Hypersensitivity Pneumonitis: Current Concepts of Pathogenesis and Potential Targets for Treatment

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Hypersensitivity pneumonitis (HP) is an immune-mediated disease triggered by a large variety of organic and nonorganic materials (“inducers”) in susceptible individuals. The disease has heterogeneous clinical presentation, and radiological and histopathological patterns based on the interaction of individual host susceptibility factors, type and extent of exposure, and biological features of inducing matter (1). In some patients, the clinical, radiological, and pathological features of chronic HP (CHP) may be similar to idiopathic pulmonary fibrosis (IPF), including a progressive fibroproliferative reaction with distortion of lung architecture leading to a pattern that is usual interstitial pneumonia (UIP)-like (2). In some patients, emphysema may be a consequence of the chronic course of inflammation and manifest as “emphysema or combined fibrosis emphysema syndrome,” especially in farmers’ lung disease (3). Knowledge of current concepts in the pathogenesis of HP is crucial to diagnose and distinguish HP from idiopathic interstitial pneumonias and to take necessary steps to completely avoid further exposure to the identified inducer/s and unveil new molecular targets for treatment (4). To better understand the cascades of immune-mediated inflammatory and fibrotic pathways in the pathogenesis of HP, we discuss the process of development of HP as a step-by-step process and surface the critical points and “therapeutic” strategy for interventions to prevent onset of HP and/or to abort disease progression (Figure 1). Some of the results of studies on HP pathogenesis have been previously reported in the form of abstracts (5–12).

Pathogenetic Process of HP: Concepts

Genetic Susceptibility to HP

Most of the gene polymorphisms that may increase susceptibility to HP have been traced in the molecules involved in processing and presentation of external antigens. The high level of polymorphisms and heterogeneity within the major histocompatibility complex (MHC) genomic region provide the immune system with a selective advantage against the diversity of pathogens, but has the added risk of generating diverse immunopathological disorders. Class II MHC molecules appear to be the primary susceptibility locus in HP, followed by polymorphisms of genes potentially involved in altered lung homeostasis and wound repair and telomere-related gene mutations (Table 1). Familial clustering was reported in 20 of 114 (17.5%) patients with CHP; importantly, the affected patients had lived apart from one another for at least several decades, and the familial cases were younger than the nonfamilial at onset of the disease (13) (Figure 1A).

Exposure to Environmental Factors: “Inducers”

In a genetically predisposed individual, HP is a consequence of an immune-mediated reaction caused by recurrent exposure to overt or occult inducing environmental agents—“HP inducers” (1, 14). The exposure may occur at the work place, home, other places the person visits, and/or related to hobbies, and the duration of which is variable from days to weeks, months or longer (14–19). A list of the published, proven, and suspicious antigens and sources of exposure is provided in

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ACUTE HP

LYMPHOCYTIC INFLAMMATORY PATTERN
Humoral response
Deposition of B-cells
rituximab, Mabs against IgG
Depletion of B-cells

Figure 1. Pathogenesis of hypersensitivity pneumonitis with targets for current and future treatment modalities. (A) Genetically susceptible individual (major histocompatibility complex [MHC] and transporter for antigen presentation [TAP] polymorphisms). (B) Exposure to environmental factors—inducers—a mixture of matter. (C) Innate immune response: 1) antigen recognition with pattern recognition receptors; 2) phagocytosis; 3) antigen processing, MHC I and II pathways; MHC I pathway: after phagocytosis, soluble forms of antigens are formed and escape from phagosomes to cytosol; in cytosol, antigens are connected to TAP and transported to the endosome, where they are connected with MHC I molecules; MHC II pathway: foreign peptides degrade in the proteasome to antigens that are bound to MHC II molecules; and 4) antigen expression: expression of the complex of peptide and MHC I ([presented to CD8+ cells]) or MHC II ([presented to CD4+ T cells]) at the surface of antigen-presenting cells (APCs). (D) Sensitization: recognition of antigen by CD8+ or CD4+ T lymphocytes as a danger signal (caused by genetic variations of TAP and MHC), contribution of infection and common dust particulate matter, and triggering of an immune reaction leading to cellular and humoral immune memory. (E) Immune reaction after reexposure to antigen: T helper cell type 1 (Th1), Th2, and Th17 immune response leading to lymphocytic inflammation: bronchitis and bronchiolitis, alveolitis, granuloma formation, and lymphocytic pneumonitis. (F) Fibroblast accumulation and fibrosis: contribution of factors of antigen and host. AG = antigen; ER = endoplasmic reticulum; HP = hypersensitivity pneumonitis; TLR = Toll-like receptor.
PULMONARY PERSPECTIVE

Table 1. Reported Genetic Factors in Hypersensitivity Pneumonitis

<table>
<thead>
<tr>
<th>Genes and Genetic Variants</th>
<th>Population Race or Nationality</th>
<th>First Author (Year) (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC II polymorphisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>White</td>
<td>Ritter (1983) (63)</td>
</tr>
<tr>
<td>HLA-DR7</td>
<td>Mexican</td>
<td>Selman (1987) (64)</td>
</tr>
<tr>
<td>HLA-DQ3</td>
<td>Japanese</td>
<td>Ando (1989) (65)</td>
</tr>
<tr>
<td>HLA-DRB1*04</td>
<td>Mexican</td>
<td>Falfán-Valencia (2014) (66)</td>
</tr>
<tr>
<td>HLA II haplotypes</td>
<td>Mexican</td>
<td>Camarena (2001) (67)</td>
</tr>
<tr>
<td>Increased DRB1<em>1305-DQB1</em>0301; decreased DRB1<em>0802-DQB1</em>0402 Proteasome and transporter polymorphisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSMB8 KQ</td>
<td>Mexican</td>
<td>Camarena (2010) (68)</td>
</tr>
<tr>
<td>TAP1 637, 661</td>
<td>Mexican</td>
<td>Aquino-Galvez (2008) (69)</td>
</tr>
<tr>
<td>Mucin polymorphisms</td>
<td>White</td>
<td>Ley (2017) (70)</td>
</tr>
<tr>
<td>MUC5B rs35705950</td>
<td>White</td>
<td>Ley (2017) (70)</td>
</tr>
<tr>
<td>Telomere length and mutations</td>
<td>White</td>
<td>Newton (2016) (71)</td>
</tr>
<tr>
<td>Telomere-related gene mutations</td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>TIMP-3-915 TIMP-3-1296 (protective role)</td>
<td>White</td>
<td>Hill (2004) (72)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: MHC = major histocompatibility complex; TAP = transporter for antigen presentation; TIMP = tissue inhibitor of metalloproteinase.

Table E2 in the online supplement; however, it is inevitably incomplete, as it continues to grow (Table E2). Although the sources are numerous and diverse, we can anticipate that the antigens (i.e., molecular structures triggering the immune hyperreactivity response) belong to similar species (i.e., bacteria including mycobacteria, molds, and some animal proteins). Identification of source of the antigen is crucial for the management of HP (i.e., elimination of exposure, which itself can improve prognosis) (4).

Importantly, in a considerable number of patients with a diagnosis of HP ascertained by histopathological features besides typical clinical and radiological features, the alleged “inducer” remains undetected/unknown, despite thorough elicitation of exposure history, and/or serologic testing (3, 17). In this context, we propose that these patients be grouped under the term “cryptogenic HP” (1). In interstitial lung disease (ILD) centers specialized in HP that use home/industrial hygienists and to prepare “à la carte” precipitins, the cause/source for the inducer of HP is often detected, and thus the “unidentified/unknown etiology” for the HPs is relatively rare in patients evaluated by experts in specialized centers. Future studies are warranted to ascertain this apparent observation/experience among experts.

The inducers need to be absorbed in the mucosa (respiratory, gastrointestinal) or skin. The inhalation route is the most frequent one, and we believe that the ingestion or dermal route is reserved solely for the prescribed drugs. The inducers can be of both organic (most common) and, less frequently, inorganic origin. The organic particulate matter group comprises protein and microbe subgroups, and the inorganic particulate matter group consists of chemicals and metals, which become antigenic after connecting to human proteins as haptons (1). The unique molecular structure and shape characteristic for each inducer influence a complex immune response, and thus also clinical phenotype of the disease. For instance, bird feathers, serum, and droppings contain antigens that seem to induce a more likely severe, fibroproliferative response (19). Likewise, although avian antigens induce primarily peribronchiolar inflammation and fibrosis, exposure to thermophilic bacteria and fungi may provoke mostly bronchiolitis obliterans (20). For the purposes of discussion of the concepts in the pathogenesis of HP, we will focus on the pathogenetic pathway provoked by inhaled inducers, because they trigger the majority of HP cases.

Environmental exposure is usually complex, and exposure to monoclonal antigen is rather rare. The composition of dust inhaled by farmers has included various bacteria and fungi, but also mycotoxins, volatile organic compounds, endotoxins, or peptidoglycans, which may contribute to the biopathology of the disease (21, 22). The bacterial and fungal walls contain allergenic molecules inducing hypersensitivity and several pathogen-associated molecular patterns, mycotoxins, and β-d-glucans. They are recognized by pattern-recognition receptors (PRRs) on immune cells, and stimulate transcription of proinflammatory cytokines and IFNs, which enhances the pathogenetic process of HP (23). Mites are also important components of the farming environment and, because mite antigens were proven to have protease activities, they may further modify other proteins that form organic dusts (24).

In addition, inert particulate matters (common dust) and chemicals can participate in the immune process in HP pathogenesis (25).

Paradoxically, cigarette smoke reduces the risk of HP, and, moreover, smokers exposed to an environment with high concentrations of potential inducers develop lower levels of specific antibodies than nonsmokers (26). The mechanisms by which cigarette smoke appear to protect from HP are unclear, but experimental approaches attribute this effect to nicotine. Indeed, activation of nicotinic acetylcholine receptor α7 reduces the secretion of several proinflammatory cytokines by macrophages, whereas, on lymphocytes, it decreases the reactivity of the T-helper cell type 1 (Th-1) and Th17 lineages, increasing the Th2 response (27). On the other hand, when smokers develop HP, they often follow a chronic fibroproliferative course, which is assumed to be caused by tobacco’s decelerating role on the sensitization process and decreasing inflammation and lymphocyte proliferation (28). Smoking probably has a dual effect, dependent on duration of the exposure. Short-term exposure to cigarette smoke lessened the lymphocytosis in BAL fluid and lymphocyte proliferation, but, after long-term exposure, cigarette smoke increased lymphocytosis hand-in-hand with lung hydroxyproline content in the model of murine CHP. These results suggest that
short-term cigarette smoking attenuates lung inflammation, but long-term cigarette smoking enhances lung inflammation and fibrosis (29). Recently, air pollution has been implicated as a risk factor for progression of ILDs, because the ambient particulate matter is associated with an increase in the rate of decline of FVC in IPF (30). We hypothesize that air pollution can play a role in priming the bronchiolar epithelium, and manifestation and progression of HP as well (Figure 1B).

Innate Immune Response

Antigen recognition. The innate immune response plays a substantial role in antigen recognition in the first contact with inducers, namely, in phagocytosis, antigen processing, expression, and recognition by lymphocytes as a danger signal. The proteinaceous parts of the inhaled inducers are identified by antigen-presenting cells (APCs) based on recognition of their specific molecular structures. Viral respiratory infections may affect the innate immune response during the process of sensitization, decreasing antigen clearance, increasing the antigen-presenting capacity of alveolar macrophages through the upregulation of B7 costimulatory molecules and inducing the release of proinflammatory cytokines (31). Likewise, tissue injury caused by microbial inducers also results in exposure of immune cells to danger-associated molecular patterns, which may influence immune response to the inducer (32). Reactivity of the immune system to HP inducer is a result of activation of several different PRRs, including TLRs (Toll-like receptors), NODs (nucleotide-binding oligomerization domain–like receptors), and dectins. The most-often-cited PRRs in the context of HP pathogenesis are TLR6, TLR9, and dectins (32–34). Components of the fungal cell wall may suppress expression of dectin-1, TLR2, and TLR4, the PRRs responsible for induction of normal anti-infectious immunity, which after prolonged and/or massive exposure to fungi, may lead to immunopathological hypersensitivity reaction (35). Signal via different PRRs leads not only to innate immune cell activation, but also to production of cytokines, namely, IL-4, IFN-γ, IL-13, and IL-17, which contribute to the diverse clinical presentation of HP in different inducers (32, 36, 37) (Figure 1C).

Inducer processing and expression of antigens. The inducers undergo processing, either in the proteasome of APCs and are expressed in the context of MHC I–type molecules, or can bypass the proteasome and are expressed in context with MHC II molecules on the APC surface (38). Before binding to MHC molecules, the antigens are formed, or edited by transporting proteins (i.e., tapasin in the MHC I pathway and HLA-DM [HLA DO] in the MHC II pathway) (39). The dual MHC I and MHC II expression might elucidate both CD4+ and CD8+ T lymphocyte recruitment in different types and different phases of HP. In general, helper CD4+ T cells recognize peptides with a nonameric core sequence, but often with C- and N-terminal extensions presented on MHC II molecules, whereas cytotoxic CD8+ T cells react to octa- or nonameric peptides presented on MHC I molecules. It is tempting to speculate that some kind of antigens (e.g., mycobacteria, prefer MHC I over MHC II presentation) (38).

Exposure and Sensitization

Sensitization to inhaled antigens demands repeated exposure in individuals with genetic susceptibility to HP (see Genetic Susceptibility to HP). Most individuals do not react to the potential inducers at all, some develop only subclinical changes, and only a few develop clinically apparent disease. Immune tolerance is believed to be induced and maintained by T-regulatory cells (Tregs), and it seems that dysfunction of this subpopulation is probably one of the factors contributing to HP development. It has been demonstrated that BAL fluid and blood Tregs (CD4+CD25+ and mostly FoxP3+ cells) from healthy control subjects and asymptomatic antigen-exposed individuals suppressed the proliferation of effector T cells, whereas those from patients with HP showed no functional suppressive activity (40) (Figure 1D).

Inflammation: IgG- and T Cell–mediated Immune Response

The antigen recognition and processing by innate immune system are followed by activation of the cells of innate and adaptive immunity and the production of a number of proteins, including antibodies, chemokines, and cytokines. HP is mostly believed to be characterized by T cell–mediated immunity, primarily by Th1 cells; however, immune complex–mediated lung injury with specific IgG antibodies (sIgGs) may participate as well (41–43) (Figure 1E).

- Humoral response. Presentation of processed antigens by innate immune cells to B lymphocytes, either with or without T cell contribution, leads to production of IgG, because organic dusts usually contain both T cell–independent antigens (unmethylated CpG DNA and polysaccharides) and T cell–dependent antigens (proteins). IgG and antigens form immunocomplexes, leading to activation of complement via classical pathway and tissue injury. However, immunocomplexes also have important immunoregulatory functions dependent on FcγR type and their preferential binding to IgG subtype, and may even show immune-suppressive effects (42).
- Lymphocyte accumulation in lung tissue, granuloma formation. T cells themselves after interaction with antigen presented by APCs can evolve a variety of effector subsets in dependency to the cytokine milieu. IL-12 and IFN-γ polarize lymphocytes toward the Th1 cell subtype with consequent stimulation of granuloma formation, which is still reversible from the prognostic point of view. By contrast, a switch of Th1 to Th2, with a predominant Th2 response leads to maintenance of inflammation and development of fibrosis in later stages of HP (40, 42). In addition, decrease of apoptosis in lymphocytes can contribute to T cell persistence, activation, and accumulation in lung tissue, whereas apoptosis of alveolar epithelial cells and granulocytes enhances maturation and chemokine production of CD11c+ dendritic cells, resulting in further recruitment of immune cells into the lungs (43). Th17 immune response appears parallel with Th1, and is triggered by increased production of IL-17 by lymphocytes, but also neutrophils. IL-17 is a potent stimulator of chronic inflammation, and its depletion in animal models substantially decreases inflammatory response to an inducer (44).
Relevance of Concepts in Pathogenesis for Treatment Strategy: Need for Clinical Trials

Despite increasing insights in HP pathogenesis, there have been no clinical trials to determine the safety and efficacy of pharmacological treatment other than one trial using corticosteroids (54). However, the treatment effect is evident only in acute HP or the early phases of CHP where inflammation is significant. The available empirical treatment for progressive HP with mix of inflammatory and fibrotic changes is the combined immunomodulating treatment (corticosteroids with azathioprine or mycophenolate), although the evidence of its usefulness is based on retrospective studies. However, combined treatment—if chosen—may be associated with fewer side effects than high-dose steroid monotherapy (55). Although the harmful effects of combined azathioprine, prednisone, and N-acetylcysteine have been well documented in patients with IPF, it is unknown if prednisone plus azathioprine is harmful for patients with CHP (56). We advise caution with the use of this combination treatment in patients with fibrotic CHP showing a UIP-like pattern (44). A prospective study of five patients with CHP treated with one single dose of rituximab showed a significant improvement of the distance walked, as measured by the 6-minute-walk test, at 8 months, but without improvement in the pulmonary function test (57). No treatment has demonstrated a benefit in CHP with an extensive or progressive fibrolamellar pattern and fibrosis, or with a radiologic/histopathologic pattern resembling UIP. The current anti-fibrotic drugs for IPF, nintedanib or pirfenidone, could be a reasonable option. Indeed, clinical trials using these drugs are under way (see www.clinicaltrials.gov).

However, taking into consideration the concepts of the steps outlined here in the pathogenesis of HP, it is hoped that the following blockade of pathogenic steps will lead to prevention of disease in patients susceptible to manifest HP and/or abort the progression in patients manifesting the disease. We hypothesize that combinations, rather than a single modality of therapeutic approach, is beneficial for different phenotypes of HP (i.e., inflammatory pattern with fibrosis, fibrosis with granulomas, continuous exposure).

Genetic Background and Exposure to Inducer

The single most essential step is strict avoidance of the identified source of the inducer of HP. The first step in causative antigen identification is to meticulously collect a detailed patient history of exposure in their occupational and domestic environments as well as regularly visited places. The use of a questionnaire may be very useful in identifying exposures that may otherwise be missed in an informal discussion with the patient (1). The identification of environmental triggers may require input from ancillary specialists, such as occupational physicists or industrial/environmental hygienists, to collect reliable samples from the patient’s environment for microscopic/microbiology analysis. The second step is laboratory investigation for confirmation of the suspect antigen or for screening of unrevealed exposure by identification of serum slgGs. The antigens can be obtained as commercially available extracts, or can be prepared from collected material in specialized laboratories (58, 59). The specific inhalation challenge can be performed to provide causality between exposure and the disease. This test, although not standardized or validated, is useful if performed in centers experienced with specific inhalation challenge testing (60).

Indeed, prevention is better than cure, and thus we believe that the individuals at risk to manifest HP (e.g., those who have, although yet undefined, genetic susceptibility and first-degree family members of probands diagnosed with HP) will be at lower risk to manifest HP (and may not manifest HP) if they avoid strict exposures to potential inducers of HP at work, home, or elsewhere. To date, there is only one study revealing gene mutations (telomerase components) in patients with HP, and we have very little evidence of common variants of candidate genes increasing the risk of developing the disease (50). Thus, the relatives of patients with HP are not screened for genetic background, yet we can anticipate that, in the near future, the individuals at genetic risk of HP will be offered counseling to avoid exposure that might trigger the disease (Figures 1A and 1B).
Currently, the inhibitors of proteasome are antigen and immune reaction against it. This process in antigenicity of particles resulting from this role in degradation of external particulate matter, and the size, shape, and antigenicity of particles resulting from this process influence the presentation of antigen and immune reaction against it. Currently, the inhibitors of proteasome are used mainly in hematopoiesis (bortezomide) (61).

Sensitization Process
Specific antigen immunotherapy (i.e., vaccines) might be appropriate to changing the way of antigen presentation and stimulate regulatory T lymphocyte mediated Immune Response [mediated by IgE (Figure 1D)]. Sensitization Process

Inflammation: IgG- and T Cell–mediated Immune Response

- Lymphocyte accumulation and granuloma formation. Nonspecific antiinflammatory drugs are currently used to influence inflammation (i.e., corticosteroids and immunomodulating agents [mycophenolate mofetil and azathioprine]) (55). However, in the near future, a blockade of specific cytokine and chemokine pathways might be more accurately targeted with fewer side effects (anti–IL-4, anti–IL-13, anti–IL-17, anti–IFN-γ, etc.). In addition, Tregs may be used to decrease lymphocyte lung proliferation and activation. Currently, several phase-1/2 clinical trials are ongoing, primarily in chronic graft-versus-host disease, and some autoimmune diseases (e.g., NCT02428309 and NCT02749084). Potential antiinflammatory and immunomodulating drugs that may prevent granuloma formation include agents that block TNF-α (infliximab, etanercept, and adalimumab), IFN-γ (e.g., AMG 811, an anti–IFN-γ mAb), or other mAbs against specific cytokines.
- Humoral response–specific IgGs. Currently, we also have the possibility of influencing slgG production by nonspecific inhibition–depletion of B cells (rituximab); however, mAbs tailored against slgGs might be a better solution in the future (Figure 1E).

Fibroproliferation
Likewise, anti–IL-4 and anti–IL-13 (e.g., the anti–IL-13 mAbs tralokinumab and lebrikizumab) may contribute to control the Th2-biased response that participates in fibrotic remodeling. Purified serum amyloid P, also known as pentraxin 2, inhibits monocyte differentiation into profibrotic fibrocytes, and is also a potent inhibitor of monocyte differentiation into proinflammatory macrophages and production of TGF–β1 (transforming growth factor–β1), which is a key mediator of pulmonary fibrosis. In a recent phase-2 trial in patients with IFP, pentraxin 2 was associated with decreasing the rate of disease progression; thus, the therapeutic potential of this drug to modulate the innate immune response in patients with CHP is worth pursuing (Figure 1F) (62).

Conclusions
HP is a complex clinical problem, and there are substantial gaps in knowledge of pathogenesis and lack of current clinical practice guideline on diagnosis and treatment. Despite large cohorts of diseased individuals all over the world, there are still many areas of uncertainty in the field of HP. Further studies must be focused on the mechanisms of immune response in the pathogenesis of HP with the hope that specific treatment strategy will lead to abort the disease progression, despite avoidance of exposure of the identified source of the HP inducers in genetically predisposed persons.

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References


