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Viral infection of the lung: Host response and sequelae

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Activity Objectives

1. To understand the involvement of the innate and adaptive immune responses during viral respiratory tract infections.
2. To review the mechanisms of viral clearance.
3. To recognize the consequences of acute viral infections.
4. To provide evidence of the effect of viral infections in asthmatic patients.

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Because of its essential role in gas exchange and oxygen delivery, the lung has evolved a variety of strategies to control inflammation and maintain homeostasis. Invasion of the lung by pathogens (and in some instances exposure to certain noninfectious particulates) disrupts this equilibrium and triggers a cascade of events aimed at preventing or limiting colonization (and more importantly infection) by pathogenic microorganisms. In this review we focus on viral infection of the lung and summarize recent advances in our understanding of the triggering of innate and adaptive immune responses to viral respiratory tract infection, mechanisms of viral clearance, and the well-recognized consequences of acute viral infection complicating underlying lung diseases, such as asthma.
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Key words: *Viral sensor molecules, innate immunity, adaptive immunity, T-cell immunity, B-cell immunity, viral clearance, tissue repair, stem cells*

Viewed as an organ, the lung is a highly compartmentalized structure with the primary function of gas exchange. Like other organs, such as the skin and gastrointestinal tract, that are exposed to the external environment, the lung possesses physical and chemical barriers to microbial invasion. Thus the conducting airway epithelial cells provide both mechanical (ie, ciliated epithelial movement and mucus production) and biochemical (ie, antimicrobial enzymes/peptides) barriers that inhibit colonization of the lungs by most microorganisms. However, many respiratory pathogens (and some commensal microbes), including viruses, have evolved to successfully colonize and replicate on or within the lung epithelial cells, occasionally causing life-threatening diseases.

The cellular constituents of the normal lung include cells of hematopoietic origin ($CD45^+$), as well as stromal cells ($CD45^-$). Among the stromal cell types, type I and II alveolar epithelial cells and several epithelial cell subtypes lining the conducting airway are of particular importance because they are the primary cell types targeted by certain respiratory tract viruses and importantly by the subsequent host immune response to infection. Cellular destruction produced by the virus, host response, or both can, if extensive enough, result in severely compromised

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Abbreviations used
AIM2: Absent in melanoma 2
APC: Antigen-presenting cell
ASC: Apoptosis-associated speck-like protein containing CARD
CTL: Cytotoxic $CD8^+$ T-cell
DAMP: Damage-associated molecular pattern
DC: Dendritic cell
GC: Germinal center
HMGB1: High-mobility group box 1
IAV: Influenza A virus
ILC: Innate lymphoid cell
ILC-II: Type II innate lymphoid cell
IRF: Interferon regulatory factor
LAPC: Late activator antigen-presenting cell
MAVS: Mitochondrial anti-viral signaling
MLN: Mediastinal lymph node
NK: Natural killer
NLRP3: Nod-like receptor family protein 3
PAMP: Pathogen-associated molecular pattern
PRR: Pattern recognition receptor
RIG-I: Retinoic acid–inducible gene I
RLR: RIG-I–like receptor
RSV: Respiratory syncytial virus
T_{FH}: Follicular helper T
TLR: Toll-like receptor
Treg: Regulatory T

pulmonary function. Therefore efficient suppression of early viral replication and minimization of immune-mediated injury are quintessential hallmarks of effective recovery from pulmonary viral infection.

In this review we will discuss recent developments in the process of innate immune recognition during viral respiratory tract infection, immune effector mechanisms involved in viral clearance and injury development, recovery from infection, and the effect of viral respiratory tract infection on underlying lung diseases.

INITIATION PHASE

Initiation of antiviral innate immunity in the lung

The successful initiation of the host immune response to microbial invasion requires the recognition of pathogen-associated molecular patterns (PAMPs). This is achieved through recognition of microbial PAMPs by 1 or more of a variety of cellular receptors (pattern recognition receptors [PRRs]) for these PAMPs displayed by $CD45^-$ stromal cells, such as respiratory epithelial cells, as well as $CD45^+$ cells, within the lung.[1-3] Recent studies also emphasize the importance of host immune cell recognition of damage-associated danger signals (damage-associated molecular patterns [DAMPs]) typically composed of sequestered self-constituents released from infected cells, damaged cells, or both.[4] These PAMP and DAMP molecular "red flags" can also activate the intracellular innate protein complex, the inflammasome, which also can play a key role in orchestrating both the innate and adaptive immune responses to viruses.[5,6] In addition, the role of complement in controlling early viral replication and in the initiation of innate and adaptive immunity is being increasingly appreciated. Thus an emerging view from recent investigations is that that the recognition and subsequent eradication of invading viral pathogens at mucosal sites, such as the airways, requires the concerted action of PRRs, as well as immune sensors of cellular stress/damage arising from viral infection.

Recognition of viral pathogen–associated molecular patterns

Viral infection of epithelial cells is first detected by a germline-encoded set of sensors expressed by epithelial cells and innate immune cells (ie, PRRs), which recognize PAMPs originating from the invading viral pathogens.[3,7,8] PRR sensors include the Toll-like receptors (TLRs); RNA-sensing RIG-I–like receptors (RLRs), such as retinoic acid–inducible gene I (RIG-I) and melanoma differentiation-associated protein 5; and C-type lectin receptors (Fig 1). PRR recognition depends on the detection of evolutionarily conserved microbial ligands that are critical for -microbial structure/function, such as viral envelope proteins and nucleic acid motifs within the DNA or RNA genomes of the virus. Although RLRs sense microbial constituents in the cytosolic compartments, TLRs and C-type lectin receptors detect microbes on the cell surface and in endosomes.[8]

RIG-I is the prototypical member of the RLR family of cytosolic PRRs that recognize nucleotide motifs displayed by RNA viruses (Fig 1). Its primary function is to activate interferon genes through the adaptor mitochondrial anti-viral signaling (MAVS), which in turn engages the interferon regulatory factor (IRF) 3/7 transcription factor signaling pathway.[9] RIG-I signaling is also important for activation of the inflammasome and IL-1β production (see below). Infection of cells by vesicular stomatitis virus or transfection of cells by RNA activates the RIG-I pathway and leads to pro–IL-1β production through a MAVS–CARD9–nuclear factor κB signaling pathway. In parallel, RIG-I can also directly activate the inflammasome complex by binding the adaptor apoptosis-associated speck-like protein containing CARD (ASC) (see below).[10,11] Recently, the interferon-inducible protein absent in melanoma 2 (AIM2) has been identified as a novel sensor for cytosolic DNA, such as DNA virus genomes, through an HIN-200 DNA-binding domain.[12] AIM2 can activate caspase-1 and the inflammasome in addition to inducing type I interferons.[13] (Other potential cytosolic DNA recognition molecules, such as cyclic-GMP-AMP [cGAMP] synthase [cGAS] and DNA-dependent activator of IFN regulatory factors [DAI], have also been implicated as sensors triggering type I interferon responses.) Although RIG-I and AIM2 detect viral PAMPs in the cytosol, TLRs sense these PAMPs within endosomes (eg, TLR3, TLR7, and TLR9) or on the cell surface (eg, TLR2 and TLR4; Fig 1).

The type I interferons (IFN-α and IFN-β) are under tight transcriptional regulation and are induced after recognition of pathogen components during infection by various host PRRs (Fig 1).[14,15] The type I interferons are responsible for inducing transcription of a large group of genes that play a role in host resistance to viral infections, as well as activating key components of the innate and adaptive immune systems, including antigen presentation and production of cytokines involved in activation of T cells, B cells, and natural killer (NK) cells.[15] Plasmacytoid dendritic cells (DCs) are well recognized as the cell type specialized for the production of large amounts of type I interferons.[14] In addition, type III interferons, consisting