmatic sensor molecules like NLRP3, absent in melanoma 2, the adaptor protein ASC, and the effector protein procaspase-1. The caspase-1 activation result in the caspase-1-dependent proteolytic maturation and secretion of interleukins (IL-1ß and IL-18). This then activates the expression of other immune genes and recruitment of lymphocytes to the site of infection.

The inflamasome canter the viral replication and removal of infected immune cells through pyroptosis. (39)

Complement system is activated locally and systemically during pulmonary viral infection and is the bridge between innate and adaptive immune systems. It’s specific contribution to lung diseases are just beginning to emerge.

Pneumocyte type II epithelial cells synthesize and secrete complement proteins C2, C3, C4, C5 and factor B, and human bronchiole epithelial cells secrete C3. Inflammatory cytokines can

trigger the complement system in local polymorph nuclear leukocytes, epithelial cells and fibroblast. (40,41)

The adaptive immune system is responsible of the viral clearance and the recovery of the lung functions.

Cytotoxic CD8+ T-cells and the antibody response plays important roles to clear the virus from the airways. The adaptive immune cells, CD45+ innate immune cells, and CD45- lung stromal cells begin the process of restoring the normal structure and function to the infected lung.(42)

The restoration of the lung tissue restores the lung barrier integrity and essential cellular functions, with the elimination of the cellular debris due to the infection.

The restoration process is divided into three phases that overlap with each other. Local spreading and migration of neighboring epithelial cells to the cleared area of infection. Migration and proliferation of stem cells to repopulate the lost epithelium.

The differentiation of stem cells and epithelial cells to restore the barrier and respiratory function.(43)

Sequelae after a viral respiratory tract infection may have many manifestations systemically such as central nervous system inflammation, myositis or myopathies, myocarditis, increase risk for asthma, and increase risk of bacterial infections.

How targeting killer T-cells in the lung could lead to immunity against respiratory viruses- The CD8 T-cell response to respiratory viral infections The respiratory mucosa is highly susceptible to viral infections and the severity of the disease is closely associated with the type of viral strain, the age and immune status of the host.

To this the main strategy employed in the vaccine development is the induction of robust neutralizing antibody response, but it is suggested that the antibodies response to the respiratory viruses may decrease over time. CD8 T-cells are responsible in virtual clearance, so the induction of virus-specific CD8 T-cells response could improve the efficacy of vaccination strategies.(44,45)

The dendritic cells have taken the viral antigen, after an acute respiratory infection, activates the naive CD8 T-cells in the lymph nodes of the lungs to produce virus-specific CD8 T-cells response: increase the number and frequency of total and antigen-specific CD8 T-cells in the airways and lungs.

The maximal peak expansion of the antigen-specific CD8 T cells corresponds to the lung viral clearance. Afterwards, the CD8 T-cells decreases and the memory virus-specific CD8 T-cells remain in the lung parenchyma.(46,47)

The virus-specific CD8 T-cells will remain in the host lung parenchyma to form a long-lasting memory population that will provide protection to subsequent infections, regulated by inflammatory chemokine signaling.

Even though these populations of virus-specific CD8 T-cells can be detected several months after the infection, they will decline severely with age in the peripheral blood.(48,49)

There is another population of CD8 T-cells that are present in the peripheral tissues, such as gastrointestinal tract, skin, female reproductive system and lungs, known as tissue-resident memory CD8 T-cells.

The virus-specific tissue-resident memory CD8 T-cells are found at large in the large airways and tissue surrounding bronchioles and alveoli; below the basement membrane and cluster in lymphoid structures to optimize its interaction with the antigen-presenting cells. They can be identified by their expression of CD69 and CD103, which promote their migration and retention to the lung tissues.

Even though the tissue-resident CD8 T-cells are crucial in the first-line defense from re-infection, they exhibit short longevity (months) and enhanced apoptosis after the infection. (50,51,52)

The CD8 T-cells have an important role in viral clearance after an acute respiratory viral infection. Pre-existing CD8 T-cell numbers, CD8 T-cell effector functions correlate with a reduced viral load.

The CD8 T-cells use various mechanisms to induce apoptosis of virus-infected cells. First, use a direct cell-to-cell contact through surface molecules such as Fas (CD95) and FasL (CD95L). The TRAIL expressed on the CD8 T-cells interact with receptors CD4 or CD5 to induce destruction, as well.

Finally, the CD8 T-cells produce inflammatory cytokines (IFN-gamma and TNF) that will directly or indirectly promote lysis of the infected cells. (53,54)

Research programs for the next generation world

The main goal of most vaccination strategies is to be able to induce a strong and healthy virus-specific neutralizing antibody response in the host. By doing so through the induction of virus-specific CD8 T-cell response and its humoral immunity.

This dual approach may allow optimal viral control. Nowadays with viruses such as Respiratory Syncytial Virus, Parainfluenza Virus, Influenza Virus, Human Metapneumovirus, Rhinovirus, Parainfluenza Virus and Coronavirus. Researches are exploring different technologies to tackle with these respiratory infections. Virus vaccines: by using the virus in a weakened form or inactivated.

Viral-vector vaccines: by genetically engineering the measles of adenovirus (weakened) to produce coronavirus proteins in the body. Two types are those that can still replicate within the cells without producing a disease and the other one that cannot reproduce in the cells by disabling key genes. Nucleic-acid vaccines: by using genetic instructions, in the form of DNA or RNA, for a coronavirus protein that will encourage in the host the immune response.

The nucleic acids are inserted into human cells that will churn out copies of the virus protein. Protein-based vaccine: injection of the virus proteins, fragments or protein shells that mimics the virus outer coat, directly into the host. (55)

Immunity

After an attack of influenza, the ensuing immunity persists for an year or more and confers resistance to the virus strains concerned. It is related to the amount of neutralizing antibody (IgA) in the mucous secretions of the respiratory tract as well as to the titre of serum antibodies. The

greatest incidence in measles is the age group 1-5 years, and by the age of 20 years, 90 % of persons have had an attack of the disease. After first six months of life passively acquired maternal immunity disappears and susceptibility is practically universal. Infection with the respiratory syncytial virus appears to be common in 66% of all persons over the age of 5 years possess both complements fixing and neutralizing antibodies in serum; and over the age of 15-years,93 % have neutralizing antibodies. One attack of Rubella confers life-long immunity. Immune mothers transmit antibodies to breast fed infants. With reference to RSV, IgA in nasal secretions appears to be protective against reinfection.

Treatment and prevention

Influenza patient should be kept in bed until the fever has subsided. A mild analgesic usually relieves the head and backache. Vaccine is administered in cold countries to protect elderly people with preexisting cardiopulmonary or nasal disease and to other high-risk individuals with influenza outbreak is imminent. Objective of vaccination in Rubella is to protect unborn babies rather than the vaccine. Live attenuated vaccine, RA 27/3 grown in human diploid cell is now widely used. Recently, measles vaccine is being used in combination with mumps and rubella (MMR Vaccine). RSV is worldwide in distribution and causes a winter epidemic in infants and children below one year of age Both formalin inactivated crude whole-virus vaccine as well as live vaccine have been tried but none is found satisfactory. Attempts to prepare vaccine with purified F and G surface glycoproteins of RSV are in progress.

CONCLUSION

With the notable exception of influenza viruses, there are no approved vaccines for the prevention of most respiratory viral infections despite continual efforts in this field. However, the immunoprophylactic agents RespiGam and Synagis constitute an effective strategy for the prevention of severe HRSV infections in premature and at-risk infants. (56)

Advances in immunology, immunopathology, and immunopharmacology have already opened a way to a clearer understanding of the nature of certain respiratory diseases. Immunology has a further contribution to make in the field of respiratory infection.

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