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Humoral Immune Responses to *Streptococcus pneumoniae* in the Setting of HIV-1 Infection

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Abstract

Streptococcus pneumoniae (pneumococcus) remains one of the most commonly identified causes of bacterial infection in the general population, and the risk is 30-100 fold higher in HIV-infected individuals. Both innate and adaptive host immune responses to pneumococcal infection are important against pathogen invasion. Pneumococcal-specific IgA antibody (Ab) is key to control infection at the mucosal sites. Ab responses against pneumococcal infection by B cells can be generated through T cell-dependent or T cell-independent pathways. Depletion of CD4⁺ T cells is a hallmark of immunodeficiency in HIV infection and this defect also contributes to B cell dysfunction, which predisposes to infections such as the pneumococcus. Two pneumococcal vaccines have been demonstrated to have potential benefits for HIV-infected patients. One is a T cell dependent 13-valent pneumococcal conjugate vaccine (PCV13); the other is a T cell independent 23-valent pneumococcal polysaccharide vaccine (PPV23). However, many questions remain unknown regarding these two vaccines in the clinical setting in HIV disease. Here we review the latest research regarding B cell immune responses against pneumococcal antigens, whether derived from potentially invading pathogens or vaccinations, in the setting of HIV-1 infection.

Keywords

Humoral immune responses; B cells; *Streptococcus pneumoniae*; HIV

Introduction

Streptococcus pneumoniae is one of the most commonly identified causes of bacterial infection in the general population and a major cause of otitis media, meningitis and empyema in children and elder adults. Based on differences in the polysaccharide capsules of the pneumococcal cell wall, *Streptococcus pneumoniae* is classified into over 90

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serotypes, which present different antigenic properties and induce different inflammatory responses [1-7]. Epidemiologically, the prevalence of pneumococcal serotypes causing disease varies around the world. As shown in Table 1, the serotypes 1, 14, 23F, 19F, 6A and 19A are common invasive strains worldwide. Serotypes 1, 3, 7F, 14, 6B, 6A, 19A, 19F, 23F, 22F account for almost 90% of invasive pneumococcal infections in the USA [8-12].

Pneumococcus is a relatively common colonizer of the human nasopharynx and therefore its isolation from the mouth of healthy asymptomatic individuals is generally considered to be harmless. However, invasion of pneumococcus into other, normally more sterile sites, such as the lower respiratory tract, the lungs, and the blood, can cause serious disease [13, 14]. In the setting of a weakened or immature immune system (young children, elderly patients, and especially patients with AIDS), the bacterium can explosively amplify on the surface of epithelial cells [15, 16]. *Streptococcus pneumoniae* is a major cause of bacterial infection in HIV-infected patients and there is a 100-fold increase in the setting of AIDS compared with the general population [17, 18]. An inverse correlation between plasma levels of HIV RNA and serum opsonic activity against type 3 and type 9 strains of *S. pneumoniae* has been detected in asymptomatic HIV-infected persons [19]. Invasive pneumococcal diseases (IPD) have been a commonly reported, severe complication among HIV-1 infected patients [20, 21]. In HIV-infected children, IPD was noted in the era prior to effective antiretroviral therapy to occur with nearly a three times higher incidence than among HIV-negative children, leading to poorer outcomes and a higher mortality rate [22-24].

Research suggests an association between impaired humoral immune responses and IPD in HIV infection [25]. Effective antiretroviral therapy likely cannot fully restore B cell function. HIV infected patients have low antigen-specific IgG titers in serum and a diminished antigen-specific IgA activity in the epithelial lining fluid from the lung. These immunoglobulins display an extremely low immune killing activity against various serotypes of *S. pneumonia* [26-29], reflecting both impaired quality and quantity of antigen-specific Abs. Therefore, in this review we will focus on recent studies regarding humoral immune responses to pneumococcal antigens, either in the setting of *S. pneumoniae* infection or pneumococcal vaccination, in HIV-infected patients.

Humoral immune responses against *Streptococcus pneumoniae* infection

Innate immune responses play a pivotal role in host defense against the pneumococcus at the earliest stages of infection. These responses are determined through innate immune elements called pattern recognition receptors (PRRs), consisting of the Toll-like receptors (TLRs), the cytosolic NOD-like receptors (NLRs) and DNA sensors. *Streptococcus pneumoniae* has been shown to activate phagocytic cells and then be destroyed through different mechanisms involving TLRs, subsequently inducing B cells to produce cytokines including TNF- α , IL-6, and pro-IL-1 β [30-35]. The complement system is activated through a C3-dependent cascade in response to *Streptococcus pneumoniae* infection [36]. Knock-out of early components in the classical complement pathway and C3 can increase risks of pneumococcal diseases [37], showing that the complement system is important for controlling pneumococcal infection early on. Moreover, as a bridge to adaptive immunity, C3 consequently leads to B cell activation through complement receptors CD21 and CD35 [38]. After antigen stimulation by

pneumococcal capsular polysaccharides, naïve B cells can differentiate into IgM+ memory B cells and produce pneumococcal-specific IgM without T cells help; later, during hypermutation and class switching, some pneumococcal-specific IgM+ B cells will differentiate to pneumococcal-specific IgG+ or IgA+ memory B cells or plasma cells [39].

IgA is mainly located at mucosal sites and is recognized as a key humoral defense against pneumococcal infection. After pneumococcal infection, pneumococcal-specific IgA can be detected at the nasal and salivary mucosal sites [39-41]. In an IgA^{-/-} mouse model, high numbers of colony-forming units (CFU) were still detectable after pneumococcal infection despite a high level of antigen-specific IgG Abs after priming with pneumococcal surface adhesion A (PspA). In contrast, no pneumococcus was found in IgA^{+/+} mice immunized by PspA before pneumococcal infection [42]. Moreover, a nanogel-based PspA nasal vaccine protects mice against pneumococcal respiratory infection [43]. The observations from clinical studies also support these findings: IgA-deficient patients have reduced vaccine responses to pneumococcal vaccination and have higher rates of recurrent infections and bronchiectasis [44, 45].

Interestingly, Park S et.al found that the protective effect of Abs against pneumococcus in young adults was abrogated by the removal of IgM, but not IgA [46]. Moreover, a decline of CD27+ memory B cells, particularly IgD+IgM+CD27+ memory B cells, has been implicated in the high incidence of lethal pneumococcal infections in the elderly population, suggesting that IgM is also critical for immune responses against infection [47]. After pneumococcal vaccination, the pneumococcal polysaccharide (PPS)-specific B cell population was identified on CD27+IgM+ memory B cells or switched memory (CD27+IgM-) B cells [48-51]. Since IgM is the first Ab after neo-antigen stimulation, prior to IgG or IgA, defects in IgM may impact on antigen-specific IgG+ or IgA+ B cell maturation and function, thereby impairing late humoral responses and consequently leading to more severe bacterial infections [52-55]. Consistently, patients with low levels of IgM+ memory B cells have impaired immunity to pneumococcal infection and often develop recurrent respiratory infections [56, 57]. Severe IgM deficiency has been linked to particularly poor Ab responses against all pneumococcal polysaccharide serotypes, leading to more frequent, life-threatening pneumococcal infections [58]. In mouse models, depletion of IgM-producing B cells results in impaired immune responses against pneumococcal polysaccharide [59]. Furthermore, transplant of B cells and CD4+ T cells from immunized mice into naïve recipients can enhance the immune response to PCV13 vaccination [60]. Findings from these studies point to the pivotal role of IgM, especially IgM+ memory B cells, in host immune responses against pneumococcal infections.

Moreover, the decline of IgM+ memory B cell has been suggested to account for the reduced IgG responses to pneumococcal infection in otitis-prone children [55]. Common variable immunodeficiency (CVID) patients with decreased percentages of switched memory B cells have lower levels of serum IgG and reduced responses to pneumococcal vaccination [61]. These CVID patients have more frequent recurrent bacterial pneumococcal infections and bronchiectasis compared to those with normal IgM [62-65]. Collectively, these studies indicate that IgA and IgM-producing memory B cells are critical for the local humoral immune response against pneumococcal bacterial infection [53].

Memory B cell dysfunction in HIV disease

HIV infection is associated with B cell dysfunction: memory B cell depletion, polyclonal B cell activation, and impaired vaccine responses [66-71]. However, the mechanism of B cell dysfunction in HIV disease is not fully understood. The lack of CD4⁺ T cells, especially follicular helper CD4 T (Tfh) cells, may account for some of these deficiencies. Blockage of PD1 expression or delivery of Fc-fused IL-7 can restore Tfh cell function and enhance the secretion of Abs from B cells in response to influenza virus challenge, suggesting a critical role of Tfh cells in humoral immunity [72-75]. Similar results were found in bacterial infection, as which blockage of PD1 can reverse chronic salmonella infection induced high levels of Abs via its inhibitory effect on Tfh cells function [76]. In addition, Tfh cells dysfunction decreased the secretion of IgA plasma cells in the gut of PD1 deficient mice [77, 78], subsequently destroying the integrity of the intestinal barrier and increasing the translocation of microbial products from gut, which has been implicated as an important mechanism for B cells dysfunction in HIV infected patients [79-81]. Although HIV infection is characterized by CD4⁺ T cell decline, a relatively higher percentage of Tfh cells among total CD4⁺ T cells than the percentage of other subsets has been found in HIV-infected patients compared to controls [72, 82, 83]. In HIV-infected individuals, the functions of Tfh cells are relatively preserved in terms of IL-21 and Bcl-6 production, but they are impaired in terms of their capability to support B cells in the production of high affinity Abs [73, 82, 83]. The depletion of absolute CD4⁺ T cells including Tfh cells could account for the reduced quality and quantity of antigen-specific Abs in HIV-infected patients; however, the ratio of Tfh to B cells may not be decreased due to a commensurate severe depletion of B cells as well. In addition, B cell dysfunction (e.g., apoptosis) has been shown at the single cell level [70]; thus, the reduced antigen-specific Ab in HIV infection could be due in part to intrinsic B cell dysfunction rather than Tfh cell dysfunction.

Intrinsic B cell problems have been shown in HIV disease, including hypergammaglobulinemia, spontaneous B cell apoptosis, enrichment of CD21^{low} B cells, impaired proliferation responses to T cell-independent B cell antigens, CD40L and CpG ODNs [84-87]. The enriched CD21^{low} fraction of B cells in HIV infected patients has been considered as a pool of exhausted tissue-like memory B cells with defects in antigen-induced B cell proliferation responses [88, 89]. Microarray data reveal that this CD21^{low} fraction of B cells highly express tumor necrosis factor superfamily (TNFSF) receptor CD95, which is correlated with increased susceptibility to Fas/FasL cell signaling mediated apoptosis [88, 90]. Exhausted tissue-like memory B cells isolated from the tonsil have a short life and poorly respond to viral infections [70, 91]. Moreover, the data from our group and other groups suggest that pDCs produce cellular apoptotic mediators (e.g., TRAIL, FasL) in response to HIV through type I interferon, mediating the B cell apoptosis [92-95].

Generally, ineffective B cell responses lead to a decreased IgG response to *Streptococcus pneumoniae* infection [96], which is accounting for the incidence of otitis in young children [97, 98]. HIV-infection is associated with the depletion of memory B cells in children compared with those in healthy control children [99]. Moreover, HIV infection leads to a progressive memory B cell depletion and consequently an extremely low levels of pneumococcal-specific Abs in antiretroviral therapy (ART)-naive HIV-infected individuals,

which make the patients in a high risk of severe *streptococcus pneumonia* infection and hypo-responsiveness to pneumococcal vaccination [66, 100]. Importantly, successful ART treatment does not appear to fully rescue memory B cell function (58,129). In the patients treated long-term with ART, impaired antigen-specific IgM and IgG responses are detected post-immunization with the 23-valent polysaccharide pneumococcal vaccine [25, 101, 102]. Similarly, a significant reduction of IgM+ memory B cells was found among pneumococcal polysaccharide vaccine (PPV) immunized patients with defects in PPV-specific Ab production [57], confirming that dysfunction of memory B cells likely plays a key role in the loss of immunity against this pathogen in HIV patients. From these studies, we conclude that loss and dysfunction of memory B cells in HIV patients are associated with impaired humoral immune responses, contributing to the increased risk of invasive pneumococcal infection and related mortality (Figure 1) [25, 68].

Increased levels of total bacterial rDNA can be isolated from the bronchoalveolar lavages of asymptomatic HIV-infected individuals compared to HIV-uninfected controls. The range of bacterial colonization varied in different locations of the lower respiratory tract [103-105]. These results suggest that the lower respiratory tract is a uniquely major microbial reservoir in the lungs of HIV-infected individuals. Bacterial products such as LPS have been shown to enhance HIV replication in macrophages *in vitro*, suggesting a favorable environment for the interaction between HIV and bacteria such as *Streptococcus pneumoniae* in the lower respiratory tract [106-113]. Alveolar macrophages (AM) release GM-CSF and further induce the accumulation of macrophages and neutrophils in the lungs of HIV-infected subjects [114], and an increased amount of total and pneumococcal-specific Ab in the alveolar space [101, 115, 116]. However, due to the immune deficiency, opportunistic bacterial infections can create an inflammatory environment facilitating viral replication through up-regulation of cytokines and chemokines, which enhance HIV infection and replication, and perhaps promote viral egress from latent reservoirs [19, 117, 118]. HIV infection also impairs immune responses within the respiratory tract as well as M mannose receptor C-type lectin-mediated phagocytosis through the inhibition of Cdc42 and Rho activation, leading to a susceptibility of *S. pneumonia* infection in HIV infection [119]. Indeed, HIV infection reduced mannose receptor-mediated endocytosis by half, and reduced *P. carinii* binding and phagocytosis by two-thirds, compared to uninfected alveolar macrophage controls *in vitro*, suggesting that HIV infection could impair antigen-presenting function of macrophages at local sites and subsequently overall humoral immune responses [19, 114, 120, 121].

Pneumococcal polysaccharide vaccine in HIV-1 infected patients

Prior receipt of pneumococcal vaccination is associated with a 40%–70% reduction in the risk of in-hospital death by community-acquired pneumonia [122]. In HIV-infected patients, the contribution of pneumococcal vaccination to the reduction of risk of pneumonia has also been verified by several clinical trials [123, 124]. To date, the polysaccharide vaccine, containing purified polysaccharides from 23 pneumococcal serotypes, has been the most commonly used. In the USA, serial administrations of pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23) are now recommended to all HIV-infected patients (CDC new guidelines). Hereby, we focus on the recent application of

PCV13 and/or PPV23 in the protection of HIV infected people from *S. pneumococcal* infection.

In theory, immunization with inactivated *S. pneumonia* and soluble pneumococcal capsular polysaccharides should induce a protective reaction from memory B cells, especially IgM+ memory B cells, after 6-7 days [50-52, 125]. IgM+ memory B cells are depleted and pneumococcal-specific Ab responses to pneumococcal vaccination are impaired in HIV-infected patients, even in patients who have received long-term ART [25, 126]. Due to the high risk for HIV patients to develop IPD [25, 66, 68, 100, 127], research is critically important to better understand Ab concentrations against pneumococcal polysaccharide serotypes in PPV- and PCV-immunized HIV-infected individuals. Research studies have shown that PCV immunization initiated an enhanced serotypic-specific IgG response to PPV, which led to an increased Abs against PPS 14, 19F and 23F serotypes, both in HIV-infected individuals and healthy individuals, compared with those immunized with PPV alone, suggesting that immunization with both PPV and PCV induced a better protective effect [128-131]. Interestingly, immunization efficiency differs for PPV and PCV in HIV-infected patients. PCV has a greater and more stable immune-protective effect than PPV, especially in individuals with CD4+ T cell counts < 200 cells/ μ L [132-134], indicating that T cell-dependent Ab responses are more effective. Moreover, ART improves antigen-specific Ab responses to PPV in children and to PPV and PCV in adults with normal CD4+ T cell counts [135]. Although ART has been demonstrated to provide a strong protective effect against pneumococcal infection, a series of 2 PCVs and 1 PPV are more immunogenic and safe than individual using PPV in ART-treated HIV-infected children from 2 to 19 years of age who have low to moderate plasma levels of HIV RNA [136]. Higher CD4+ T cell counts and lower plasma levels of HIV RNA pre-vaccination predict greater vaccine responses in ART-treated HIV-infected children [130, 137, 138], suggesting that ART treatment improves humoral immune responses possibly through CD4 T cells dependent pathway in HIV-infected children.

Recently, PPV23 has been shown to have a significant, independent, promising protective effect against *S. pneumonia* in HART treated HIV-infected patients, even in patients with CD4+ T cell counts < 200 cells/ μ L [123]. A large-scale clinical survey found that patients who received PPV23 had a lower incidence of all-cause *pneumonia* [139]. Moreover, PPV23 is safe and recommended for pregnant mothers. Newborns may receive 46–72% of maternal Ab titers from PPV23-vaccinated mothers, suggesting prolonged passive protection induced by maternal PPV23 vaccination [140, 141]. More effective vaccination strategies to elicit robust and sustained Ab responses against pneumococcal infection are needed for HIV-infected infants.

A 7-valent pneumococcal conjugate vaccine (PCV7) has a significant impact on the occurrence of IPD across all ages, especially among USA children [9]. The introduction of PCV7 has further reduced the incidence of IPD [142]. Although these are promising developments for the general population, HIV-infected patients with low CD4+ T cell counts still have relatively reduced specific Ab responses and less protective humoral immunity after vaccinations with PPV and PCV. More research is needed regarding the pneumococcal strains most commonly colonizing HIV-infected patients, the manner in

which *pneumococci* interact with other bacterial species at mucosal surfaces in the setting of immunocompromised individuals, and the mechanisms involved in reduced effectiveness of vaccination and the higher incidence of IPD in this setting. Therefore, a better understanding of the optimal pneumococcal vaccine/revaccination strategy in HIV disease remains a high research priority.

Conclusion

HIV infection induces memory B cell depletion and dysfunction that results in increased incidence of pneumococcal infection. Pneumococcal vaccination is recommended for all HIV-infected patients to prevent *S. pneumonia* infection. Although ART treatment partially restores B cell function, the pneumococcal vaccine responses are impaired especially in HIV-infected patients who have peripheral CD4+ T cells less than 200 cells/ μ L. Optimizing vaccine strategy to enhance memory B cell responses and efficacy in HIV disease remains a high research priority.

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Figure 1.

Pulmonary infection due to *Streptococcus pneumoniae* in HIV-infected patients. HIV infection induces DCs and Tfh cells to secrete cytokines such as type I interferon and IL-6 in the germinal center. HIV infection also attenuates the helper function of Tfh cells on B cells, which leads to the inhibition of humoral immune responses and decreased the production of antigen-specific IgA, IgG and IgM. Impaired memory B cells further facilitates *S. pneumoniae* uptake in AM. Meanwhile, pneumococcal infection stimulates AM to release inflammatory factors and chemokines, and recruit macrophages, neutrophils and CD4⁺ T cells, which also provides a favorable environment for HIV pathogenesis.

Table I

The distribution of Streptococcal pneumococcal serotypes

Country	Streptococcal pneumococcal Serotype	Reference
Argentina	14, 5, 1, 6A, 6B, 9N, 19A, 9V	[143]
Bangladesh	6, 19, 15, 23, 10	[144, 145]
Belgium	14, 6, 9, 19, 23, 18, 4, 10, 8, 12	[146]
Canada	14, 4, 9, 19, 6, 3, 18, 7, 8, 23, 15, 22, 10, 11	[147]
Chile	5, 14, 1	[148]
China	19F, 19A, 23F*, 6B, 14, 15, 4, 9, 18, 5, 3	[149-151]
Colombia	14, 5, 23F, 1, 6B, 19F, 6A	[152]
Denmark	14, 6B, 19F, 23F, 18C, 7F, 4, 6A, 9V, 12F, 1, 24F, 38, 22F, 9N, 15C, 3, 5, 20, 33F, 34, 10A	[153]
England	14, 4, 23F, 6b, 19a, 19f, 3, 6a, 9, 1, 8, 12, 18	[154, 155]
Greece	14, 19F, 23F, 6B	[156, 157]
Iran	19, 6, 14, 17, 20, 23, 21	[111]
Italy	14, 23, 6, 4, 3, 9, 19, 8, 1, 12, 18, 7	[103]
Japan	6B, 19F, 23F, 6A, 14, 22, 3, 10	[112, 113]
Malawain	19F, 23F, 14, 6A, 19A, 7	[158]
Malaysia	19, 23F, 14, 6A, 6B, 15, 18, 1, 3, 34	[159]
Poland	14, 6B, 19F, 3, 1, 4, 23F, 12F	[160]
Portugal	1, 19A, 7F, 3, 33F, 9N, 10A, 5, 15A, 16F, 22F, 23A, 15C, 17F, 35F, 15B, 18A, 8, 18F, 37, 23B, 19C, 20, 11A, 34, 7C, NT	[161]
Santa Fe	14, 1, 6B, 18C, 7F, 19 F, 5	[162]
South Africa	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 6A, 9N, 12F, 19A	[163]
Spain	1, 7F, 19A, 3, 19F, 5	[164, 165]
Switzerland	1, 3, 4, 6B, 7F, 14, 19F, 23F	[166]
Thai	6B, 23F, 14, 19F	[167]
Turkey	9, 19, 23, 19F, 11, 22, 23B, 10, 6, 18	[168, 169]
USA	19A, 14, 6B, 19F, 18C, 23F, 4, 9V, 3, 35B, 23A, 15A, 33, 22, NT, 16F, 11A, 7F, 15C, 15B, 31, 12, 10, 35F, 38, 23	[170, 171]