Armando E. Fraire
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Editors

Viruses and the Lung

Infections and Non-Infectious Viral-Linked Lung Disorders

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This book is dedicated to the memory of S. Donald Greenberg, M.D., friend, colleague, teacher, and a superb pulmonary pathologist.

Preface

Worldwide, infectious disease remains a major cause of morbidity and mortality. In developing countries, infection represents a substantial proportion of all recorded deaths. Likewise, in developed countries, pneumonia alone accounts for a significant number of deaths, second only to cancer, stroke, cardiovascular disease, and accidental deaths. Along with bacteria and parasites, viruses are responsible for much of the infections afflicting the human host. In the last decade alone, viruses have been responsible for two major outbreaks, the first related to corona viruses (severe adult respiratory distress syndrome) and, more recently, the outbreak of H1N1 influenza. These two viruses (corona and H1N1) and other viruses discussed in this book primarily target the lung, resulting in significant pulmonary pathology. There are several excellent texts of pulmonary and infectious disease that adequately address viral illnesses affecting the lung but none that focus exclusively on viruses, hence the name of this book: *Viruses and the Lung*.

This is not a comprehensive textbook of virology. Epidemiology, clinical manifestations, and ultrastructural features of virions are covered only superficially. Nor does this volume fully explore vaccination issues or management of the acutely ill patient with viral pneumonia. What this volume offers is a structured discussion of histopathological changes in the lung of virus-infected patients with sections on clinical manifestations and differential diagnosis in many of the chapters. Viral diseases in children are not the same as those of adults, and issues related to the young are covered in a special section dedicated to viral diseases in childhood. Globally, it has been estimated that about 10 % of human cancers are secondary to oncogenic viruses, and to address this critical issue, an entire section of this work is dedicated to lung neoplasia related to viral infection. In a multiauthored volume such as this one, different perspectives reflecting the individuality of the contributors will be evident in their chapters. For example, in terms of neoplastic lung disease, the reader will find Kaposi's sarcoma and primary effusion lymphoma, among others, are discussed in more than one chapter. To facilitate cross-referencing, appropriate notes are inserted in key places. A highly illustrated chapter on viral diseases affecting a number of animal species is included, and we hope this may appeal to those interested in comparative medicine. We hope this

book will appeal to a busy pathologist facing a difficult case of giant cell pneumonia or an infectious disease specialist wishing to brush up on his/her pathology. Lastly, we also hope this book will appeal to medical students at large, particularly those with an interest in the lung.

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Part I

Lung Defenses and Taxonomy

Introduction

1

Armando E. Fraire

The origin of viruses is not known. It has been hypothesized viruses may have evolved from DNA or RNA nucleic acid components of host cells that became able to replicate autonomously and independently, resembling genes that have acquired the capacity to exist on their own (Brooks et al. 2010). There is no evidence that viruses evolved from bacteria, though other obligately intracellular organisms, e.g., rickettsiae and chlamydiae, presumably did so (Brooks et al. 2010).

Viruses are very small infectious agents (ranging from about 20 nm to about 300 nm in diameter) and contain only one kind of nucleic acid encased in a protein shell, which may be surrounded by a lipid-containing membrane. The entire infectious unit, although very small (termed a virion), can be exceedingly complex (Ryan George Ray 2010) (Fig. 1.1). Viruses are inert in the extracellular environment; they replicate only in living cells, being parasites at the genetic level (Brooks et al. 2010). During the replicative cycle, numerous copies of viral nucleic acid and coat proteins are produced. The coat proteins assemble together to form the capsid, which encases and stabilizes the viral nucleic acid against the extracellular environment and facilitates the attachment and penetration by the virus upon contact with new susceptible cells. The virus infection may have little or no effect on the host cell or may result in cell damage or death (Brooks et al. 2010). As noted viruses are exceedingly small in size and are best visualized with the aid of the electron microscope. However, some viral particles may aggregate within the cells they infect forming characteristic inclusion bodies, which are visible with the light microscope and are useful for diagnosis (McAdam and Sharpe 2010). Examples include inclusion bodies of infections secondary to herpes, rabies, small pox, measles, and the well-known inclusion bodies of CMV infection (Figs. 1.2, 1.3, and 1.4). Concurrent with the development of these inclusions, fusogenic properties imparted upon the host cells by the viral particles will often but not always result in multinucleation, a phenomenon appreciated in the same Figs. 1.2, 1.3, and 1.4.

Viruses may preferentially infect tissues and organs of selected systems but are virtually capable of damaging any organ or tissues in the human host. Clinical respiratory manifestations of pneumotropic viruses are varied; some of these are outlined in Fig. 1.5 (Corrin and Nicholson 2006). Viruses primarily affecting the upper respiratory apparatus (rhinoviruses and non-SARS corona viruses) are not discussed here. In this volume, we are primarily concerned with viruses affecting the lung but recognize that pneumotropic viruses have the potential to infect other anatomical sites resulting sometimes in complex multisystem disease entities. Likewise,

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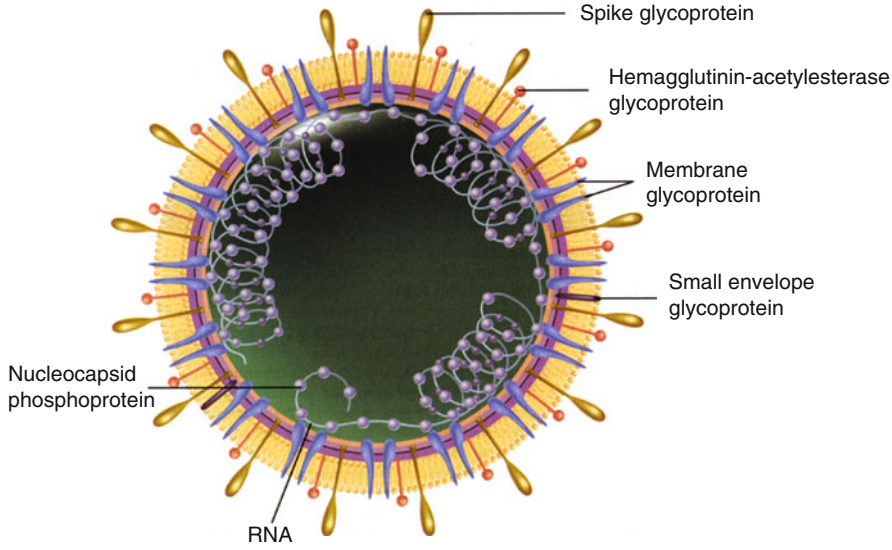

Fig. 1.1 Coronavirus. Structure of a virion (Reproduced with permission from Sherris Microbiology. McGraw Hill)

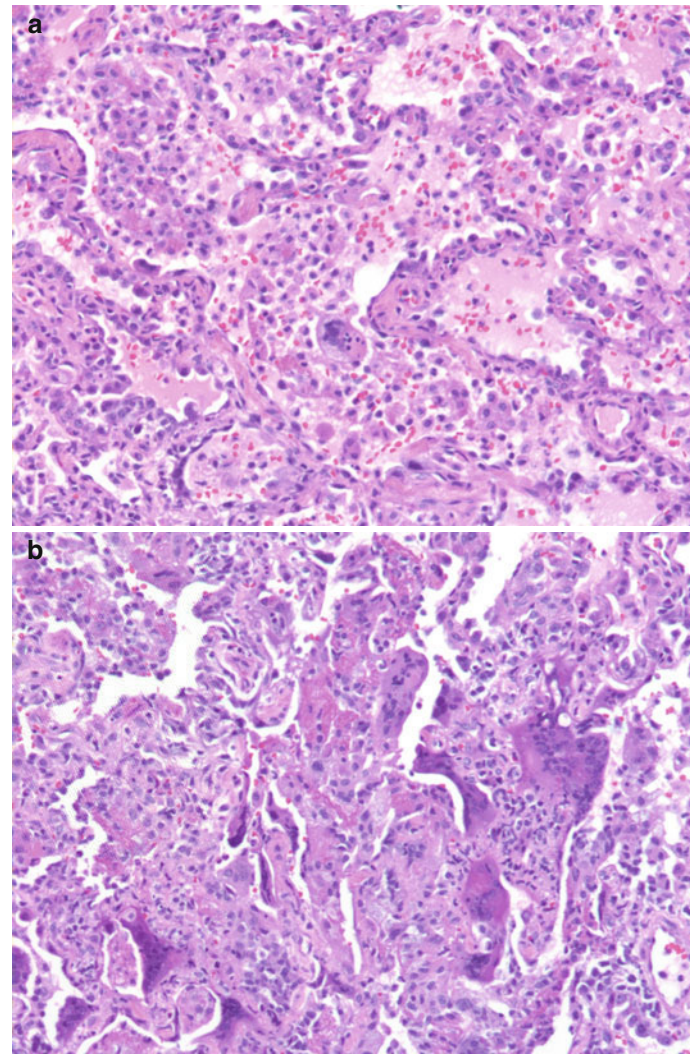

Fig. 1.2 Measles giant cell pneumonia. (**a**) Low-power view showing pneumonic consolidation. (**b**) Cytoplasmic inclusions and multinucleation. Hematoxylin and eosin

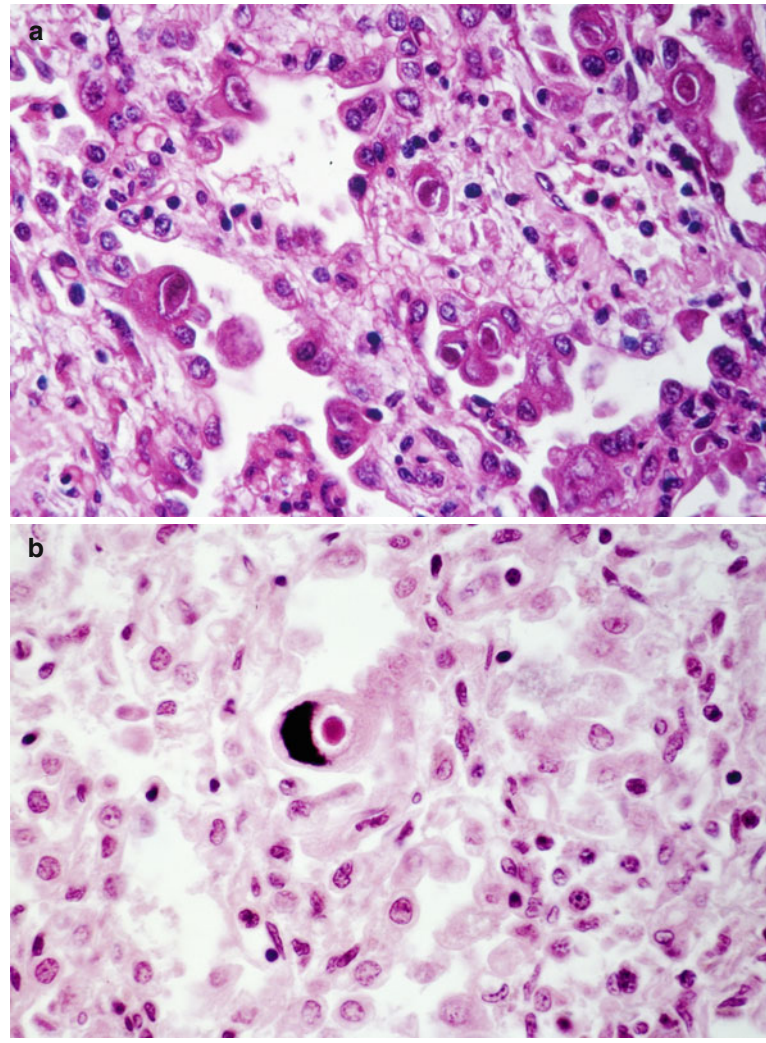

Fig. 1.3 Cytomegalovirus pneumonia. (**a**) Note prominent alveolar epithelial cells. (**b**) Note large "owl's-eye" inclusions. Hematoxylin and eosin

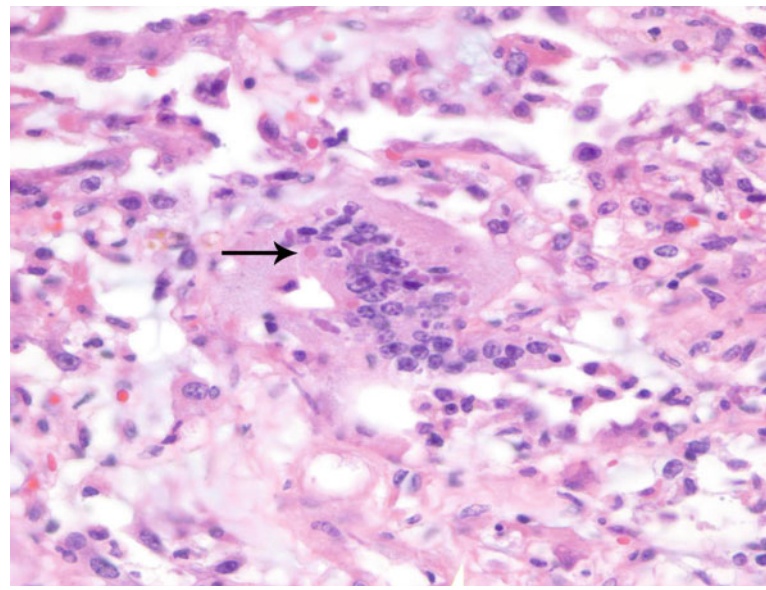

Fig. 1.4 Giant cell pneumonia secondary to parainfluenza. Note multinucleation and *pink* (eosinophilic) viral inclusions (*arrow*). Hematoxylin and eosin

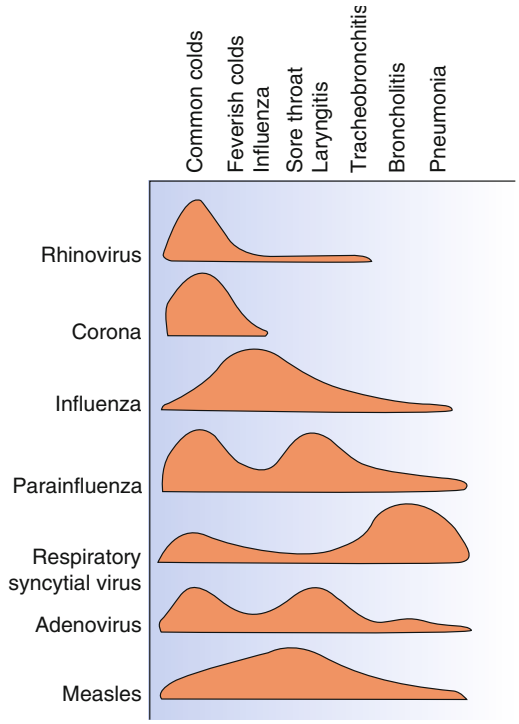

Fig. 1.5 Clinical features of common respiratory viruses (Reproduced with permission from Pathology of the Lungs. Corrin and Nicholson. Churchill Livingstone)

Table 1.1 Viruses that infect the lower respiratory tract

Normal host
Primary respiratory infection
Respiratory syncytial virus
Adenovirus
Parainfluenza virus
Influenza virus
Secondary to systemic infection
Measles virus
Adenovirus
Varicella zoster virus
Immunocompromised host
Cytomegalovirus
Varicella zoster virus
Adenovirus
Herpes simplex virus

With permission from Corrin, page 150 (Churchill Livingstone Elsevier)

viruses that primarily target other organs or systems such as the gastrointestinal tract or the central nervous system may also secondarily involve the lung (Table 1.1) (Corrin and Nicholson 2006).

Acute viral respiratory tract infections remain a leading cause of morbidity, mortality, and economic loss. Although often self-limiting in healthy adults, these infections are responsible for a substantial loss of productive time and are important factors in the illness and death of the very young, immunocompromised individuals, and elderly individuals (Gillim-Ross and Subbarao 2006). In the last 10 years a number of novel human viral respiratory pathogens have been identified, leading to a heightened level of awareness and the development of measures to control them. The identification of novel viruses is both a result of the application of new, more sensitive techniques enabling the detection of viruses that have been circulating in the human population for years and the result of the recent introduction of viruses into the human population (Gillim-Ross and Subbarao 2006).

Interactions between animals and the human host are critical elements in the epidemiology of some viral illnesses (Bhatia and Narain 2010). Diseases transmitted from animals have assumed substantial public health importance. Avian influenza, severe acute respiratory syndrome (SARS), and Nipah virus infection are examples of a growing number of diseases that humans can contract from animals. These diseases can cause huge economic losses in addition to mortality and morbidity. In certain areas of some developing Asian countries, there is a continuous and close contact between animals and humans, especially in rural settings. The prevailing sociocultural practices and weak public health infrastructure further enhances the vulnerability of Asia and the Pacific Islands as the epicenter of outbreaks due to zoonotic infections. There is a clear need for greater awareness and application of a multisectoral and multidisciplinary approach to prevent and control zoonotic infections (Bhatia and Narain 2010). In recognition of said interactions between various animal species and human hosts, this volume contains a chapter of important animal pathogens, including some with potential to generate pandemics (Bhatia and Narain 2010).

Table 1.2 Potential viral agents of bioterrorism

Category A[a]
Smallpox virus
Viral hemorrhagic fever viruses
Category B
Viruses responsible for viral encephalitis (i.e., Venezuelan equine encephalitis)
Category C
Nipah and Hendra viruses

Adapted from data derived from the Centers for Disease Control and Prevention. Atlanta, GA

[a]Agents in category A pose the highest risk of contagiousness, can be readily transmitted from person to person, and can impact significantly on public health. Agents in categories B and C carry a lower level of contagiousness

The threat of avian influenza to the human population and the potential for the reemergence of SARS-associated coronavirus underscore the necessity for the development of therapeutic and preventive strategies to combat viral infection (Franks et al. 2003). Vaccine development is a key component in the prevention of widespread viral infection and in the reduction of morbidity and mortality associated with many viral infections (CDC 2000; Franks et al. 2003). Regrettably, the efficacy of vaccines has not been as adequate as may be expected in human respiratory infection due to viruses; see Chap. 11, Respiratory Syncytial Virus. The threat of emerging infectious agents responsible for disease other than influenza and SARS as potential agents of bioterrorism is a major public health concern and is closely monitored by agencies such as the Centers for Disease Control and Prevention (Table 1.2) (CDC 2000).

The way in which viruses are characterized changes rapidly, with genomic sequencing now affording accurate identification of new virus families and species. A variety of features other than genomic sequencing have been used as bases for the taxonomic classification of viruses. These features, including antigenicity, virion morphology, and physicochemical characteristics, are useful aids contributing to the classification of viruses and are described in the next chapter, dedicated to the taxonomy of viruses.

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Lung Defenses

2

Armando E. Fraire and Raymond M. Welsh

The lung is a vulnerable organ. Along with the skin and the gut, the lung is at the interface of the sterile body sanctuary and the environment and is thus exposed to numerous agents capable of inflicting injury (Fraire 2008; Berman and Center 1998). These agents include viruses, bacteria and physicochemical factors, against which the lung may respond by eliciting an inflammatory reaction and/or mounting an immune response. This chapter briefly considers the remarkably effective and biologically complex defense mechanisms of the lung, particularly those that apply to viral-associated infections.

Classic defense mechanisms such as cough and mucociliary clearance offer only limited protection against viruses, primarily due to their exceedingly small size. Given these limitations, much of the needed defense to combat viral infections is derived from soluble mediators. Two of the most abundant soluble mediators found in airway secretions are lysozyme and lactoferrin. Most of the antimicrobial effects of these two mediators are focused on gram-negative bacteria in the case of lysozyme and both gram-negative and gram-positive bacteria in the case of lactoferrin (Kobzik 2008). In vitro defensins are potent microbicidal agents against many gram-positive and gram-negative bacteria, yeast, fungi, and some enveloped viruses (Kobzik 2008).

The immune response to infection encompasses innate immunity and adaptive immunity. Innate immunity is provided by physical, cellular, and chemical systems that are in place and respond to all classes of foreign invaders (Sherris 2010). These include mucosal barriers, phagocytic cells, and the action of circulating proteins such as complement molecules and mannose-binding protein (Sherris 2010). Further, many cells, including dendritic cells (DC) and macrophages, have recognition molecules that detect pathogen-associated molecular patterns (PAMPS), including nucleic acids, proteins, and glycolipids. Pathogen engagement of these recognition molecules, which include Toll-like receptors, cytoplasmic helicases, and other cellular sensors, can stimulate the synthesis of inflammatory cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF) and antiviral cytokines including interferons. These and other cytokines will activate innate cells such as DC, macrophages, and natural killer (NK) cells and contribute to an early antiviral response that sets the stage for the adaptive immune response. Adaptive immunity, which is also called acquired immunity, refers to the ability to develop new responses that are highly specific to antigens derived from infectious agents. This is a consequence of the expansion of antigen-specific clones

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of T cells and antibody-producing B cells. In regard to viruses, it has been shown that previous immunity to one certain virus can influence a host response to an infection by a subsequent unrelated virus or viruses (Chen et al. 2003). Immunity to viral infections can also be influenced by commensal bacteria. Commensal bacteria are crucial in maintaining immune homeostasis in the gut, but the role of such bacteria in immune response of the lung and other mucosal surfaces is not well known (Ichinohe et al. 2011). Ichinohe examined the role of commensal bacteria in the initiation of adaptive immunity after respiratory infection with influenza virus and demonstrated that commensal bacteria contributed to immunocompetence of the lung. This was mediated in part by providing signals for robust priming of pro-IL-1B and pro-IL-18 expression, at steady state. These authors concluded that a key role exists for commensal bacteria in controlling adaptive immunity against respiratory virus infections, in this case influenza.

As noted by Land, viruses are macromolecular complexes made up of proteins plus DNA or RNA. Upon gaining access to the host cell source of energy and synthetic organelles, viruses effectively redirect host cell metabolism and synthetic capabilities in order to replicate and transmit their progeny (Land 2008). At this point, the immune system is activated and recognizes the virus as a foreign antigen. This protective mechanism is accomplished via the innate mechanisms cited above or by adaptive immunity. Soon after gaining entry into a host, viruses disseminate further by spreading via lymphocytes or the blood stream, leading to damage manifested as inflammation. Damage is the result of cell lysis and influx of cytokines (Land 2008).

2.1 Cellular Elements

In the complex process of cellular defense in the lung, lymphocytes and pulmonary macrophages stand out, as they play key roles in the inflammatory response, with some direction by dendritic cells . T and B lymphocytes display antigen specificity and play a significant role in defense against viruses. NK cells can also display some antiviral activity by virtue of their ability to sometimes distinguish between self and virus-infected self (Berman and Center 1998). Lymphocytes derive from progenitor stem cells in the marrow and thymus, leaving their initial milieu in a static state, designated to become B cells or T cells. The B cells mature in the bone marrow and then circulate in the blood to lymphoid organs (Sherris 2010). T cells mature in the thymus and then, like the B cells, circulate into the lymphoid organs, where they can interact with the B cells. NK cells are also derived from the bone marrow and circulate throughout the body. In the lymph nodes, B cells transform into plasmacytoid lymphocytes and eventually into plasma cells, which produce antibodies. T cells, on the other hand, mature in the thymus and then circulate, awaiting activation by antigen presented most efficiently by DC. This activation results in production of cytokines, which are effective molecules for multiple immunocytes and somatic cells (Sherris 2010).

2.2 Cytokines

Cytokines, broadly defined as active molecules released from a certain cell type and designed to have an effect on another or different cell population, play a critical role in antiviral defense mechanisms (Sherris 2010). Cytokines include chemokines, which are chemotactic factors for inflammatory cell migration, and interleukins, which are regulators of growth and differentiation of lymphocytes, monocytes, and DC. Cytokines also include TNF, an inducer of apoptosis, and interferons, which block viral replication and are critical to activation of NK cells, T cells, DC, and macrophages. Among these cytokines, interferons are of particular interest due to their antiviral properties. Interferons are regulatory cytokines produced by many nucleated cells, especially DC, in response to viral infection and are crucial in the early stage of viral infection. Interferon-stimulated cells shut down viral protein synthesis and effectively destroy viral mRNA. Interferons can also stimulate the activity of T cells and NK cells, thus accelerating the immune response to viral infection. The

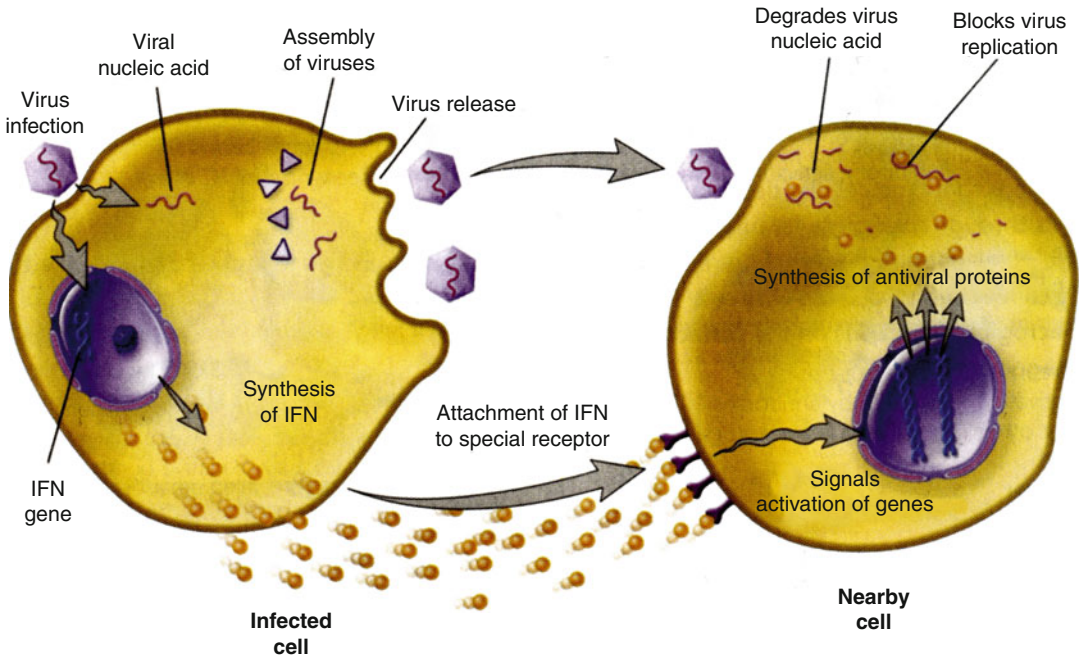

Fig. 2.1 Antiviral action of interferon: Interferon (IFN) synthesis and release are often induced by a virus infection when cellular sensors recognize their pathogen-associated molecular patterns such as double-stranded RNA or cytoplasmic DNA. This releases transcription factors that stimulate the synthesis of mRNA, and the translated IFN protein is secreted onto a neighboring cell. IFN binds to receptor on the plasma membrane of a second cell, and that binding stimulates the activation of genes encoding antiviral proteins. Two important antiviral proteins are the enzymes 2–5 oligo (A) synthetase and protein kinase R (PKR). When an IFN-stimulated cell is infected, viral protein synthesis is inhibited by a 2–5 A-activated endoribonuclease that degrades viral mRNA and by the PKR, which phosphorylates and inactivates the initiation factor eIF-2 required for viral protein synthesis (Reproduced with permission from Wiley J, Sherwood L, Woolverton C, Eds. Prescott's Principles of Microbiology, New York: McGraw-Hill; 2008)

complex antiviral effects of interferon are graphically illustrated in Fig. 2.1.

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Taxonomy

3

Michael Mitchell

This chapter addresses the classification and taxonomy of viruses with special attention to viruses that show pneumotropic properties. Information provided in this chapter supplements that provided in other chapters in Parts II–V of this volume that discuss individual viral pathogens.

3.1 Brief Introduction

Taxonomy may be defined as a logical discipline for the identification and classification of biological entities based on objective, measurable characteristics of relevant entities. Useful taxonomic systems should be broadly applicable across diverse types of biological groups. They should also be flexible, so that new data from technological advances may be integrated into the classification scheme. Primary goals of systemic taxonomy, regardless of biological discipline, include the following:

- Establishing groups (taxa) that reflect varying degrees of evolutionary relatedness among the different biological entities studied
- Establishing criteria for assignment of known or unknown clinical isolates to a given group
- Establishing a clear and unequivocal nomenclature

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The origins of biological taxonomy are firmly rooted in botany and zoology. Early taxonomic systems relied on gross characteristics, like biological niche, internal and external morphology, reproductive strategies and compatibilities, and fossil records. The seminal works of the Swedish botanist Carl Linnaeus used a hierarchical scheme to represent biological relatedness and established the simplified binomial system of nomenclature that serves as the basis for modern classification systems. The modern scientific classification in biology is designed to describe all biological entities within a hierarchy consisting of the following taxa:

Domain → Kingdom → Phylum → Class → Order → Family → Genus → Species

A basic assumption for the establishment of such a hierarchy assumes that all biological entities have evolved from a single common cellular life-form. Different biological entities have evolved as a result of accumulated changes in DNA that have provided survival advantages in different ecological niches. Species may be classified on the basis of phylogenetic and evolutionary relatedness: members of a given species are the most closely related, different species within a single genus are more closely related to each other than to a species within a different genus, and so on. Newer technologies like microscopy, improved biochemical and physiological analysis, and advanced protein and molecular analytical methods have resulted in an enormous

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