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Pathogenesis of Viral Respiratory Infection

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Additional information is available at the end of the chapter

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1. Introduction

Speaking of viral pathogenesis, it must describe the features and factors of viral pathogen, hosts and environment. Over its lifetime, an individual is exposed to many infectious agents, however, in most situations does not develop a disease thanks to factors such as physical and chemical host barriers. In other cases, pathogens circumvent these barriers and cause infection; however, a “biological war” will start between the determinants of pathogenicity and early host defenses. If the virus is able to overcome these first lines of defense, a type of highly specialized and specific protection will be activated. This defense will achieve, in most situations, the infection control and subsequent eradication of the disease. Furthermore, this process will initiate the generation of the immunological memory, enabling the individual with a more quickly and effectively response at the next contact with the same agent. On the contrary, if the foreign agent can overcome both defenses, the result is disease. In certain cases, the line of defense, when triggered, can also cooperate with the damage instead of healing, making the disease more severe. Thus, the immunopathology viral respiratory infection is a frequent consequence of the immune response against many of respiratory pathogens. Furthermore, if the infection is established, the factors or viral virulence determinants and physiological conditions of the host cell will determine which direction the infection will take. A virus is pathogenic when it is able to infect and cause disease in a host, while it is virulent when it causes more severe disease than another virus of a different strain, although both remain pathogens. Each virus can cause different cytopathic effects in the host cell, which may lead to several symptoms and disease. In addition, developing a disease reflects the existence of an abnormality of the host, either structural or functional, induced by the invading virus.

2. Viral pathogenesis

The term “pathogenesis” refers to the processes or mechanisms to generate an injury or illness, in this case induced by a viral infection. The results of a viral infection depend on factors related to the nature of the virus, the host and the environment. They include: number of infectious particles, the way to reach the target tissue, the rate of multiplication, the effect of virus on cell functions and the host’s immune response. Three requirements must be satisfied to ensure the infection of an individual host [1]:

- Sufficient virus must be available to initiate infection,
- Cells at the site of infection must be accessible, susceptible, and permissive for the virus
- Local host anti-viral defense systems must be absent or initially ineffective.

To infect its host, a virus must first enter cells at a body surface. Common sites of entry include the mucosal linings of the respiratory, alimentary and urogenital tracts, the outer surface of the eye (conjunctival membranes or cornea), and the skin.

Among the factors that affect the infection process are:

1. **Virus-dependent factors.** They usually are dependent on the virus structure.
 - a. **Virulence.** Virulence is under polygenic control and is not assignable to any isolated property of the virus, but is often associated to characteristics that favor viral replication and cellular injury. For example, virulent viruses multiply themselves readily at high temperatures prevailing during the disease, block the synthesis of interferon and macromolecules related to immune system. Viral virulence is a quantitative statement of the degree or extent of pathogenesis. In general, a virulent virus causes significant disease, whereas an avirulent or attenuated virus causes no or reduced disease, respectively.
 - b. **Measuring Viral Virulence.** Virulence can be quantified in a number of different ways. One approach is to determine the concentration of virus that causes death or disease in 50% of the infected organisms. This parameter is called the 50% lethal dose (LD50), the 50% paralytic dose (PD50), or the 50% infectious dose (ID50), depending on the parameter that is measured. Other measurements of virulence include mean time to death or appearance of symptoms, as well as the measurement of fever or weight loss. Virus-induced tissue damage can be measured directly by examining histological sections or blood samples. For example, safety of live attenuated poliovirus vaccine is determined by assessing the extent of pathological lesions in the central nervous system in experimentally inoculated monkeys. Indirect measures of virulence include assays for liver enzymes (alanine or aspartate amino-transferases) that are released into the blood as a result of virus-induced liver damage [1].
 - c. **The amount of inoculum.** The impact of virus dose on the outcome of infection is poorly understood. It has been shown that, for rhinovirus, the size of the inoculum contrib-

utes to the kinetics of viral spread [2]. The amount of virus inoculated may influence or determine if it causes a mild or severe infection.

- d. **Speed of replication.** Some viruses replicate so rapidly that they often cause acute infections, others are slow virus replication, or some have to travel greater distances, which slows replication.
- e. **Viral Spread.** Following replication at the site of entry, virus particles can remain localized, or can spread to other tissues. Local spread of the infection in the epithelium occurs when newly released virus infects adjacent cells. These infections are usually contained by the physical constraints of the tissue and brought under control by the intrinsic and immune defenses. Respiratory infections are the typical example of local spread. An infection that spreads beyond the primary site of infection is called disseminated (for example: measles virus). If many organs become infected, the infection is described as systemic. For an infection to spread beyond the primary site, physical and immune barriers must be breached. After crossing the epithelium, virus particles reach the basement membrane. The integrity of that structure may be compromised by epithelial cell destruction and inflammation. Below the basement membrane are sub-epithelial tissues, where the virus encounters tissue fluids, the lymphatic system and phagocytes. All three biological environments play significant roles in clearing viruses, but also may disseminate infectious virus from the primary site of infection. One important mechanism for avoiding local host defenses and facilitating spread within the body is the directional release of virus particles from polarized cells at the mucosal surface. Virions can be released from the apical surface, from the basolateral surface, or from both. After replication, virus released from the apical surface is outside the host. Such directional release facilitates the dispersal of many newly replicated enteric viruses in the feces (e.g., poliovirus). In contrast, virus particles released from the basolateral surfaces of polarized epithelial cells have been moved away from the defenses of the luminal surface. Directional release is therefore a major determinant of the infection pattern. In general, viruses released at apical membranes establish a localized or limited infection. Release of viruses at the basal membrane provides access to the underlying tissues and may facilitate systemic spread [1].
- f. **Virulence genes.** Despite modern technology, identification and analysis of virulence genes is not easy. Part of the problem is that many of the effects of viral pathogenesis are the result of the action of the immune response mechanisms, including both innate and adaptive, and can not reproduce these effects in tissue culture assays. Another problem limiting the studies is that no one knows precisely what is being observed and what for. So, to address this field, most studies begin with the premise that if a virus has a defective virulence gene, it may not cause disease or, if at all, can only cause a weak disease, such that this reasoning can cause confusion. Molecular directed mutations has been a tool that, although difficult to control, has greatly contributed to the characterization of virulence genes. Thus, the reversion of mutations (mutations repair), the mixture of mutant and wild viruses, among others, have identified genetic defects in virulence. Some mutations lead to eliminated, reduced or increased protein function, whereas other proteins affect

the level of transcription, translation or replication of the genetic information [1]. The viral genes that affect virulence status can be classified into four groups or classes: 1. those affecting the ability of the virus to replicate; 2. genes that modify the host's defense mechanisms; 3. genes that allow the virus to spread in the host, and 4. genes that codify proteins having toxic effects [1].

2. **Host-dependent factors.** There are factors that are innate to host such as: race and genetic load, sex, age, immunological and nutritional status, weight, etc.. These factors and the presence of specific cellular receptors for a given virus can determine resistance or susceptibility to viral infection. Subsequently, adaptive immune defense will enter into action and influence the success or the elimination of the infection.

Cellular virulence genes. Numerous studies have shown that certain cellular genes can be considered as virulence determinants [1]. Among the candidate genes are genes encoding components of the host immune response such as proteins required for T- and B-cell function, as well as cytokines. When these genes are altered, proteins do not perform correctly their function, which can have adverse effects during viral infection; thus, the disease may be more or less severe. Other candidate genes are cellular genes that encode proteins required for replication, translation, transcription and mRNA synthesis and are considered cellular virulence determinants; however, there are few studies that demonstrate this condition [1]. This field is still poor studied, but with the current tools and knowledge on the pathogenesis mechanisms, results are being achieved that in a near future will help us to learn more about the subject.

3. **Environmental factors.** Environmental conditions such as temperature, moisture, pH, aeration, etc., can influence the viability of the virus before reaching their target organ and affect or facilitate its infectivity. A well-known example is the winter predominance of respiratory viral viruses and the summer propagation of enteric viruses.

3. Cellular level pathogenesis

Molecular interactions between the virus and the cell result in a phenomenon called pathogenesis. It can be analyzed at different levels ranging from the early interactions (cellular receptors) to the expression and suppression of cellular and viral genes, resulting in the production of inflammatory, pro-apoptotic or anti-apoptotic proteins, whose presence or absence induce the activation of complex networks of proteins that interact in cellular signaling pathways [3]. The sensitivity or resistance of a cell to viral infection is determined by early interactions with the virus, such as the adhesion and release of nucleic acids in the cell, and is strongly related to the characteristics of the cell, such as physiological maturation, genetic characteristics and specific receptors for a given virus [4].

Molecular gateway and viral spread. The site of entry of a virus is defined by the presence of specific receptors for a virus. Also, the gateway sets the path of its spread and consequently the disease process, which in some viral infections are not always predictable.

Usually, viruses that cause respiratory infections penetrate through the epithelium replicating at the site and causing localized infections. Sometimes, as in the case of herpes infection, virions bind to nerve endings in the nasopharyngeal cavity until they find the trigeminal ganglion and even spread to the brain, causing encephalitis; other viruses, such as measles, rubella, mumps etc., may enter through airways not being this site its target organ, so viral particles will be spread through various mechanisms.

Tropism. It is the ability of a virus to infect or damage specific cells, tissues, organs or specific cells. In some virus is strictly limited, other are pantropic and are able to infect and replicate in different types of cells and tissues. The tropism contributes significantly to the virulence and pathogenesis of viral infections, and is determined by several factors that intervene in the virus-host relationship such as the gateway and route of viral spread, the permissibility of the cell (receptors, cell differentiation), the nature of the innate and adaptive immune response of the host and specific tisular features.

Cell membrane receptors. A cell may be susceptible to viral infection if viral receptors are present and functional. In other words, if the viral receptor is not expressed, the tissue can not be infected. In epithelial cells from human respiratory tract, some receptors have been identified such as N-acetyl neuraminic acid, glycosaminoglycans and glycolipids, ICAM integrin and molecules of the Major Histocompatibility Complex. In airways the sialic acid receptor that binds to the influenza virus has been identified. This receptor is found in several tissues of the body, although the infection in humans is restricted to the respiratory tract. Influenza A viruses infect a variety of animals. While viruses that infect humans bind to sialic acid type α -2,6, in birds they bind to α -2,3 type that is localized in the gastrointestinal epithelium where the virus replicates. In pigs, the virus can recognize both types, which facilitates the generation of gene arrangements between strains of different origin [1, 5, 6].

Virus-cell interaction. The interaction of a virus with its cellular receptor is mediated by one or more surface proteins. In enveloped viruses, the envelope glycoproteins (e.g. the influenza virus hemagglutinin); in naked viruses, the capsid proteins (e.g. exon protein of the adenovirus). Enveloped viruses have the ability to fuse directly to the cell membrane allowing the entry of the nucleocapsid into the cytoplasm. Naked viruses and some enveloped viruses have the capacity to fuse to the cell membrane by means of endocytosis. Some viruses require co-receptor molecules to penetrate the cell as happens with Adenovirus [7].

Some viruses require cellular proteases that cut viral proteins to form an infectious viral particle. During an influenza virus infection, a cellular protease cuts an HA precursor generating two subunits in order to activate and allow the fusion between the viral envelope and the cell membrane. It has been described that alterations in the cleavage site of the HA of influenza virus causes changes in the pathogenicity of the virus, in fact, highly pathogenic strains of birds contain multiple basic amino acids at the cleavage site of the HA that is recognized by different proteases. As a result these strains are capable of infecting various organs such as spleen, liver, lung, kidney and brain. This same cutting activation procedure is performed with the F protein of the virus of the *Paramyxoviridae* family.

Sensitive cells. These cells have specific receptors on the cell membrane, capable of interacting with the virus antigenic proteins and to allow the infectious process. According to whether the cell allows or not the virus replication, it can differentiate them into permissive and non-permissive [8].

Permissive cells. Are those that allow the virus enter and allowing the complete viral life cycle, dividing, and producing offspring. So, the virus enters to the cell cytoplasm or nucleus, depending on the type of virus. In what is called early phase, several viral components are synthesized such as viral proteins. In the subsequent phase, these components are assembled and, in the final or lytic phase, cell death occurs, then freeing new generation virus. The infection becomes productive.

No permissive cells. These cells have viral receptors, but not allow productive infection. The infection is aborted at any step of the viral replication cycle. Upon access of the virus to these cells there is no synthesis of viral components. In some cases, if the virus is lysogenic, or it is an oncogenic virus, it can be observed the phenomenon of integration of the viral genome into the host 'genome.

Resistant cells. In all types of infection, the initial event is the interaction between the virus and the corresponding receptor present on the cell surface. If a cell lacks the appropriate receptor for a particular virus, is then automatically resistant to infection by that virus [8].

4. Cell damage caused by virus and cytopathic effect

Virus-induced cell damage. This damage may be a direct result of viral replication as well as the innate or adaptive immune response of the host; here we mention only those caused by viruses.

Direct effects on cells mediated by cytopathic viruses. Viruses cause morphological alterations known as cytopathic effect (CPE) and occur in both the cells of living organisms and *in vitro* culture cells. The alterations produced in virus infected cells ranging from those that do not immediately lead to cell death and those that destroy rapidly and kill the infected cell.

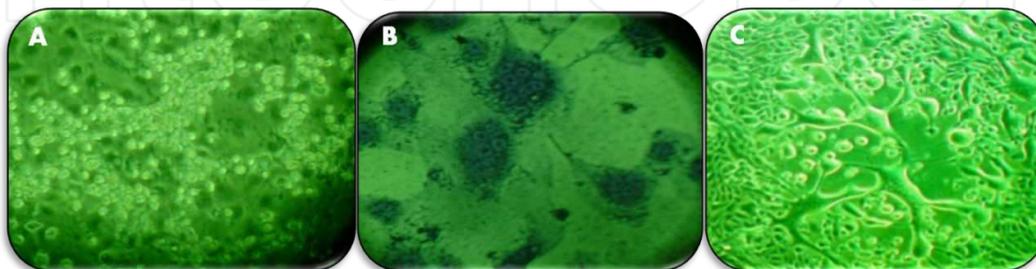


Figure 1. Diferent cytopathic effects in cell cultures. A) MDCK cells infected with influenza A H1N1 virus; B) A549 cells infected with respiratory syncytial virus, the virus includes syncytia formation; C) Vero cells infected with herpes simplex virus 1, the cytopathic effect of the virus is also the syncytia formation.

During the viral infection, cells may respond in different way, such that the ECP is different for each type of virus which might allow us to identify the virus. However, there are cases in which the cells show no apparent change. The ECP is a manifestation of the infectious process, and is defined as "morphological and functional changes of cells caused by a virus and is visible under the microscope, resulting in cell death". In cultures infected with influenza virus, cells were rounded and clustered like a bunch of grapes (Figure 1a) Adenovirus also rounded the cells but retract into a sphere. Respiratory syncytial virus (Figure 1b) and herpes simplex type I and II induce fusion of cell membranes forming syncytia or multinucleated giant cells (figure 1c).

Alteration of membranes. The plasmatic membrane is the first part of the cell with a virus contacts, this interaction occurs at the junction between the individual components of the cell surface proteins and the virus surface. After entry of the intact viral particle, and if penetration was by endocytosis, the genome is released into the cytoplasm after disruption of the membrane endocytic. In the case of paramyxovirus, a family of enveloped viruses and RNA genome, viruses contain two glycoproteins on its surface, one is the F protein that is able to initiate membrane fusion at acidic pH, the viral genome is introduced directly into the cell as a result of the fusion between the viral envelope and the cell plasma membrane. During the acute infection by cytolytic virus, especially the non-enveloped in the infected cell which finally releases large amounts of virus, the plasma membrane is damaged until to rupture. At this time, cytoplasmic proteins that are filtered, and ions such as Na^+ and K^+ allow the entry of water and the development of cellular inflammation (cell swelling), which leads to cell lysis.

Cell lysis. Besides membrane damage by the entry of viral particles there are difference cell membrane alterations, including the nucleus and organelles that lead to cell lysis. Cell lysis is mainly due to the inhibition of cellular macromolecular synthesis by some viral proteins. DNA viruses inhibit early the cellular DNA synthesis and during late periods cellular RNA and proteins (e.g. adenovirus). RNA viruses inhibit the synthesis of RNA and proteins from earlier periods. The accumulation of viral products causes cell lysis and release of virions.

Effect on the cytoskeleton. Some viral and cellular proteins synthesized during infection act on the cell cytoskeleton. This alteration induces that cell is made round; this occurs mainly in cells infected with adenovirus. Other changes in the cytoskeleton are caused by oncogenic viruses that cause a cell morphology change (e.g. human papilloma virus in laryngeal papillomatosis). Cells that possess cilia, such as respiratory tract, lack their ciliary functionality during influenza virus infection [9].

Cellular fusion. Some viruses have structural proteins (e.g. F protein) which have the property of fusing cell membranes. In infected cells, same viral protein allows the fusion between neighboring cells, giving rise to multinucleated cells that are called polykaryocytes or syncytia. Among the viruses that show syncytia formation are RSV, measles, parainfluenza, herpes simplex, as they have fusion proteins and are able to move from one cell to another without having to leave cell.

Inclusion bodies. The inclusion bodies are intracellular granules consisting by virions or viral subunits. Its location is variable, can be intracytoplasmic as those induced by rabies virus, nuclear such as adenovirus or those caused by the virus of measles which are both nuclear and intracytoplasmic. Another example is the eosinophil corpuscles observed in cells infected by herpes simplex. Inclusion bodies break or change the cellular structure and function inducing cell death [1].

Induction of chromosomal aberrations. Viruses can cause changes at nuclear level that lead to the disintegration of the chromatin of infected cells as occurs in the herpes simplex virus infections. However, nuclear or chromosomal abnormalities can be as subtle to be detected by molecular methodologies, as example, as in the integration of viral genomes into the cellular genome during transformation mediated by certain viruses, in which the cell is alive, but altered in its properties. Other viruses that cause aberrations are mumps virus, measles, rubella, parainfluenza and adenovirus [10].

Cellular Transformation and cell proliferation. DNA and RNA viruses may integrate its genome into the cell, generating transformed cells that behave similarly *in vitro* to cancer cells. Cellular transformation corresponds to a phenomenon that occurs both *in vivo* and *in vitro* and has yielded valuable information regarding the etiology of certain cancers. Some viral proteins inactivate cell proteins which control the cell cycle and hyperplastic processes occur, inducing proliferation or cell growth, for instance, papilloma virus causing laryngeal papillomatosis that can lead to cancer [11]

5. Description and characteristics of virus

Viruses are microscopic infectious agents that are composed of genetic material (DNA or RNA), surrounded by a protein coat called capsid (naked virus), other viruses have a lipid membrane (enveloped viruses) showing glycoprotein spikes. The entire infectious unit is called virion. The proteins of the capsid of both, naked and enveloped viruses and the glycoproteins of enveloped viruses are the major antigens for inducing immune response of the host. The viruses replicate only in living cells, its genome contains the information needed to program the host cell to synthesize the virus specific molecules required for production of viral progeny [11, 12].

The pathogenicity of a virus is the ability to cause disease and is measured by the degree of virulence which in turn provides for determinants such as: ability to infect, replicate, invade cells, evasion of the host immune system and cause cellular damage. These virulence determinants are encoded by viral genes.

During the pathogenesis of an acute respiratory infection (ARI) are aspects that are shared by all the viruses that cause them:

Adherence capacity. Viruses must evade host innate immunity and defense mechanisms, such as mucociliary barriers, phagocytic cells and NK cells, and to adhere to achieve target.

Incubation period. Most ARI causing virus, have short incubation periods.

Viremia. Generally viruses causing the ARI do not cause viremia.

Immunity of short duration. As a result of the alteration of immunity mentioned above, usually the immune response shows short duration or it is incomplete.

Evasion of the immune response. The strategies used by viruses to evade the immune response are varied, from antigenic variation to the blocking of an inflammation process, and decrease of apoptosis levels [10-12].

Association with other microorganisms. Not much is known about this, but there have been some events that suggest it, for example, the bacterium *Staphylococcus aureus* produces a protease that can activate the influenza virus hemagglutinin, thus increasing the virulence level of the virus.

6. Types of infection

The interactions that occur between the virus and the host can take many forms, there are four basic patterns of infection:

1. **Subclinical infections.** Refers to infections that do not show clinical symptoms of disease in a host. They are very common in airways and are epidemiologically important because they represent an important source of transmission.
2. **Clinical infections.** These infections show symptoms and signs, the most common are acute respiratory infections which are characterized by quickly presentation with short incubation period as well as the duration of the disease. Usually, the virus is eliminated by the immune system and the physiological condition of the organism. Sometimes the disease becomes severe.
3. **Abortive infections.** Infection is interrupted in any step of the virus replication cycle. A clear example is the infection with poliomyelitis virus, which causes frequent abortive infections in early stages.
4. **Persistent infections.** After an acute infection, the virus is not eliminated and it can still replicate for long periods. The course of the infection can take one of three ways:
 - a. **Latent infections.** The virus remains most of the time hidden without replication, however, it can reactivate resulting in clinical manifestations. The organs or tissues where the virus remains dormant during respiratory tract infections are: The Herpes simplex virus in the trigeminal ganglion; varicella in sensory ganglia; Epstein Barr virus in B lymphocytes; Cytomegalovirus in renal and salivary cells; adenovirus in adenoids.
 - b. **Chronic infections.** After clinical or subclinical infection, the virus continues to multiply very slowly but continuously. Some viruses can integrate their genome into the cell, some not. Clinical manifestations may take years to develop but once manifest progress very fast. A typical example, although not a respiratory infection, is the Hepatitis B virus.

- c. **Slow Infections.** This kind of infections have a long incubation period that lasts for months or years, symptoms usually do not occur during the incubation period. A well known example is the persistent infection showed by measles in the nervous system causing SSPE, usually conducting to death.
- 5. **Transforming infections.** Few respiratory viruses induce transforming infections, usually, the viral genome integrates into cellular DNA or remain as an episome. Some of the expressed proteins interact with genes and other cellular proteins, causing changes in cell growth rates. One example is found in laryngeal papillomatosis [10, 11].

7. Respiratory system

- a. **Description of the respiratory system and functions.** The respiratory system consists of a set of organs that are grouped into upper respiratory tract (nasal cavity, pharynx, larynx, trachea) and lower airways (bronchi, bronchioles and lungs). The inner part of these organs is covered by epithelial cells which constitute an active physical barrier against pathogens being an important part of the innate immunity. Another structure of the respiratory membrane is a mucociliary structure found from the nasal cavity to the distal areas of the lungs, consisting of a layer of mucus produced by goblet cells that maintain a continuous flow through the ciliary movement in the luminal surface respiratory epithelium. The lungs have not these structures, alveolar macrophages are the cells that are responsible for eliminating pathogens. These structures providing protection against respiratory viral infections. However, despite these protection mechanisms, respiratory system of a host may be infected by a virus by binding to specific receptors present in epithelial cells of the mucosa, thereby avoiding its removal by the mucociliary system or by phagocytic cells. Most viruses that infect humans enter into the body through the respiratory tract as in aerosols produced by coughing or sneezing of other infected hosts. Large particles are usually trapped in the turbinates and sinuses and could cause upper respiratory infections. Smaller particles can reach the alveolar spaces and cause infections in the lower respiratory tract [1, 13]. The viruses that cause respiratory infections in both upper and lower airways are distributed in different families: *Orthomyxoviridae*, *Paramyxoviridae*, *Picornaviridae*, *Reoviridae*, *Adenoviridae*, *Herpeviridae* and *Coronaviridae*. After penetration of the virus, they can cause local respiratory infections as with most respiratory viruses such as influenza, rhinovirus, respiratory syncytial virus, parainfluenza virus, coronavirus, bocavirus and metapneumovirus occasionally causing lower respiratory infections. Other viruses such as herpes, measles, rubella, mumps and varicella among others enter through airways but move to other organs.
- b. **Viral infection in upper respiratory tract.** Infections of the upper respiratory tract usually present acutely and are the most common infections in humans, arise throughout the year but the incidence is higher in winter, are generally of low severity, however, are the main cause of medical consultation and, in consequence, school and work ab-

senteeism is frequent. The virus originated 70-90% of these episodes and viruses that are associated with infections of the upper respiratory tract are: respiratory syncytial virus (RSV), rhinovirus (RV), parainfluenza (PIV), influenza A (IA), adenovirus (AD), human metapneumovirus (hMPV), human bocavirus (HBoV) and coronavirus (CoV). A virus can cause several syndromes, also too a syndrome may be caused by different viruses such that the clinical manifestations are variable. All individuals can be infected by these viruses, however, it has been observed that children are the most affected. The most common syndromes in upper airway are: nasopharyngitis, adenoiditis, pharyngitis, sinusitis, laryngitis and croup [14].

- c. **Viral infection in lower airways.** Viral infections in lower respiratory airways occupy a smaller percentage, but with high mortality rates. The groups most at risk are young children and older adults. The disease is increased by several factors including anatomical disorders, immunological, metabolic or other diseases such as AIDS, asthma or chronic obstructive pulmonary disease (COPD).

In the next series of X-ray images are examples of lung damage caused by viral infections, upper and lower respiratory tract.

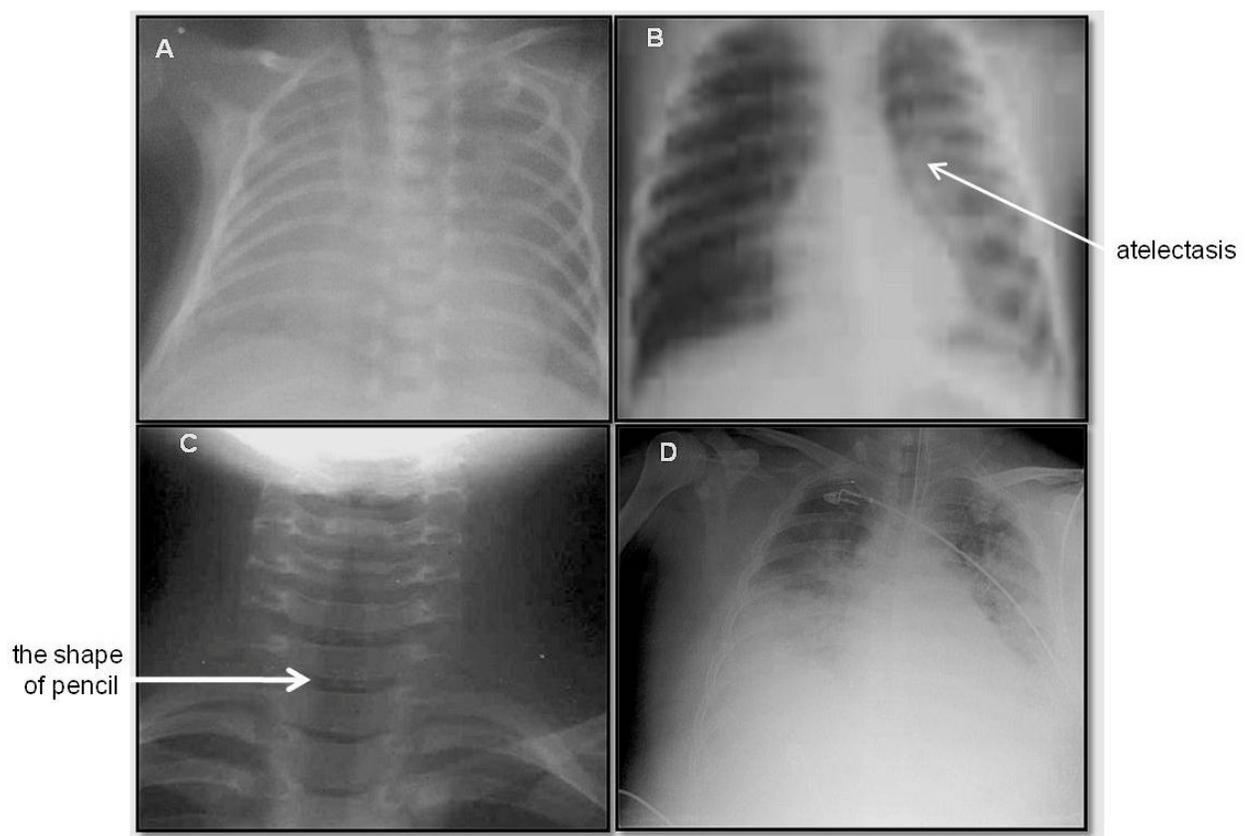


Figure 2. Radiographic images of airways infection by viruses A) pneumonia caused by respiratory syncytial virus; B) bronchiolitis in children caused by respiratory syncytial virus; Croup parainfluenza virus; pneumonia caused by influenza virus A (H1N1).

The main syndromes caused by viral infections at the lower respiratory tract are bronchiolitis and pneumonia. Bronchiolitis occurs primarily in young infants and preschool children, the most related virus to this syndrome is the RSV (50-75% of the cases). Pneumonia occurs most often in children younger than 3 years of age, as in bronchiolitis, the RSV virus are involved (50%), as well as the parainfluenza 1 and 3 virus (25%), other viruses participate with lower percentages. In elderly influenza A virus is the most important agent in causing severe pneumonia with high mortality rates [14], Figure 3.

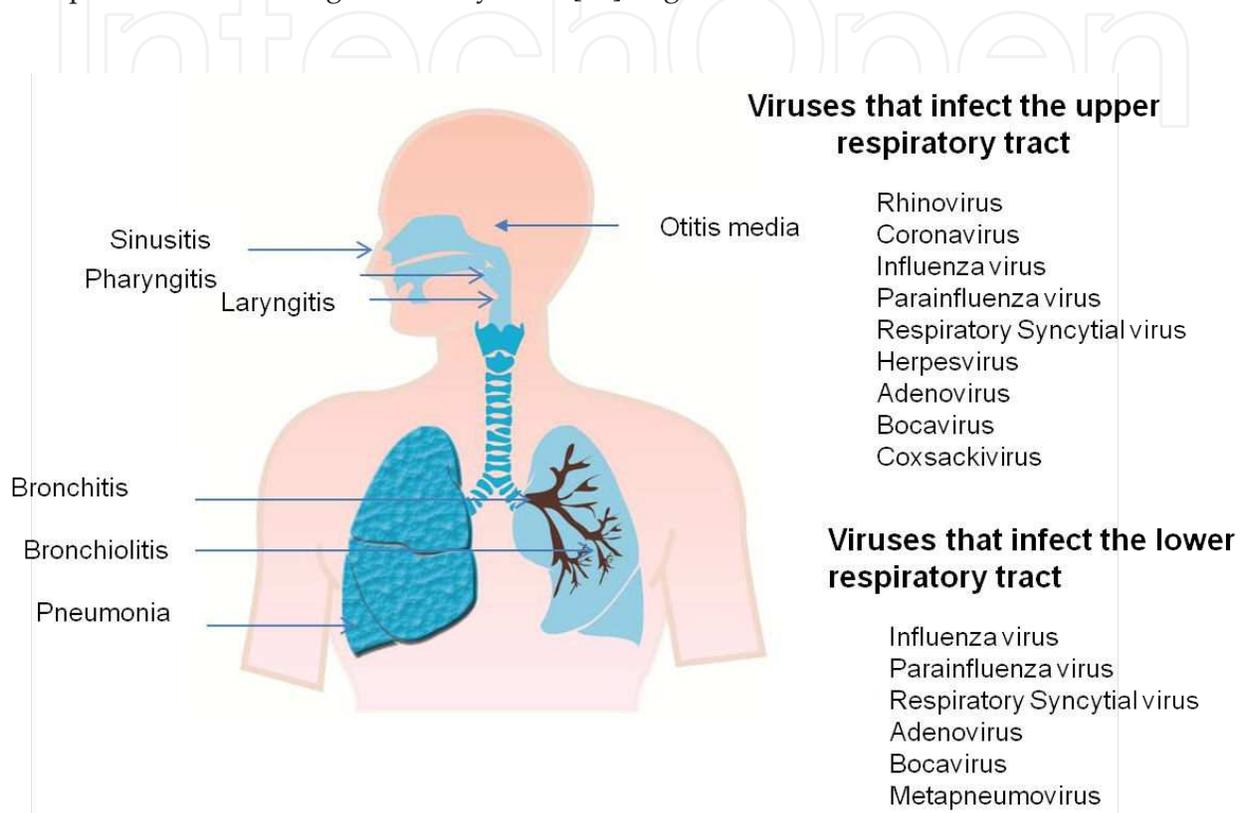


Figure 3. The Respiratory tract and the main syndromes caused by viral infections. The viruses can infect the respiratory tract upper and occasionally, some of them can cause infections in the lower respiratory tracts. Others enter through the respiratory tracts but they move to other organs.

8. Immune response in the respiratory system (innate and adaptive), cells and mechanisms

The human immune system is divided in two defense mechanisms or responses: a) Innate or nonspecific response that lacks specificity and memory, is the first line of defense of the organism, its components are always present to act immediately and b) Specific or adaptive response. This response is more complex, has a memory and identifies the viral specific peptides processed by antigen presenting cells, which activate the humoral immune response mediated by B cells or a T cell mediated cellular response. An efficient immune response depends on a correct interaction between the innate and adaptive immune system.

Nonspecific or innate response. Airways use several mechanisms to recognize a virus and to mount a protective response. Cells of the innate immune system use a pattern recognition receptors (PRR) that are expressed on their surface and bind to pathogen-associated molecular patterns (PAMPs), which are present in microorganisms. Viral PAMPs can be: double stranded RNA or RNA produced during replication, surface proteins or glycoproteins. Toll-like receptors (TLR) represent a PRR family expressed in most cells of the organism, it has been identified 10 human types. The TLRs are formed by a binding domain ligand consisting of leucine repeats that interact directly with viral antigens; a transmembrane domain and a cytoplasmic domain responsible for initiating the extracellular signaling. Viral infections activate different TLR receptors (TLRs 3, 7, 8 and 9) that generally induce a protective immune response, however, also can be a part of pathogenic mechanisms. Recently, it has been shown that activation of TLRs in epithelial cells by viral infections participate in the regulation of expression of several genes encoding for cytokines, such as: tumor necrosis factor-alpha (TNF- α), Interleukin-1 (IL-1), IL-6, IL-8, IL-18, interferon alpha and beta (IFN- α and - β), chemokines (leukotrienes, prostaglandins) and antimicrobial peptides (α and β defensins), which are of great importance in the organization of the innate and adaptive immune response.

The components of the innate immunity are the physical and chemical barriers (epithelia and mucosae), the phagocytic process includes the participation of phagocytic cells (monocytes, macrophages and neutrophils), dendritic cells (DC) and natural killer cells (NK), also includes the production of soluble molecules (interferons, complement, acute phase proteins and antimicrobial peptides) [15- 19].

Epithelial cells. These cells are actively involved in the production of proteins (lactoferrin), enzymes (lysozyme) and antimicrobial peptides (defensins) which together eliminate or neutralize the virus. When the epithelium loses its integrity by the effect of viral infection, it can be observed the following consequences: exposure of sensory nerve endings, receptors found in the basal membrane is increased, the substances that modulate muscle tone and sensitivity are not working properly, finally, the active inflammatory response results in the alteration of inflammatory mediators.

Natural killer cells (NK). They are large lymphocytes with intracellular granules. An antibody binds to the surface of a cell infected by a virus, interacts with the Fc receptors and NK cells release proteins (perforins and granzymes) causing cell death. NK cells can be activated by the stimulation of IFN- β and α and other cytokines such as IL-12, IL15 and IL18 produced by infected cells, dendritic cells (DC) or macrophage (fig.3), [16, 17, 18, 19].

Dendritic cells (DC). DC are present in various tissues as skin, epithelium and mucosal. DC express MHC molecules on their surface localize the virus and migrate to the closest lymph node traveling through the lymphatic vessels eliminating the microorganism [17, 18].

Soluble molecules. Among the soluble molecules involved in innate immunity are: complement, interferons, antimicrobial peptides and acute phase proteins.

Complement. Complement is a system consisting of over 30 proteins that are activated by proteolysis in sequence. The complement is found in the human plasma as an inactive form and can be activated by three different pathways: the classical pathway, the alternative path-

way and the lectin pathway; viral infections can trigger the three pathways. Complement is more efficient during the attack to enveloped viruses, because complement activation finished with the formation of an attack complex which is inserted into viral membrane, causing the lysis of the virus [16, 19]. Complement anaphylatoxins (C3a and C5a) induce histamine, prostaglandins and leukotrienes release, promoting bronchoconstriction. C5a is a chemotactic factor for a variety of inflammatory cells. C3a and C5a have been found in high concentrations in the upper airways during infection by influenza virus. It has also been shown that RSV-infected cells activate complement [13, 15].

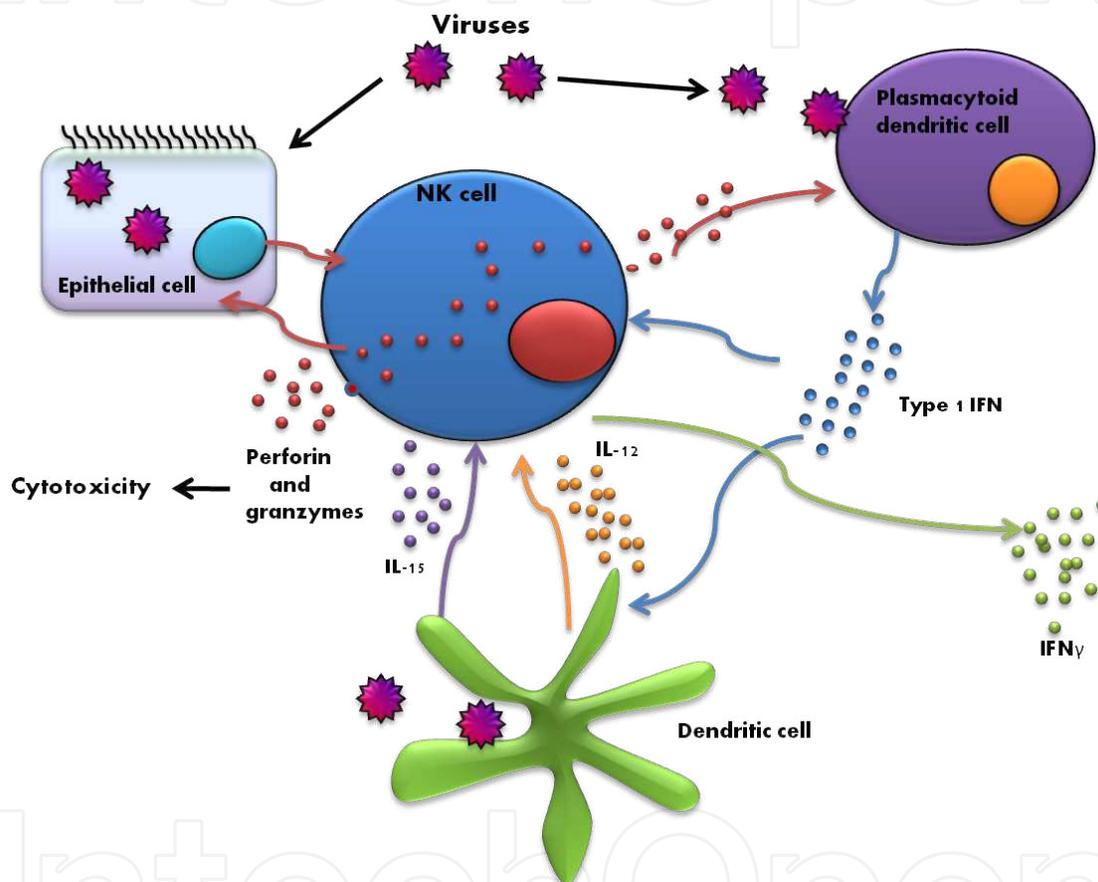


Figure 4. Activation of NK, dendritic cells and soluble molecules during virus infection. The viruses trigger the production of type – 1 interferons (IFNs) by plasmacytoid dendritic cells and other cytokines as interleukin – 12 (IL – 12). IL – 12 and IFN induce the production of IL – 15 by dendritic cells DC). IL – 15 is presented to NK cells, so that NK cells are activated. IL – 15 trigger other pro – inflammatory cytokines, including either the secretion of IFN – γ by NK cells or the release of perforin and granzymes, which leads to cytotoxicity. Modified from: Lanier 2008.

Interferons (α and β). Interferons are cytokines that are produced in small amounts by cells infected with virus. Are efficiently induced by the presence of double-stranded viral RNA (viral replication intermediary), the process involves three antiviral proteins: protein kinase (PKR), Oas1 and RnasaL, which block the translation and degradation of viral and cellular RNAs. Interestingly, influenza virus induces high levels of interferon with protective properties [20, 21, 22, 23] figure 5.

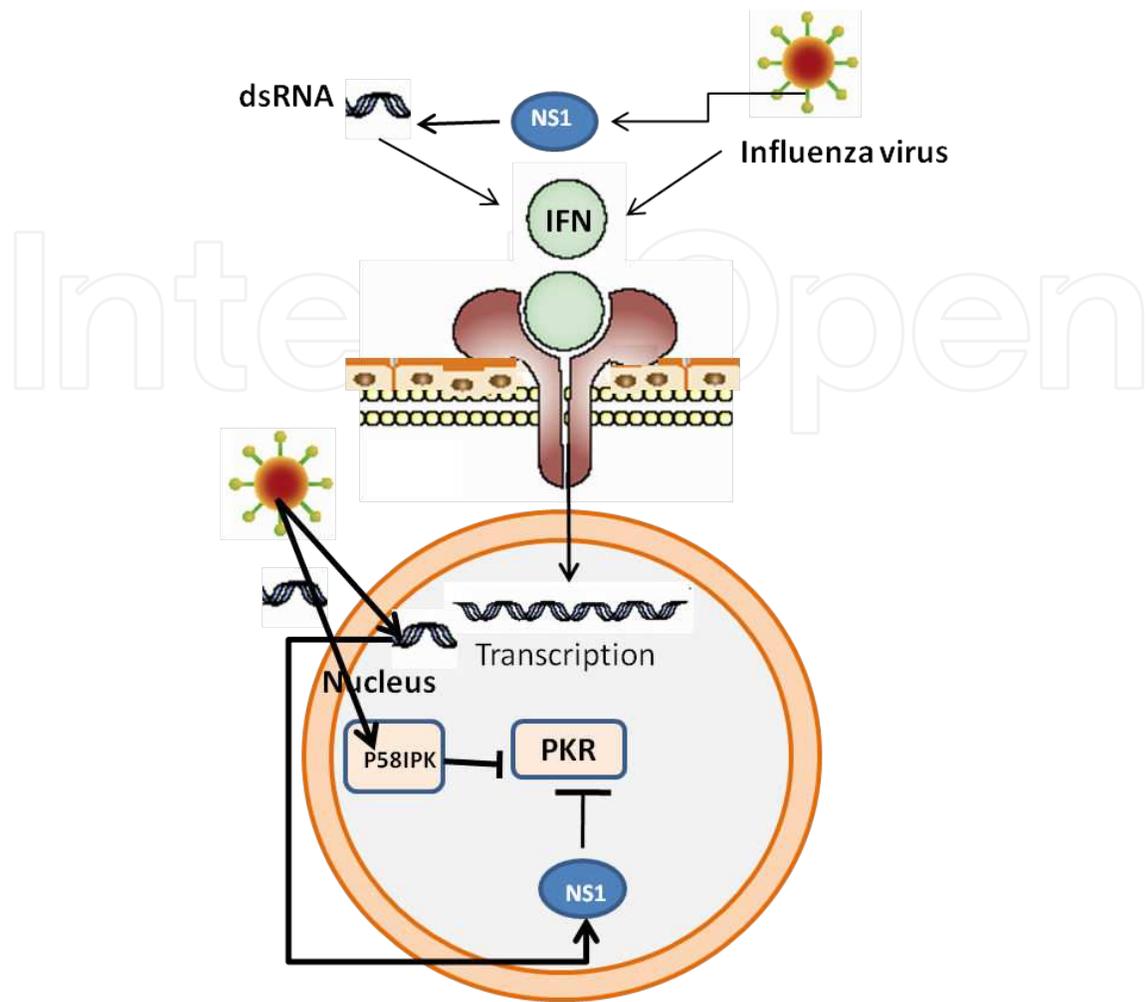


Figure 5. Influenza virus mechanisms to evade interferon action. The, NS1 protein encoded by the virus genome suppresses induction of IFNs- α/β . P58IPK is a cellular inhibitor of PKR that is activated by influenza – virus infection. Modified from: Katze 2002.

Defensins. They are cationic small peptides rich in arginine. They are synthesized in leukocytes, macrophages and epithelial cells constitutively, in response to infection or during inflammation. In humans, there are two types: α and β -defensins. Viral infections induce the production of defensins, which regulate the innate and adaptive immune response (positive and negative). The mechanisms of action and induction of defensins are multiple, generally depend on the type of infecting virus (enveloped and non-enveloped), defensin type and the target cell infected [18, 24].

The respiratory epithelium induces production of β -defensins, mainly of β -defensin-2. The mechanisms of action include: a) direct, when the peptide binds to the viral membrane by electrostatic attraction, form pores and cause lysis of the viral membrane. This mechanism occurs in the majority of enveloped viruses (influenzavirus, herpes, HIV); and b) indirect, when the defensin inactivate any signaling pathway in any step of the virus replication cycle (herpes, adenovirus). There are few studies on the mechanisms of induction of β -defensins

in the respiratory epithelium. When rhinovirus infects the respiratory epithelium, the β -defensin-2 is induced by virus replication, mRNA activates the transcription factor NF- κ B, and therefore, the gene that codifies for defensins; however, defensin has no direct effect on the virus. Influenza virus induces the expression of β -defensin-3, which inhibits the binding of the viral hemagglutinin with epithelium membrane. This same defensin inhibits viral fusion with the cell membrane during a RSV infection [25, 26].

Acute phase proteins (APP). APP are serum proteins whose its concentration increases or decreases when there is an infection. APP are induced by pro-inflammatory cytokines like TNF- α , IL-6 and IL-1 that are synthesized in the liver. Examples of APP are the lectin that binds to mannose, C reactive protein and surfactant proteins A and D. Acute phase proteins recognize PAMs viruses, activate complement and enhance the phagocytic capacity of immune cells [24].

8.1. Specific or acquired immunity

When the adaptive immune system contacts with a antigen it is developed a primary response that generates immunological memory, which at a second contact (secondary response) the response is more rapid and intense. There are two specific types of responses: humoral and cellular.

Humoral response. The humoral response has as a major component the B lymphocytes that differentiate into antibody-producing plasmatic cells. The antibodies are displaced by the body fluid to bind to antigens. When antibodies interact with phagocytic cells and complement, the viruses are neutralized. In humans, there are five classes of immunoglobulins (IgA, IgM, IgG, IgE and IgD). In viral respiratory infections, IgA is of great importance as it is secreted by mucous epithelia, preventing the establishment of virus. IgM is the first antibody that is synthesized and prevailing in a primary response, also fix complement. The IgG is found in greater concentration in serum and is the only one that can cross the placenta in humans. Presents an Fc fragment that binds to complement receptors on phagocytic cells. Most respiratory viruses induce such antibodies that persist, and when a second exposure to the same antigen, the disease is less severe; unfortunately, virus may have mutations that are not recognized by the antibodies, therefore, reinfections are common. IgE is the antibody with the lowest concentration in the serum, but is the most important in allergic disorders. It has been reported that some viruses such as RSV, influenza, bocavirus, parainfluenza and metapneumovirus produce bronchial hyperreactivity or asthma increasing concentrations of this immunoglobulin in blood and secretions. Basophils and mast cells have receptors for these antibodies, when the antigen-antibody binding occurs and consequently activate, these cells release inflammatory mediators that cause many manifestations of these respiratory diseases [27].

Cellular response. The cellular response has as its principal components the T lymphocytes, which are divided into two populations according to their surface markers and the pattern of cytokines produced: CD4+, also called helper T cells (Th) and CD8 +, the cytotoxic lymphocytes (CTL). These specialized cells can proliferate and differentiate into effector and memory cells.

In viral infections, CD8+ T cell response is essential for viral clearance. Lymphocytes are able to recognize through its receptor (TCR) by antigen processing performed by antigen presenting cells (dendritic cells or macrophages) associated with MHC molecules. For the differentiation and activation of T lymphocyte are required two signals are required: the first is the specific recognition of the antigen on the target MHC class I-associated cell, and the second produced the cytokines produced by CD4+ T cells which recognize MHC-associated viral antigens class II. Cytotoxic T lymphocytes exert their antiviral effects by three mechanisms: producing lysis of infected cells, stimulate the production of enzymes that degrade viral genomes, and secrete cytokines. In severe viral infections including pneumonia caused by RSV, influenza and metapneumovirus, this type of response is important for the resolution of the disease; however, it has been observed that in severe cases this response has no effect and the pattern that develops is through cytokines produced by CD4 Th2 specialized cells that induce an inflammatory response increasing damage and thereby aggravating the condition.

9. Evasion of the immune response

Despite effective defenses, some virus can to evade it by using different mechanisms, for example, in respiratory tract infections influenza virus inhibits the production of interferon by the protein NS1, a non-structural protein that is abundantly expressed in the nucleus of infected cells. NS1 binds to double-stranded RNA by preventing activation of the dsRNA-dependent protein kinase (PKR) [28], commonly synthesized during induction of interferon (Figure 5). Another mechanism is the antigenic variation that occur mainly in the HA and NA proteins. PI and RSV respiratory viruses have a surface protein (F), which mediates the fusion of the viral membrane with the cell membrane. This mechanism enables the virus to spread from one cell to another without exposure and avoiding the effect of circulating antibodies. Another strategy is to make a latent infection. Viruses such as adenovirus and herpes employ transcription and replication strategies to maintain the viral genome in any cell type where the immune response is not efficient and viral particles are not produced for long periods. Other viruses interfere with antigen processing or complement. In summary, viruses use several strategies to evade the immune response [11].

10. Other mechanisms used by respiratory viruses in the pathogenesis

In most infections, the viruses cause upper respiratory infections, while others reach the lower airways, may even cause necrosis and cell death, also induce inflammatory processes such as wheezing and hyperreactivity, both important in the development of chronic diseases such as asthma and chronic bronchitis for which some mechanisms have been proposed. In summary, the strategies used by viruses that cause respiratory infections can be very varied; however, there are always some strategies are shared between different types of viruses.

Inflammatory cells. In viral respiratory infections has been observed recruitment of inflammatory cells such as eosinophils, neutrophils, basophils, monocytes, macrophages, mast cells and T lymphocytes. Thus, when activated, these cells release mediators, cytokines or other compounds that increase inflammatory response [29, 30]. **Macrophages.** Alveolar macrophages are one of the first lines of cellular defense against virus infections. During viral replication in macrophages antiviral mechanisms are activated by stimulating, by stimulating the release of interferons or other cytokines, for example, studies have shown that alveolar macrophage infection by RSV, causes increased secretion of tumor necrosis factor alpha (TNF- α), as well as interleukins IL-8 and IL-6. It has also been observed that the macrophages express high levels of intercellular adhesion molecule-1 (ICAM-1), receptor molecule specific for some virus [17, 31, 32].

Monocytes. Also express high levels of ICAM-1. When human monocytes are infected by viruses, monocytes are activated, producing and releasing IFN- α , IFN- β , IL-1 β , IL-6 and TNF- α . The production of these cytokines (with the exception of IFN- β) potentiates the production of granulocyte macrophage-colony stimulating factor (GM-CSF) [33].

T Lymphocytes. T lymphocytes act as immunomodulators and as producers of cytokines. According to the pattern synthesis of cytokines, helper T cells (Th) are classified into two types: Th1 cells secreting IL-2, IF- γ and lymphotoxin, while Th2 cells secrete IL-4, IL-5, IL -6 and IL-10. The Th1 response is associated with the antiviral immunity. The RSV G protein stimulates Th2 type response and this would explain the symptoms of lower respiratory tract caused by this virus [34].

Neutrophils. In viral respiratory infections, neutrophils are activated and recruited into the airways and probably generate oxygen metabolites or other metabolites or inflammatory cytokines that cause damage and late hyperreactivity [36]. They are found in high concentrations in bronchial secretions of children infected with RSV, with parainfluenza virus and in nasal biopsies of subjects with rhinovirus infection [34].

Eosinophils. Eosinophils release mediators such as leukotrienes (LTC₄), platelet activating factor (PAF), major basic protein and cationic eosinophilic protein. When eosinophils are activated by virus are recruited into the airways causing damage and causing a late hyperreactivity reaction [35]. *In vitro* studies have shown that RSV in humans activates eosinophils [36].

Basophils. *In vitro* assays using basophils obtained from patients infected with RSV, adenovirus, influenza A, parainfluenza and rhinoviruses have observed an increase in the release of histamine [37, 38, 39].

Mast cells. These cells have a high affinity receptor for IgE and participate in hypersensitivity reactions, the release of histamine and leukotrienes, molecules that are increased in infants with respiratory wheezing [38, 39].

Stimulation of chemical mediators. It has been proposed that in the respiratory infections, viruses are able to originate the release of inflammatory mediators, either directly or through viruses-activated cells. Whatever leads to a vigorous inflammatory response, airway ob-

struction induces exacerbation of asthma. Several mediators have been reported, which suggests that during infection can exist the interaction of more than one. Among the most mentioned are:

Histamine. Histamine is released from various cells as basophils, leukocytes, mast cells, among others. The secretion of this mediator is inflammation and airway is inflammation and airway obstruction. *In vitro* and *in vivo* studies with respiratory virus have demonstrated high concentrations of histamine in nasopharyngeal secretions and in the plasma of infected individuals. However, therapeutic success with antihistamines in asthma has not been confirmed so several authors have questioned the effect of histamine [36, 38].

Leukotrienes. Leukotrienes are inflammatory lipid mediators derived from arachidonic acid. Leukotrienes are released by primary inflammatory cells involved in inflammation, as well as endothelial and epithelial cells of the airways. They are very potent bronchoconstrictors that affect both the upper and lower airways. It has also been shown to increase vascular permeability and production of mucus, in addition, some evidence suggests that leukotrienes play an important role in the origin of wheezings. Respiratory viruses such as RSV, parainfluenza 3 and influenza A, induce the release of leukotrienes which are detectable in nasopharyngeal secretions. High concentrations of Leukotrienes have been found in infants with RSV infection [40-44].

Products of cyclooxygenase, arachidonic acid, prostaglandins and thromboxane. They are potent bronchoconstrictors and have shown an increase in the concentrations of the primary metabolite of prostaglandin type 2a in plasmatic cells from infants with RSV bronchiolitis and especially in those with recurrent wheezing. It is also reported that the prostaglandin E2 type has an inhibitory effect which may protect the airways of a bronchoconstrictor effect. It is suggested that viral epithelial damage may result in the loss of these protective prostaglandins. It was also found that complexes of RSV-antibody cause an increase in the release of thromboxane by neutrophils [36].

Platelet activating factor (PAF). Induces an inflammatory response and stimulates the production of mucus in the airways, alters mucociliary clearance and enhances pulmonary microvascular permeability. PAF is released by macrophages, eosinophils and neutrophils. *In vitro* studies have shown that mononuclear phagocytes upon RSV replication, stimulates the synthesis of platelet activating factor. From these results it has been suggested that this factor may play an important role in the inflammatory response caused by RSV [45, 46].

Kinins. These molecules are potent vasoactive peptides that are produced in tissues or fluids. Kinins may be involved in the pathogenesis of diseases such as asthma by its inflammatory and bronchoconstrictor action. Kinins are potent stimulus for C fibers, and therefore, improves axon reflex [34, 36]. In unmyelinated sensory nerves in the airways is found the P substance, potent neuropeptide belonging to tachykinin group which when released by local axon reflex, potentiate the cholinergic neurotransmission [47].

Nitric Oxide (NO). Nitric oxide has a mediator function with different effects such as: antiviral agent, increase bronchial blood flow, eosinophilic infiltration, epithelial damage, potent vasodilator, inhibit the proliferation of Th1 cells due to a Th2 phenotype change, and, in

asthma patients, it has been observed that after a experimental rhinovirus infection, no increase in exhaled NO levels [48].

Cytokines. They are small proteins that act generally in cellular processes such as differentiation, activation and immune defense. All cytokines are secreted by cells due to the interaction with infectious agents and mechanical actions (e.g. cell stress). They interact through a complex network during the immune and inflammatory responses. There are a variety of cytokines and others are continually identified. There are cytokines showing chemotactic properties, therefore, these cytokines are called chemokines. In viral infectious processes it has been described the participation of various chemokines as a pathological characteristic of the infection process, so that it has been established that chemokines are directly responsible for the inflammatory processes that occur in respiratory viral infections [49]. Among the viruses that induce the release of chemokines may be mentioned: RSV, rhinovirus, influenza and parainfluenza viruses 3 [50]. It has been observed that, in cell lines, RSV increases the production of IL-6, IL-8, RANTES, macrophage inflammatory protein (MIP-1a), GM-CSF and IL-11.

Interleukin 8 (IL-8). IL-8 is a chemokine which promotes the recruitment of neutrophils and eosinophils that are responsible in part for the inflammatory process [49, 50].

RANTES. This eosinophil chemokine that induces exocytosis of the eosinophil cationic protein. It is also chemotactic for basophils and CD44 T cells [51, 52].

MIP-1 α . Less potent than RANTES as eosinophil chemotactic, but it is important mediator in the inflammatory response during virus infection because it stimulates the release of histamine by basophils and mast cells. Its properties suggest that may be important mediators of asthma exacerbations induced by viral infections. In children, have been found in high concentrations in nasal secretions during asthma exacerbations associated with infection caused by RSV and rhinovirus [50,51].

Eotaxin. It is another chemokine with chemotactic activity for eosinophils. Eotaxin has additional functions such as endothelial migration, release of reactive oxygen, Ca⁺ ions mobilization, actin polymerization and is also chemotactic for basophils and Th2 lymphocytes. It is soluble in serum and has been found in high concentrations in patients with asthma and is associated with the severity of the disease [52, 53].

Intercellular adhesion molecule 1 (ICAM-1). This a receptor is located in the vascular endothelium, epithelium of the airways and in antigen presenting cells. Its ligands are found in circulating leukocytes [54, 55]. Several studies have shown that, *in vitro*, epithelial cells of human airways produce increased levels of ICAM-1. This ICAM-1 expression is observed also during the adhesion of eosinophils and neutrophils in response to inflammatory cytokines and in infection processes of various respiratory viruses such as RSV, rhinovirus and parainfluenza [53, 56, 57]. Rhinoviruses attach to the surface of cells via ICAM-1 receptor, suggesting that infection with rhinovirus leads to an increase in the expression of ICAM-1 in the upper airways. In this way, ICAM-I and induces the recruit-

ment of eosinophils and neutrophils, thereby increasing and causing inflammatory activity and wheezing [58, 59, 60].

11. Pathogenicity and description of some viral respiratory infections

11.1. Infection with influenza virus A

The influenza A virus belongs to the *Orthomixoviridae* family, causes high morbidity and mortality. One feature of the virus is the frequent occurrence of new antigenic variants generated by both genetic mutations and recombination leading to epidemics and pandemics. Influenza viruses have a fragmented RNA genome (8 fragments). Among others, influenza virus has two glycoproteins, hemagglutinin (HA) and neuraminidase (NA), that are important in their biological activity and pathogenesis. The cellular receptor for this virus is sialic acid, which forms part of mucopolysaccharides found in glycoproteins and cell membranes. HA viral protein binds to the cellular receptor by endocytosis to enter the cell, allowing the virus to remain as an endosome, and is required to be activated so that the fusion peptide is exposed. This step is critical for virus infectivity and depends on both the virus and the cell. Once given membrane fusion, RNA migrates to the nucleus for replication, which is required for the cellular RNA polymerase II, as its polymerase is inefficient to generate mRNA, so viral replication depends on the help of the cell. Neuraminidase (NA) is the second virus glycoprotein. Its function is enzymatic and is important because once the new virions are synthesized, the glycoprotein is responsible for removing sialic acid residues from the infected cell membrane, which allows the newly synthesized virions can be released without auto aggregation. The viral M2 protein functions as an ion channel that allows the passage of protons into the virion and is the target for the action of the amantadine, its mutation or changes can lead to viral resistance to this compound.

The virus enters through the nasopharyngeal region, the target cells are mucus-secreting epithelial cells and ciliated cells, can be transmitted by droplets expelled by speaking, sneezing or coughing, by contact with contaminated material or hands. The cell binding is via the HA that binds to sialic acid receptor. The incubation time is 1 to 3 days. The virus multiplies rapidly and spreads to neighboring cells. It causes cellular necrosis and apoptosis, altering the ciliar activity and increasing mucus secretion. To exit and infect other cells, NA reduces the viscosity of mucus film breaking sialic acid residues. The damage to the epithelium causes respiratory symptoms and signs, stimulates the natural response of the tract and promotes bacterial incorporation. The inflammation process can damage bronchi, bronchioles and alveolar regions. All these events cause initial symptoms of infection like fever, chills, muscle aches, headache, anorexia and prostration. Local monocytes, lymphocytes and interferon are the main response to the virus. The virus induces an effective humoral response which is important in recovery, but it must be considered that the antibody response is specific for each variant of the virus, whereas the T lymphocytes and macrophage response is general and depends on the injury and the condition of the host to perform efficiently the epithelial repair (that can take up to one month).

In pandemics and severe cases, it has been observed that the immune response is exacerbated and may cause a greater damage [61].

The virus can evade the immune response in different ways. One is the constant genetic variation of HA and NA glycoproteins, which are the first that are recognized by antibodies. Another mechanism involves the NS1 Protein, which can block the role of interferon [15].

Until 2009, the origin of influenza pandemics was mainly due to the transmission of virus from birds to humans, by the transfer of genes from avian virus to the seasonal influenza virus that is recognized as human. When a new virus emerges, the body does not recognize it, which can lead to a pandemic. In April 2009, an epidemic arose from the emergence of a new influenza A virus. The first cases occurred in Mexico. Numerous patients with Influenza-like severe symptoms were attended at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER), Mexico, and in many cases required hospitalization. Patients arrived in a serious, advanced conditions and, for this reason many of them died.

It has been observed that when an epidemic emerges and new viruses are detected, the human body quickly begins to produce the antibodies needed to contain the new disease. Some people develop these antibodies faster than others, so that the chance of infection in them is lower, because their immune system acts quickly creating antibodies, while those that fail to quickly develop antibodies start to develop the disease. Despite that, the viruses that cause ARI do not induce a good immune response. If after some time there is antibodies production, many patients will become before producing antibodies against the new virus. Other antibodies have neutralizing capacity.

We decided to carry out a study with the following objectives: To determine the titer of anti-influenza virus in serum samples from patients infected with influenza A (H1N1), as well as household contacts of patients infected with this virus by the method of inhibition of hemagglutination.

To determine the presence and titer of antibodies were used 196 samples of sera, of which 110 were in patients with influenza A H1N1 confirmed by RT-PCR assays and to household contacts 86 patients with influenza A H1N1. In this work, antibody titer of each sample was determined using the technique of hemagglutination inhibition.

The figure 6 shows the results of some sera, as can be seen, the positive titers appear as a red spot in the center of the well as a result of inhibition of hemagglutination while negatives occur in a uniform color of lower intensity.

90% of patients confirmed influenza A (H1N1) had antibodies, the highest titer was 1:1024 and the lowest was 1:16. In the case of the sera of household contacts the highest antibody titer was 1:256 and the lowest was 1:4. In the case of the sera of healthy household contacts, antibodies are detected in only 84% of the sera.

In conclusion, the antibodies were detected during an acute late phase in the diseases acute phase but late in the disease, since patients usually arrived after two weeks of onset of the disease, and in serious condition. It is possible that after this stage titers have increased. Antibody synthesis is generally low at the beginning of the disease, and it is increased as the

immune system responds to the infective agent, that is, after approximately two weeks. Up to that moment the antibodies could not stop the damage the virus had caused.

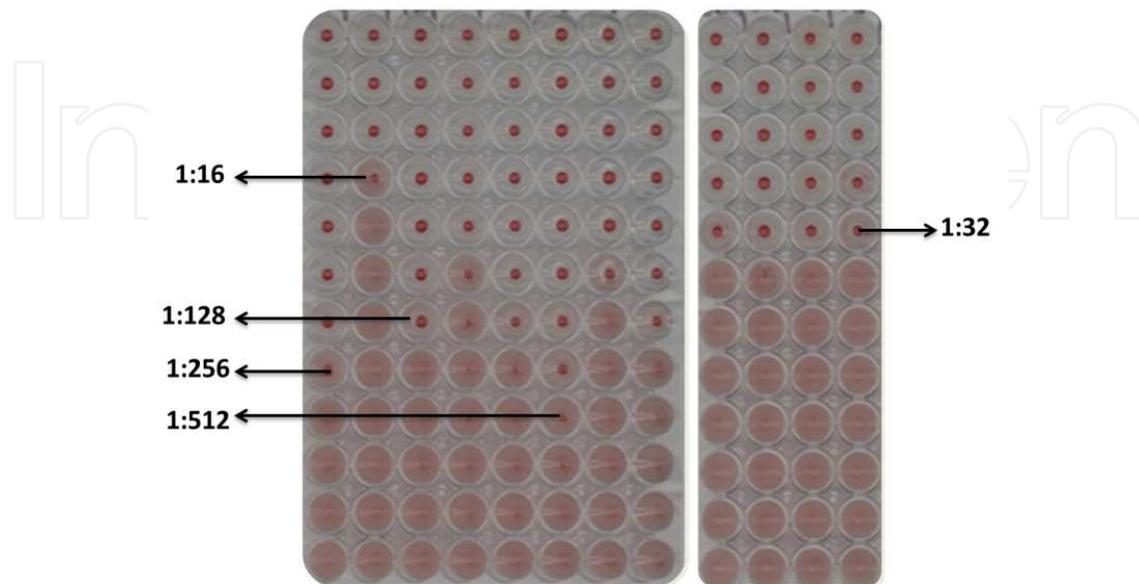


Figure 6. Hemagglutination inhibition test for the detection of antibodies against influenza A (H1N1) virus.

11.2. Respiratory syncytial virus (RSV)

RSV belongs to the *Paramyxoviridae* family is not segmented and is capable of performing polymerase mediated mRNA synthesis and is characterized by two glycoproteins, the F protein (which induces the formation of syncytia) and G protein.

In the case of RSV, this virus infects children under 2 years of age causing high rates of morbidity and mortality [61]. Usually, children between one and two years of age have had a virus infection [62]; however, reinfections are frequent, as the immune response is incomplete or immature. As all the respiratory viruses, RSV enters through respiratory airways, taking place the first replication in the nasopharyngeal region. For the ability to make syncytia, RSV virus can move from cell to cell without leaving, which prevents antibody attack. Thus, secretions or by dragging can reach lower airways, causing bronchiolitis and pneumonia with mucus production. As a child tracks are narrow, respiratory obstruction can be observed, which can be very serious. The most important mechanism of pathogenesis of the virus is its capacity to infect their terminal paths of the lung during childhood, when the diameter is quite small. The RSV virus has a propensity to infect the bronchiolar epithelium in comparison with the infection of the rest of the airways; even if the cause is unknown, pathological studies indicate that the inflammatory response is much greater in the area of the terminal airways that in the upper portions of the respiratory tract [63]. Besides, other factors are suspected important in the pathogenesis of the virus as immunological mechanisms, mainly by cytokines produced by Th2 lymphocytes. It has been suggested that the

nature of the immune response to RSV, is determined by the pattern of cytokines produced sequentially by different cells [63]. There are high-risk groups such as immunocompromised children, premature infants, infants with heart, kidney and lung problems, where mortality is high.

11.3. Parainfluenza virus (PIV)

PIV is of the same family as the RSV, so that their characteristics are similar, except that one glycoprotein has the hemagglutinin and neuraminidase activities in a single structure. IN addition, PIV has an F fusion protein.

In the case of PI virus, and despite its frequency, little is known regarding to their mechanism of pathogenesis. The PI virus also infects children causing the same syndromes. Small tracts of children, when ignited, conduce to the obstruction of the air flow allows the accumulation of secretions, so there are cases with severe obstruction [64, 65].

For either exist a vaccine, although in the case of RSV there is a monoclonal antibody which can be an important resource in the treatment of young children. However, but its cost, is only used in high-risk groups.

12. Conclusions

The viral pathogenesis represents a world of mysteries and extraordinary surprises, where apparently questions have not been able to answer. One of the main purposes of the pathogenesis study is to know and understand the molecular mechanisms by which viruses activate in the cells when generating a , and how they avoid the immune response; with that information, trying to eliminate or control the diseases that they provoke in humans.

Although there have been significant advances in different fields of medical virology, there are still many mysteries to solve, questions to answer and so many fields to explore in the pathogenesis of viral acute respiratory infections (ARI) and the viral pathogenesis in general. In spite of moving forward in the pathogenesis study, mainly in aspects such as: molecular interactions between viral factors and the host, and identification and comprehension of many of the biological, molecular, biochemical and even genetic mechanisms involved in the disease's development, many of these processes remain to be clearly understood. However, thanks to steady developments and improvements in many fields of biological sciences and technology, we hope to attain a deeper knowledge and comprehension of viral pathogenesis development.

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