

Immune Dysregulation in the Pathogenesis of Pulmonary Alveolar Proteinosis

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Abstract Pulmonary alveolar proteinosis (PAP) is a rare disease of the lung characterized by the accumulation of surfactant-derived lipoproteins within pulmonary alveolar macrophages and alveoli, resulting in respiratory insufficiency and increased infections. The disease is caused by a disruption in surfactant catabolism by alveolar macrophages due to loss of functional granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling. The underlying molecular mechanisms causing deficiencies in GM-CSF signaling are as follows: 1) high levels of neutralizing GM-CSF autoantibodies observed in autoimmune PAP; 2) mutations in *CSF2RA*, the gene encoding the α chain of the GM-CSF receptor, observed in hereditary PAP; and 3) reduced numbers and function of alveolar macrophages as a result of other clinical diseases seen in secondary PAP. Recent studies investigating the biology of GM-CSF have revealed that not only does this cytokine have an indispensable role in lung physiology, but it is also a critical regulator of innate immunity and lung host defense.

Keywords Pulmonary alveolar proteinosis · PAP · GM-CSF · GM-CSF receptor · Alveolar macrophages · Surfactant homeostasis · Immune deficiency · Autoimmunity

Introduction

Pulmonary alveolar proteinosis (PAP), a rare disorder of the lung resulting from impaired surfactant homeostasis, is clinically characterized by the accumulation of lipoproteinaceous material within alveolar spaces, often leading to respiratory failure [1]. Three forms of PAP have been described: autoimmune, hereditary, and secondary [2•, 3]. Autoimmune PAP is the most common form (90%), usually occurs in adults, and results from neutralizing autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) (Fig. 1) [4–6]. Hereditary PAP can result from mutations in genes encoding the GM-CSF receptor α (GM-CSFR α) (Fig. 1) [7••, 8••]. Although PAP has been associated with reduced expression of the β c chain of the heterodimeric GM-CSF receptor (GM-CSFR) [9, 10], definitive evidence of β c mutations in PAP is lacking. However, mice engineered to lack β c do develop PAP [11, 12], demonstrating the potential for β c mutations to cause PAP. A similar but histopathologically distinct disorder of surfactant homeostasis can occur with mutations for the genes encoding surfactant proteins B or C [13–16]. Secondary PAP develops in conditions in which there are reduced numbers or functional impairment of pulmonary alveolar macrophages and has been associated with inhalation of inorganic dust (silica) or toxic fumes, hematologic malignancies, pharmacologic immunosuppression, and certain infections [17–20].

In each disorder, the production, secretion, and reuptake of surfactant are normal, but the catabolism of surfactant is defective. The accumulated material in the alveoli consists of normal surfactant, cellular debris, and cytokines such as monocyte chemotactic protein-1 and macrophage-colony stimulating factor, which serve as useful biomarkers for PAP [21, 22].

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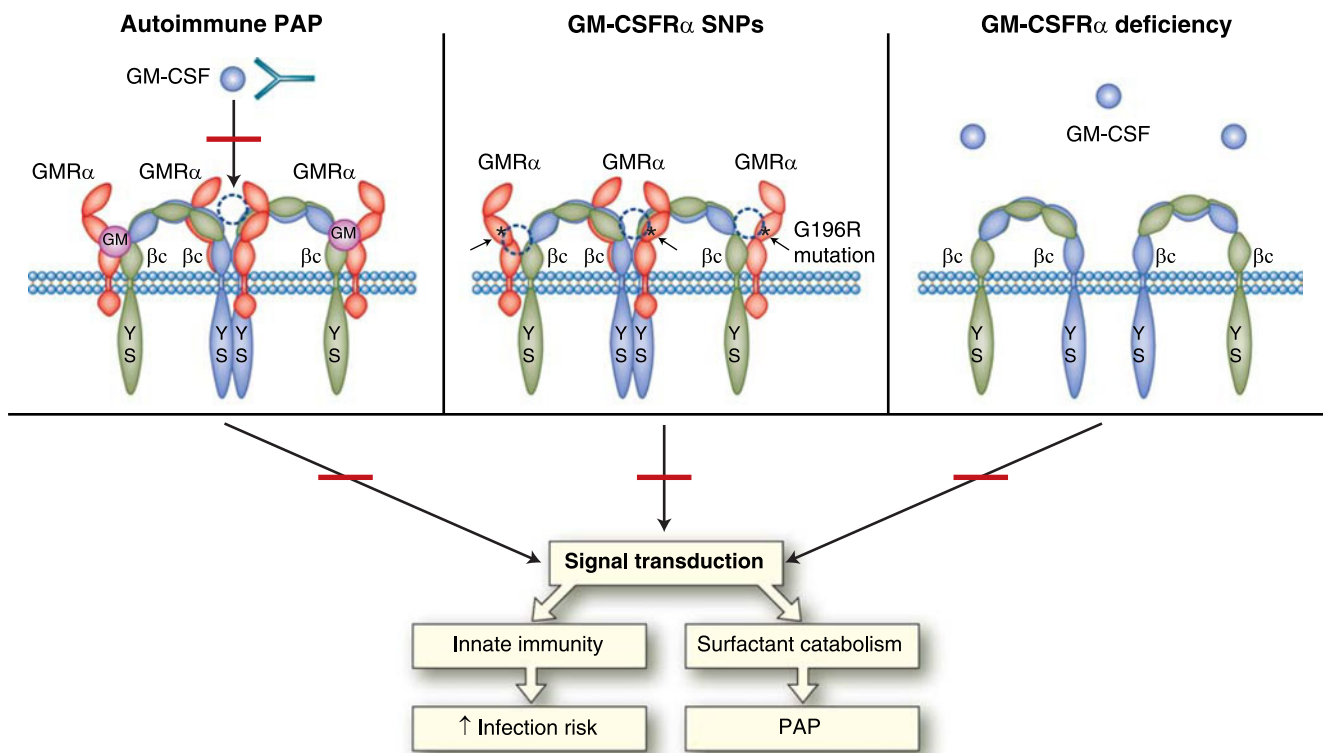


Fig. 1 Molecular mechanisms underlying the pathogenesis of pulmonary alveolar proteinosis (PAP). PAP is caused by a disruption in surfactant catabolism by alveolar macrophages due to loss of functional granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling. Illustrated are the three key molecular mechanisms causing impaired GM-CSF signaling: autoimmune PAP, caused by high levels of neutralizing GM-CSF autoantibodies (*left panel*); point mutations (asterisks) in *CSF2RA*, the gene encoding the α chain of the

GM-CSF receptor (GM-CSFR α or GMR α), as observed in hereditary PAP (*middle panel*); and genetic deletion of *CSF2RA*, as observed in hereditary PAP (*right panel*). Each of these scenarios results in defective GM-CSF receptor signaling in alveolar macrophages, resulting in defective surfactant catabolism and impaired innate immunity and leading to the development of PAP and increased risk of infection. S—serine; SNP—single nucleotide polymorphism; Y—tyrosine

The importance of GM-CSF in the pathogenesis of PAP has been confirmed in humans and mice, wherein GM-CSF signaling is required for pulmonary alveolar macrophage catabolism of surfactant [11, 12, 23]. In addition, mice with a targeted disruption of GM-CSF or β c genes developed PAP [11, 12]. Mice deficient for GM-CSFR α have not been reported but would be expected to develop PAP. Local expression of GM-CSF in the lungs of GM-CSF-deficient mice, or transplantation of bone marrow from normal mice into β c-deficient mice corrected the defective metabolism of surfactant [24, 25]. Furthermore, administration of GM-CSF has been efficacious in some patients with acquired PAP [26].

The effects of GM-CSF on macrophage function and surfactant homeostasis are regulated by a myeloid master regulator, PU.1, a transcription factor required for multiple functions of alveolar macrophages, including their terminal differentiation, surfactant catabolism, and various immune functions [27]. As such, retrovirus-mediated expression of PU.1 in an alveolar macrophage cell line derived from GM-CSF-deficient mice restored a macrophage-like appearance and corrected all the abnormalities associated with GM-CSF

deficiencies [3]. In this review, we discuss the key molecular players in PAP, pathophysiology, and consequences of GM-CSFR signaling deficiencies.

Granulocyte-Macrophage Colony-Stimulating Factor

GM-CSF, along with the related cytokines interleukin (IL)-3 and IL-5, are pleiotropic cytokines that regulate the production and functional activation of hematopoietic cells. GM-CSF, IL-3, and IL-5 all have a cytokine-specific receptor α chain and share the requirement of β c for signaling [28]. Whereas IL-3 is a major growth factor for basophils [29] and IL-5 is a major differentiation factor for eosinophils [30], GM-CSF serves as a colony-stimulating factor for the growth and maturation of monocyte/macrophage and granulocyte lineage populations [31]. GM-CSF is also a modulator of immune responses, as it can modulate myeloid dendritic cell and T-cell function, thereby serving as a link between innate and adaptive immunity [32].

Interestingly, recent evidence indicates that rather than being essential for homeostatic myeloid cell numbers or production, GM-CSF is critical for signaling emergency hematopoiesis in response to infection. In this scenario, GM-CSF signaling triggers the increased production of granulocytes and macrophages in the bone marrow and regulates their maintenance, survival, and functional activation at sites of injury or insult [33–35].

GM-CSF-deficient mice have a higher mortality from uncontrolled pulmonary and systemic infections [36] and increased susceptibility to a wide range of microbial infections, including gram-negative and gram-positive bacteria, adenovirus, *Mycobacterium tuberculosis*, and malarial parasites [3]. In PAP patients and GM-CSF-deficient mice, predisposition to infections is systemic, as infections occur at pulmonary and extrapulmonary sites [3].

Granulocyte-Macrophage Colony-Stimulating Factor Receptor and Signaling

GM-CSF signaling is mediated by the GM-CSFR composed of a low-affinity, ligand-binding GM-CSF receptor α chain (GM-CSFR α) and a homodimer of the common β chain, β c, which enhances binding affinity and is shared by IL-3 and IL-5 [28]. The two GM-CSFR subunits are always coexpressed on the surface of leukocytes, with GM-CSFR α being expressed at higher levels than β c. Recently, the crystal structure of the human GM-CSF/GM-CSFR ternary complex was solved, revealing an unexpected higher-order dodecameric (12-subunit) complex consisting of two GM-CSFR hexamers (two α chains, two β c chains, and two GM-CSF molecules; Fig. 1) [37•, 38•]. Significantly, functional studies evaluating GM-CSFR mutants altered at the dodecamer interface revealed that dodecamer formation is required for receptor activation and signaling [37•]. Furthermore, these studies revealed that JAK2 was constitutively associated with the β c homodimer.

Ligation of the GM-CSFR by GM-CSF activates three main signaling pathways: the JAK/STAT, Ras/mitogen-activated protein kinase, and the PI-3 kinase (PI-3K)-Akt pathways [39]. Like most cytokine receptors, activation of these signaling networks results in the triggering of a wide range of cellular functions, including increased survival, entry and progression through the cell cycle, early commitment to myelopoiesis, differentiation and maturation of committed progenitors, as well as multiple activation and motility functions in mature cells [31].

Interestingly, at low picomolar (pM) concentrations of GM-CSF, each GM-CSFR hexameric complex can support hematopoietic cell survival through the selective activation of the β c-Ser⁵⁸⁵/14-3-3/PI-3K pathway, independent of β c tyrosine phosphorylation [38•, 40]. At higher GM-CSF

concentrations (≥ 10 pM), an alternative survival and proliferation pathway is activated that is dependent on the dodecamer assembly; it involves β c tyrosine 577 phosphorylation and signaling by all three signaling pathways [38•, 40]. Thus, this selective and mutually exclusive GM-CSFR signaling mechanism has been termed a *binary switch* that confers the ability to respond in distinct biochemical and biological ways to increasing cytokine concentrations. Furthermore, this mechanism seems to be conserved in this family of receptors across species and in other hematopoietic receptor systems [40].

Clinical Features, Pathophysiology, and Treatment of Pulmonary Alveolar Proteinosis

PAP is characterized clinically by respiratory distress and, in severe cases, respiratory failure due to the accumulation of surfactant in the alveoli and impaired oxygen exchange [1, 2•, 3]. Surfactant is composed of surfactant proteins and phospholipids and is produced by alveolar type II epithelial cells. Developmentally, surfactant is physiologically important in that it provides a thin aqueous layer that prevents alveolar collapse by maintaining appropriate tension at the alveolar air–fluid interface. However, excess surfactant will congest the alveoli and impair oxygen exchange. Maintenance of surfactant homeostasis is dependent on relative rates of production by the alveolar type II epithelial cells and catabolism of surfactant by alveolar macrophages. Although macrophages can ingest surfactant, they must be activated by GM-CSF to catabolize this material effectively. Any impairment of the catabolic pathway can lead to congestion of the macrophages with surfactant and hence inadequate clearance of surfactant from the alveoli.

As surfactant accumulates, patients have progressive respiratory distress with hypoxia. Auscultation reveals diffuse rales, and chest x-ray reveals a diffuse alveolar “crazy paving pattern.” Chest CT demonstrates congestion of alveoli. Bronchoalveolar lavage reveals thick proteinaceous material and foamy macrophages. Lung biopsy is characterized by granular eosin staining lipoproteinaceous material in the alveoli with preservation of alveolar architecture and absence of epithelial hyperplasia or chronic interstitial changes.

Until the role of GM-CSF signaling in the molecular pathophysiology of PAP began to be elucidated in recent years, treatment was limited to extensive bronchoalveolar lavage with as much as 20 L of saline every few months, often under arteriovenous extracorporeal membrane oxygenator support. Although this remains a mainstay of therapy when oxygen exchange is sufficiently compromised, alternative treatments are emerging that may

reduce or avoid such extensive bronchoalveolar lavage procedures.

About 90% of patients develop PAP later in life rather than as a congenital condition. The etiology of this acquired form of PAP is now confirmed to be a result of neutralizing autoantibodies to GM-CSF [4–6]. Evidence for these autoantibodies being pathophysiologically causative is based on several lines of experimentation. First, GM-CSF is essential for macrophage catabolism of surfactant. Second, mice defective in GM-CSF signaling develop PAP. Third, high titers of neutralizing autoantibodies to GM-CSF are detected in most patients with PAP. Finally, it was recently demonstrated that passive transfer of human GM-CSF autoantibodies can cause PAP in nonhuman primates [41]. In addition, some patients with autoimmune PAP show clinical improvement when treated with plasmapheresis, immunosuppression, or administration of parenteral or inhaled GM-CSF.

Among patients with nonautoimmune PAP, alternative mechanisms of impaired GM-CSF signaling are logical to explore. Theoretical possibilities include impaired GM-CSF production or GM-CSF mutations that would preclude a functional protein, similar to the type I and type II forms of C1 esterase inhibitor deficiencies. However, neither of these possibilities has been described. Alternatively, mutations of the GM-CSFR α or β c genes could impair GM-CSF signaling and cause PAP. There has been only a single report of an association of decreased β c expression by alveolar macrophages in PAP, and no confirmed functional mutations have been reported for β c [9]. Conversely, two recent studies have demonstrated functional mutations of the gene encoding GM-CSFR α , which is located in the pseudoautosomal region of the X and Y chromosomes [7•, 8•].

Our laboratory reported the first GM-CSFR α -deficient human, who had PAP from birth [7•]. She also had Turner's syndrome, which resulted in the deletion of the GM-CSFR α gene on both the short X chromosome and the normal-appearing X chromosome. Such deletional mutations can be readily identified by the absence of GM-CSFR α on peripheral blood monocytes and neutrophils using flow cytometry, as well as via molecular techniques demonstrating the lack of mRNA for GM-CSFR α . Based on murine studies in which PAP caused by β c deletion could be prevented with bone marrow transplantation from a β c-competent donor [25], patients with deletion of GM-CSFR α potentially could be cured by bone marrow transplantation. This was attempted in our patient, but she died from a viral infection prior to full immune reconstitution.

An additional study reported a family with heterozygous point mutations of the GM-CSFR α gene, *CSF2RA*, in both parents. When both mutated genes were inherited by the children, it resulted in decreased affinity for GM-

CSF binding and hence decreased signaling and PAP [8•]. However, the PAP in the two affected children differed in age at onset and severity. Importantly, the decreased affinity for GM-CSF could be compensated for with increased concentrations of GM-CSF, thereby providing an available therapeutic strategy for such patients.

Although some patients develop PAP in the context of acquired macrophage defects associated with myelomonocytic malignancies or toxic or infectious impairment of pulmonary alveolar macrophage function, such etiologies are rare. Diagnosis and management of these secondary forms of PAP focus on the underlying condition.

Consequences of Impaired Granulocyte-Macrophage Colony-Stimulating Factor Signaling on Protective Immunity

A clinical observation has been the increased risk of infections in patients with PAP. This association has been attributed largely to the morbidity accompanying the repeated bronchopulmonary lavages required for treatment of the respiratory insufficiency. However, the important role of GM-CSF in activating a wide spectrum of protective immune pathways in macrophages highlighted the probability that defective GM-CSF signaling in macrophages was a direct cause of increased susceptibility to infections. In addition, GM-CSF stimulation of neutrophils rapidly increases expression of CD11b, which enhances neutrophil adhesion [7•, 8•].

Conclusions

The biology of PAP is a remarkable saga in molecular immunology and is exemplary of the diagnostic and therapeutic advances that are now possible through translational science. The recent identification in two independent studies of mutations in the GM-CSFR α gene that can result in the PAP phenotype, and that the spectrum of mutations can result in variations in the phenotype severity and treatment options, demonstrates the clinical importance of delineating the molecular basis of disease. In addition to being a newly defined primary immune deficiency, the lung-specific phenotype of genetic defects in GM-CSF signaling makes PAP a novel category of primary immune deficiencies. Likewise, the spontaneous development of autoantibodies to GM-CSF as the most common cause of PAP serves as an experiment of nature that can offer insight into diverse pathophysiologic mechanisms that can lead to a clinical phenotype shared with genetic mutations. Finally, future consideration should be given to the potential for mutations in cytokines or their receptors to have subtle but clinically relevant functional

consequences and, in the case of GM-CSF and its receptors, the potential for unexplained respiratory symptoms and unexplained increased propensity for infections.

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