Viral Infection, Adaptive Immunity, and COPD

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Abstract: Viruses are now thought to play an important role in chronic obstructive pulmonary disease pathogenesis. Viral infection and adaptive immunity show complex interactions in this disease. Tobacco, pollutants, immunosenescence, and chronic intake of steroids alter the adaptive immune response. Impairment of the adaptive response potentially predisposes to infection by respiratory viruses. Viral infection in turn impacts on the immune response, increasing the risk of bacterial infections, inducing disease impairment and chronic illness. The immunologic basis and clinical implications of this complex relationship are discussed in this study.

Key Words: adaptive, chronic obstructive pulmonary disease, immunity, virus

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Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation of the airways. This inflammation is accompanied by a phenomenon known as airway hyperreactivity, which consists of increased mucus production and an excessive propensity of the airway smooth musculature to contract in response to exogenous stimuli.[1] Inflammation in COPD is associated with a predominance of CD8 T lymphocytes and neutrophil-rich exudates contributing to lung damage. It is thought that COPD could be an autoimmune disease triggered by cigarette smoking.[2]

Although innate immunity is known to play a relevant role in COPD,[3] a growing body of evidence suggests that the adaptive immune response has much to say in the pathogenesis and progression of this disease, as evidenced by correlations of lung histological findings with the characteristics of intrapulmonary lymphocyte infiltrations.[4]

Infection-induced alterations in the adaptive immune response that produce T-cell-mediated or antibody-mediated damage to host tissues may underlie the pathogenesis of a variety of common diseases. In this sense, there is increasing evidence on the role of respiratory viruses in the pathogenesis of COPD. We review here the interactions between the adaptive response and viral infections in this disease.

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ADAPTIVE IMMUNE RESPONSE AND COPD

The adaptive immune system (or acquired immunity) is a branch of the immune system composed of lymphocytes with antigen-specific receptors that, on activation, use multiple effector mechanisms to respond to antigen challenge. This branch of the immune system is classically distinguished from the innate immune system by its ability to collectively respond to any antigen, the exquisite specificity of the receptor for its target, and the generation of a long-lived memory.[5] In contrast, the innate arm of immunity is composed of those immunological effectors that provide robust, immediate, and nonspecific immune responses.[6] Failure in developing appropriate adaptive responses against respiratory pathogens could translate into severe disease outcome.[7]

T and B Lymphocytes

The adaptive immune system is organized around 2 classes of specialized lymphocytes, T and B cells (Table 1). T lymphocytes are the fundamental actors in adaptive immunity (Fig. 1). During thymic maturation, αβ T cells randomly develop expression of CD8, allowing antigen recognition in the context of class I MHC, or CD4, linking recognition to class II MHC. Less than 5% of the lymphocytes complete thymic education, passing to bloodstream and lymph nodes as naive T cells, circulating back again in search of antigenic stimulation. TCD4 subsets play both coordinating and effector roles in the adaptive immunity response. They have been classified based on their cytokine secretion profiles as Th1, defined by production of interferon γ (IFN-γ) and interleukin 2 (IL-2), Th2 cells, defined by the production of IL-4, IL-5, IL-9, and IL-13, and Th17 cells, defined by the production of novel effector molecules, including IL-17A, IL-17F, IL-22, and IL-26 (Fig. 1). Th1 promotes defense against intracellular pathogens, such as viruses, inducing activation of macrophages and TCD8 lymphocytes (T cytotoxic).[8] Th2 response promotes the development of antibody responses against extracellular pathogens, by inducing activation of B cells (Fig. 1).[8] Circulating T cells from COPD patients are abnormally activated and elaborate proinflammatory mediators with admixed features of Th1 and Th2 responses.[4] Th17 has been described to play an important role in mucosal cell defense.[9] Disbalanced/dysregulated Th17 responses participate in the pathogenesis of autoimmune diseases, such as Systemic Lupus Erythematosus or Rheumatoid Arthritis. Th17 adaptive responses seem to play a relevant role in the defense against respiratory virus.[10,11] A potential role for the Th17 cytokines in COPD has been suggested, but their relationship with neutrophilic inflammation is not clear.[12]

Natural Killer and Dendritic Cells

The liberation of immunomodulatory cytokines and chemokines and the upregulation of adhesion molecules by lung epithelium mediate recruitment of leucocytes to the site of infection and modulate the initiation of the adaptive immune response. Inflammation recruits natural killer (NK) cells and

TABLE 1. Key Cells and Events Participating in the Adaptive Immunity

Link Between the Innate and the Adaptive Response	The T and B Adaptive Effector Response	Regulatory Mechanisms of the Adaptive Response
Myeloid DC (TLR4, TLR1, TLR2, and TLR3) Plasmacytoid DC (TLR9 and TLR7) Invariant natural killer T cells Complement NK cells Interferons, cytokines, and chemokines	T cells cellular response αβ T CD4 (Th1, Th2, and Th17) αβ TCD8 (CTLs) Naive T cells: CD45RA$^+$, CD62L$^+$, CD28$^+$ and CD27$^+$ Activated T cells CD45RO$^+$, CD38$^+$, HLA-DR$^+$ and CD25$^+$ Effector T cells CD45RA$^+$, CD62L$^-$, CD28$^-$, CD27$^-$, CCR-7-CD57$^+$ Memory T cells CD45RO$^+$, CD28$^+$, CD27$^+$, CD25$^-$ B and plasmatic cells: Humoral response and antibody production	Mucosal γδ T cells CD4$^+$CD25$^+$ Foxp3$^+$ (Tregs) Human and viral microRNAs

DC indicates dendritic cell; NK, natural killer; TLR, toll-like receptor.

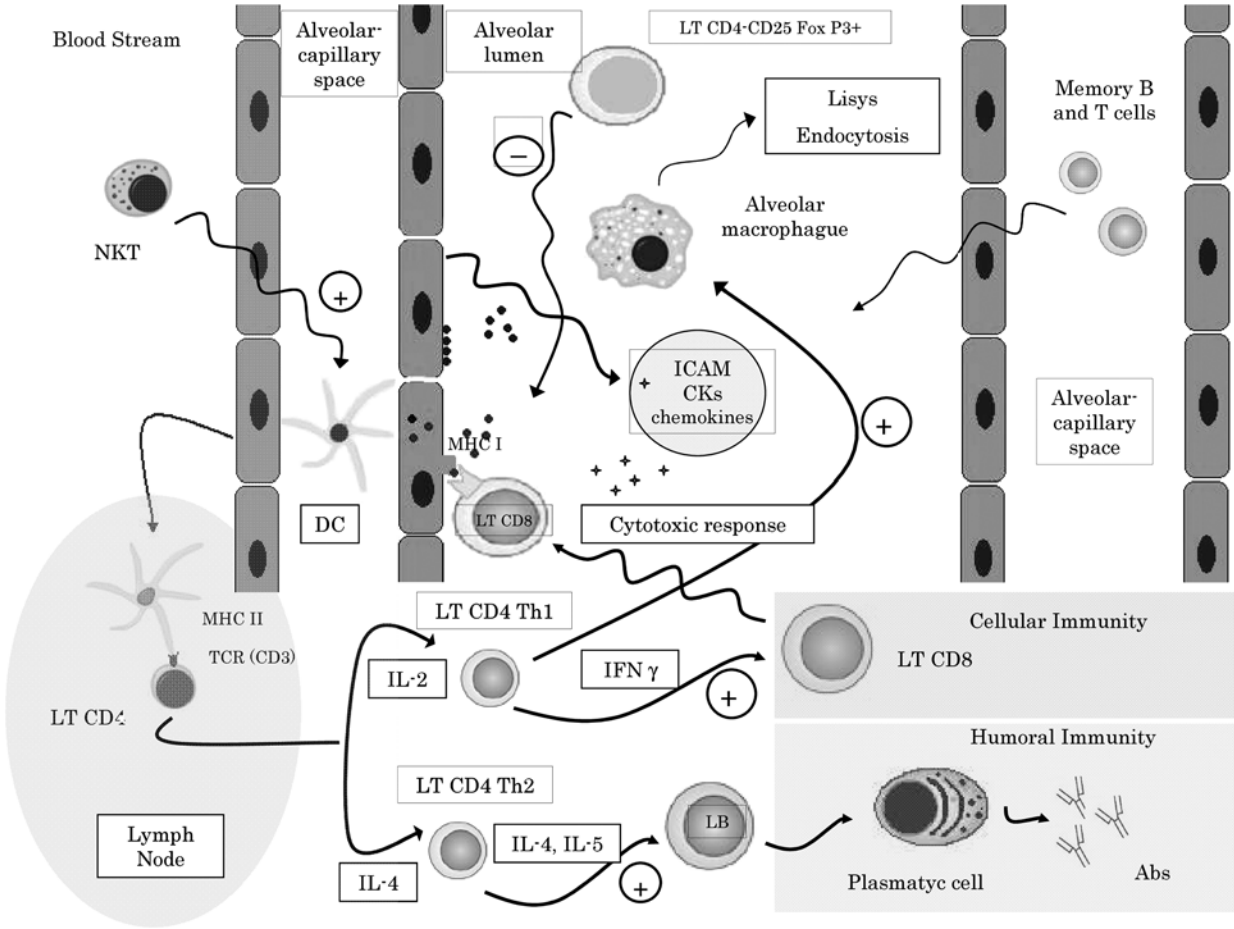

FIGURE 1. Overall view of cell-to-cell interactions participating in the development of the adaptive immunity in chronic obstructive pulmonary disease. Lung epithelial cells infected by the virus initiate the response by releasing cytokines and chemokines, which mobilize immune cells to the focus of the infection. Dendritic cells present viral antigens restricted by MHC II to T-helper cells in the regional lymph nodes, which depending on the cytokine environment, will become Th1, Th2, or Th17 cells. Th1 and Th17 cells promote cellular response to intracellular pathogens, whereas Th2 promotes humoral immunity. CD8 cytotoxic T cells migrate to the focus of infection killing infected cells showing viral peptides associated to MHC I molecules on the cell surface. CD4CD25 Treg cells modulate the response preventing immune-driven tissue damage.

dendritic cells (DCs) that interact in a contact-dependent and tumor necrosis factor-α-dependent manner within injured tissues to initiate immune response polarization. DCs are antigen-presenting cells and are therefore central to adaptive immune responses. DCs are distributed throughout the respiratory tract. In the conducting airways, intraepithelial DCs extend into the fluid within the airway lumen, where they ingest samples from the materials being swept by mucociliary transport from the alveoli toward the glottis.[13] NK cells exposed to IL-12 favor survival of DC that prime for Th1 responses, whereas NK cells exposed to IL-4 do not exert DC selection, leading to tolerogenic or Th2 response.[14] In consequence, epithelial-related actions significantly modulate the transition of the innate to adaptive immune response.[15]

Immature DCs need to express CCR7 to carry antigen from the lungs to the regional lymph nodes by afferent lymphatics. Antigen presentation by these mature DC is required to activate naive CD4 T cells, which are essential to generate polarized type 1 or type 2 effector responses and for robust immunologic memory. On signal transduction through toll-like receptors (TLRs), DCs undergo a complex differentiation program (DC maturation), characterized by upregulation of cell surface MHC molecules containing pathogen-derived peptide fragments and coreceptors (CD40, CD80, and CD86) that enhance the ability of DCs to activate T cells.[16] Two phenotypes of DC are important for lung host defenses: myeloid DC (mDC) expresses TLR4, TLR1, TLR2, and TLR3, allowing them to be activated by LPS, mycopeptides, and viral RNA with production of IL-12. In contrast, plasmacytoid DC (pDC) expresses TLR9 and TLR7, permitting them to respond to bacterial DNA and viruses with production of IFN-α. In response to the presence of microbes in the lungs, more DCs migrate into the lungs, through the tissues, and also into the draining lymph nodes.[13] Cigarette smoke seems to modulate DC function in vitro and alters DC numbers and function.[17] DCs are thought to sustain $CD8^+$ T-cell recruitment and retention in tissues in COPD.

Invariant natural killer T cells (iNKT) are cells that show a relatively invariant T-cell receptor, (Vα24-Jα18/Vβ11), coexpression of the NK cell marker NK1.1, MHC restriction for the nonclassical class I molecule CD1d, and the ability to very rapidly make large amounts of Th1 or Th2 cytokines.[18] iNKT activation modulates the function of DCs in inducing T-cell responses through modulation of particular subsets of these cells (Fig. 1).[19] In vitro data suggest that chronic inflammatory disease in COPD is driven by IL-13 produced by macrophages stimulated by CD1d-dependent iNKT cells.[3]

Regulatory T Cells (Tregs)

Immune reactions in the lung have to be tightly balanced, because the mucosal immune system has to discriminate between harmful invading pathogens, against which an effective immune response has to be generated, and harmless inhaled and self antigens, against which tolerance has to be established. Tregs fulfill a central role in the maintenance of systemic self tolerance. Tregs are capable of inhibiting and modulating diverse immunopathologic phenomena by controlling the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes in vivo. There are at least 2 types of Tregs that perform similar functions. One class, defined by the expression of CD4 and CD25, develops in the thymus under the control of the transcription factor, Foxp3, and resides in all the secondary lymphoid organs (Fig. 1).[20] In addition, inducible Tregs can be generated in the periphery as a consequence of alternative activation of naive T cells in the presence of specific cytokines. Inducible Tregs secrete IL-10[21] and/or transforming growth factor β,[22] both of which are potent regulators of inflammation capable of suppressing the proliferation of effector cells. Normal response of Tregs to tobacco smoking is blunted in patients with COPD,[23] but the exact role of Tregs in this disease remains to be elucidated.[24]

Complement

The complement system plays a critical role in the generation of a robust antibody response (a key event of the adaptive response) at several levels of B-cell biology. As complement influences the development of humoral immunity, it also influences cellular immunity and T-cell biology. There seems to be sufficient evidence supporting a link between complement activation and enhanced T-cell immune response.[6] Elevated local and systemic C5a levels (a potent inflammatory peptide) are found in COPD patients.[25]

Type 1 IFNs

Type 1 interferon (IFN-α/β) production[26–28] is part of the first line of defense against infection and a central modulator of adaptive immunity,[29] including proliferation of memory T cells, inhibition of T-cell apoptosis, enhanced IFN-γ secretion, B-cell isotype switching, and differentiation into plasma cells and NK cell activation.[30] The depletion of DCs or the interruption of type 1 IFN signaling increase susceptibility to viral infection in the lungs.[31,32]

A Proposed Model of Adaptive Immunity Response in COPD

In COPD, antigen-specific T-cell activation results in oligoclonal proliferation of $CD4^+$ and $CD8^+$ T cell subsets, which migrate to the site of inflammation in response to macrophage-derived chemokines. Infiltrating T helper cells (Th1 and Th17) amplify the inflammatory response through the secretion of specific cytokines, which promote neutrophil infiltration, macrophage activation, $CD8^+$ cytotoxic T-cell responses, and autoantibody production by activated B cells (Fig. 1).[33]

VIRAL INFECTION AND COPD

Respiratory Viruses in COPD

Viruses are now thought to play at least as important a role as bacteria in COPD pathogenesis, with viral infection detected in up to 64% of acute exacerbations of COPD (AECOPD).[34] In patients with moderate or severe COPD, the presence of a virus in upper airway secretions is strongly associated with the development of COPD exacerbations.[35] In patients undergoing acute exacerbations, rhinoviruses, coronaviruses, and influenza viruses predominate.[34,36–38] There are not much data on the incidence of coinfections by 2 or more viruses in AECOPD, but based on our own data (unpublished yet), it seems to be very limited. Viral infections have also been detected in stable COPD patients, suggesting that viruses may cause persistent low-grade infection that could contribute to the pathogenesis of the disease.[34] In this sense, the most common virus reported in stable COPD is the respiratory syncytial virus (RSV).[34]

Association of COPD With Chronic Viral Infections

HIV infection is a risk factor for COPD, and COPD is likely to contribute substantially to the morbidity and mortality of HIV-positive patients.[39] Inflammation associated with

subclinical infection has been postulated to promote COPD,[40] but it is uncertain whether the degree of HIV-related immunodeficiency or associated factors, such as an augmented prevalence of cigarette smoking among HIV-positive persons, explain the increased risk of COPD in this group. Similarly, a high prevalence of chronic hepatitis C virus infection (HCV) has been observed in patients with COPD in comparison with blood donors.[41] In addition, HCV-positive patients seem to have a more severe disease.[41]

FACTORS IMPAIRING ANTIVIRAL ADAPTIVE IMMUNITY IN COPD

Tobacco and Environmental Pollutants

Carcinogens in cigarette smoke cause a significant reduction in release of the antiviral immune mediators IFN-α, IFN-β, and nitric oxide.[42] Tobacco smoking has been previously shown to depress T-cell functions, putatively due to toxicities of acrolein and/or other constituents of complex smoke aerosols.[43,44] As recently described, cigarette smoking suppresses Th1-mediated immune responses to gram-negative bacterial infections by interfering with MyD88/IRAK signaling.[45] Viral infection has a synergistic proinflammatory effect with tobacco.[46] Environmental pollutants may also make viral persistence more likely. For example, carbon black, a component of particulate pollution, helps tip the immune response to RSV from Th1 to Th2 phenotype in the murine model.[47]

Neutrophil Enzymes

Endogenously released neutrophil elastase, increased in lung tissues of COPD patients, seems to interfere with maturation of DCs and to inhibit the ability of mature DCs to present antigens to T cells.[48]

Immunosenescence

COPD usually manifests late in life. A decline in the adaptive immune response parallels ageing.[49] Elder people have fewer CD4 and CD8T cells. Several changes with aging greatly decrease the output of naive T cells, forcing the elderly body to depend on previously existing naive T cells rather than new T cells. Moreover, B cells in older adults have reduced capacity to proliferate and impaired ability to be activated. The quantity and efficacy of antibodies produced in response to antigen exposure in older adults are also reduced. As a consequence, antiviral immunity is also affected by immunosenescence in COPD patients.[50] To compensate for the decline in the adaptive immune function, there is a paradoxical upregulation of the innate immune system resulting in a chronic proinflammatory state in COPD.

Corticosteroids

It is well known that in COPD, histone deacetylase-2 is markedly impaired as a result of oxidative and nitrative stress, so that inflammation is resistant to the anti-inflammatory effects of corticosteroids.[51] Nonetheless, there is not much evidence on the effect of chronic/repeated intake of steroids on the adaptive immune response in COPD. Combination therapy of long-acting bronchodilators with immunosuppressive corticosteroids does seem to slow the rate of lung function decline in COPD patients, but it could also influence antiviral defense. In fact, it is true for bacterial infections: the use of inhaled corticosteroids commonly used for the treatment of COPD has been shown to increase the risk of recurrent community-acquired pneumonia.[52] In contrast, bacterial pathogens apparently are not more frequent among virus infected AECOPD patients and are not associated with more severe disease.[36]

IMPACT OF VIRUSES ON THE ADAPTIVE IMMUNE RESPONSE

Participation of the adaptive immune response in mediating acute disease after respiratory viral infection has been observed in mice models.[53] This adaptive response involves high-affinity IgE receptor on conventional lung DCs, which recruit IL-13-producing CD4(+) T cells to the lower airways. The same models identify an innate immune response driving chronic inflammatory lung disease as a consequence of viral infection, relying on iNKT cells that are programmed to activate macrophages to produce IL-13. Adaptive response would also contribute to perpetuation of damage and disease progression.[4]

Viruses impact on the adaptive response in several different ways:

Modulation of T-helper Response

RSV has been shown to initiate a Th2-type response, directly induced by the RSV G glycoprotein[54] or indirectly by the induction of thymus and activation-regulated-chemokine production in respiratory epithelial cells, which is involved in the recruitment of Th2 cells.[55] RSV could, thus, skew the immune response toward Th2 and away from the antiviral response Th1, facilitating persistence of the virus in a host showing some degree of immunosuppresion at the respiratory mucosae, such as that shown by COPD patients. Viral proteinases are also able to modulate adaptive responses. Rhinovirus-encoded proteinase 2A activates DCs to skew CD4 T-cell development toward the Th1 and Th2 poles.[56] It is thought that this could contribute to AECOPD, by promoting cell-mediated inflammation.

Effect on Nitric Oxide Metabolism

RSV may remain dormant in DCs for prolonged periods replicating by suppression of endogenous NO production,[57] representing a mechanism of viral persistence in stable COPD.

Effect on Antibacterial Response

Viral infection alters antibacterial responses: rhinovirus impairs lipopolysaccharide-induced and lipoteichoic acid-induced TNF-α and IL8 secretion by macrophages. These are important cytokines to recruit cells of the adaptive immune system.[58] Viruses, such as influenza, induce the secretion of cytokines with immunosuppresive activity as IL-10 to evade the adaptive immune response.[59] Pandemic influenza virus is able to modulate adaptive responses by inducing Tregs, which could explain augmented susceptibility to pneumococcal infections in patients suffering from infection by nvH1N1.[60]

T-cell Exhaustion

Repeated viral infections select for T cells with broad crossreactivity, but can result in the dropout of some CD8 clones. For example, HIV chronic infection can lead to a process of "clonal exhaustion" of T lymphocytes by exerting a maintained pressure on the immune system, leading to limitation of TCR repertoire.

MHC Down Modulation

Viruses have a wide range of strategies aimed to escape from the cytolytic activity of CD8 and CD4T cells, which requires previous antigen presentation. One of these strategies consists of downmodulation of the MHC molecules needed for

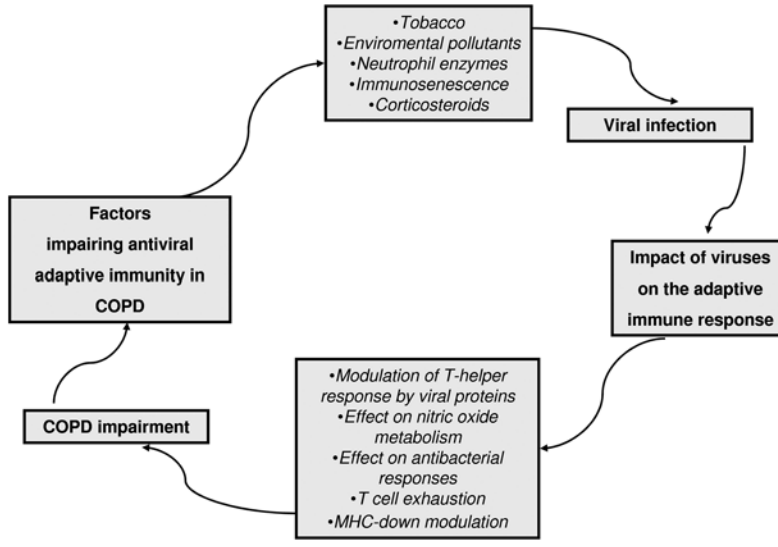

FIGURE 2. Interactions between the adaptive immune response and viruses in chronic obstructive pulmonary disease (COPD).

the antigen presentation process. Classical NK cells overcome this situation, as they mediate the lysis of cells lacking HLA molecules on their surface.

THE FUTURE

It is very important to evaluate the influence of repeated viral infections in the prognosis of COPD, as well as to clarify the potential role of viral persistence in the outcome of this disease. It is also important to know more on the potential role of COPD patients as reservoirs of respiratory viruses and their influence on the origin of the annual epidemics observed in temperate countries. The appearance of novel immunomodulators and antivirals could offer a new opportunity for the treatment of viral infections and their consequences in COPD. The emergence of new diagnostic methods and of high throughput analysis tools for the study of human and viral genome/transcriptome offers an excellent opportunity to evaluate the molecular basis of the interactions between viruses and adaptive immunity in this disease.

CONCLUSIONS

Viral infection and adaptive immunity show complex interactions in COPD (Fig. 2). Tobacco, pollutants, immunosenescence, and chronic intake of steroids alter adaptive immune response. Impairment of the adaptive response potentially facilitates infection by respiratory viruses. Viral infection in turn impacts on the immune response, increasing the risk of bacterial infections, inducing disease progression, and chronicity. Early diagnosis and treatment of viral infections in COPD patients could translate into a better control of disease evolution.

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