Phenocopies of Primary Immunodeficiency Diseases

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Abstract

The term "phenocopies of primary immunodeficiency diseases" refers to a group of diseases mimicking the phenotype of primary immunodeficiencies; however, they are caused by somatic mutations or autoantibodies against cytokines rather than germline monogenic defects. They are classified as a separate group by the International Union of Immunological Societies (IUIS).

Keywords

Fas · Fas ligand · TNF · TNF receptor · Autoimmune lymphoproliferative syndrome · Ras · GTPase · Autoantibodies anti-IL-17 · Autoantibodies anti-IL-22 Autoantibodies anti-IFN-γ · Autoantibodies anti-IL-6 · Autoantibodies anti-IL-6 Autoantibodies anti-GM-CSF · Autoantibodies anti-IFN-α · Autoantibodies anti-L-12p70

3.1 Introduction

The phenocopies of primary immunodeficiency diseases have been characterized during the last decades and manifest as a clinical phenocopy to patients with genomic mutations affecting the same biological pathway. In this chapter

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we will provide an updated description of the clinical manifestations, diagnosis, and treatment.

3.2 Phenocopies of PID Caused by Somatic Mutations

The phenocopies of primary immunodeficiency diseases manifest as a clinical phenocopy to patients with genomic mutations affecting the same biological pathway (Fig. 3.1) [1].

The traditional definition of a mosaic is any pattern or image made from multiple pieces; its individual elements can be recognized just by close inspection. In biological organisms, mosaicism denotes an individual with more than one genetically distinct cell population [2]. It might be imperceptible unless closely analyzed. If it takes place during embryonic development, germline and somatic cells will be affected. Otherwise, only somatic cells will be affected. Mosaicism can be caused by DNA mutations, epigenetic factors, and chromosomal abnormalities [3].

Somatic variants require high-throughput sequencing techniques to be detected. During data analysis specific algorithms are fundamental, as these mutations have

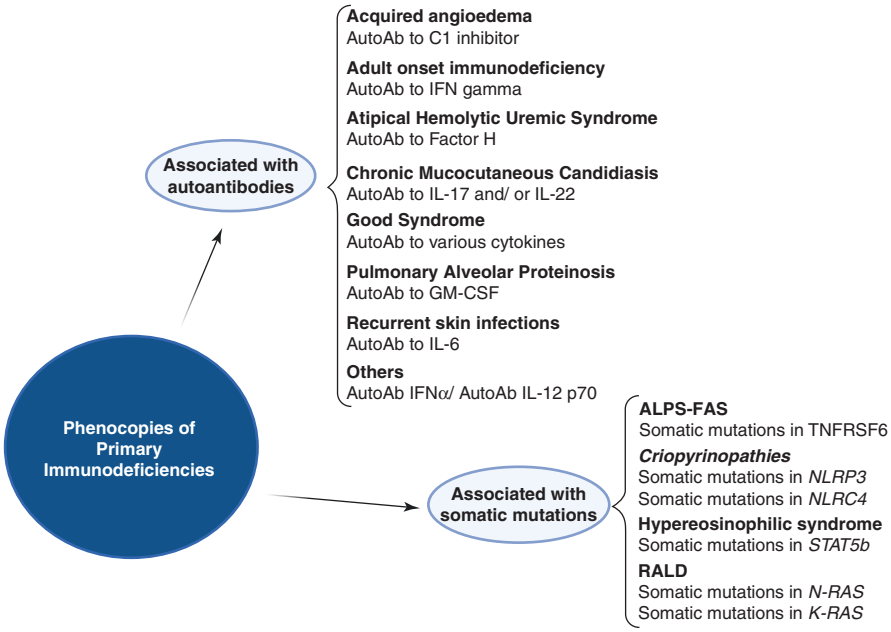

Fig. 3.1 *Classification of phenocopies of primary immunodeficiency diseases.* Phenocopies of PID are a group of diseases caused by somatic mutations or autoantibodies against various cytokines. Clinical manifestations can mimic those of other PIDs. The diseases belonging to each group are shown in the figure

very low allele frequencies in the population. High deep reads are recommended in order to increase the accuracy [4]. Single-cell sequencing has enabled us to detect somatic mutations as heterozygous variants that occur in a subset of cells [5].

Below, we describe several conditions characterized by somatic mutations and mimicking primary immunodeficiency diseases (PID) (Table 3.1).

Table 3.1 Phenocopies of PID. Immunophenotype and clinical characteristics associated with their similar genetic counterpart

Disease	Immunophenotype	Similar features to primary immunodeficiencies
Associated with somatic mutations		
ALPS *TNFRSF6*	Increased DNT cells	Autoimmune cytopenias, defective lymphocyte apoptosis, splenomegaly, lymphadenopathy
RALD *KRAS*	B cells elevated	Autoimmune cytopenias, granulocytosis, monocytosis, splenomegaly, lymphadenopathy
NRAS	Increased DNT cells, B cells elevated	Splenomegaly, lymphadenopathy, autoantibodies
Cryopyrinopathies		
NLRP3	Neutrophilic leukocytosis	Fever, arthropathy, chronic aseptic meningitis, urticarial rash
NLRC4	Neutrophilic leukocytosis	Urticarial rash, chronic meningitis, and arthropathy
Hypereosinophilic syndrome *STAT5b*	Eosinophilia	Persistent eosinophilia with organ involvement atopic dermatitis, urticarial rash, diarrhea
Associated with autoantibodies		
Autoantibodies to IL-17, **Autoantibodies to IL-22**	Normal	Recurrent candida infections of the mucosal surfaces, nails, and skin. Infections may become resistant to antifungals Thymoma
Autoantibodies to IFN gamma	Naïve T cells decreased Hypergammaglobulinemia	Chronic infections with intracellular pathogens, particularly lymphadenitis, skin, soft tissue, and bone infections; constitutional symptoms. Thymoma
Autoantibodies to IL-6	Normal	Recurrent staphylococcal skin infections
Autoantibodies to GM-CSF	Normal	Pulmonary alveolar proteinosis. Progressive respiratory failure. Cryptococcal meningitis
Autoantibodies to IFNα	Normal	Varicella zoster disseminated
Autoantibodies to IL-12p70	Normal	Thymoma, myasthenia gravis

ALPS Autoimmune lymphoproliferative syndrome, *DNT* Double-negative T cells, *RALD* Ras-associated autoimmune leukoproliferative disease

3.2.1 Autoimmune Lymphoproliferative Syndrome (ALPS) Caused by Somatic Mutation in *TNFRSF6* Gene

Autoimmune lymphoproliferative syndrome is a condition of impaired lymphocyte homeostasis, resulting from mutations in genes involved in the Fas pathway. Clinical manifestations include lymphadenopathy, splenomegaly and autoimmune cytopenias. Patients have a predisposition to malignancy, especially lymphomas [6, 7].

FAS (CD95/Apo1) is a cell receptor that belongs to the tumor necrosis factor receptor (TNFR) superfamily. It is codified by the gene *TNFRSF6*. Upon binding to its ligand (Fas ligand), Fas starts a series of events leading to apoptosis to maintain lymphocyte homeostasis [8]. Its role was initially identified in mouse models with a germline mutation in *TNFRSF6* that manifest with autoimmunity [9]. In humans, patients develop a syndrome known as autoimmune lymphoproliferative syndrome (ALPS) [10–12].

If the mutation is clear, ALPS can be categorized as ALPS type Ia (*FAS/TNFRSF6*), ALPS type Ib (FAS ligand), and ALPS type II (caspase 8 or 10 genes). ALPS type III is caused by somatic mutations, and it is the second most common type of ALPS. Somatic mutations have been described in patients without germline mutations but a clinical phenotype similar to other types of ALPS: lymphadenopathy, splenomegaly, hepatomegaly, autoimmunity, elevated DNT cells, increased serum FAS ligand, and elevated levels of IL-10 and vitamin B12 [13–16]. The number of reported cases due to somatic mutations has increased over the last years.

Patients with ALPS type III have a later onset, and the symptoms remain mild for a long period and hence lead to diagnostic delay [17]. The clinical phenotype can suggest a somatic mutation, but this is not enough to make the diagnosis. In vitro studies in cells of these patients have shown Fas-mediated apoptosis, with a higher degree compared to patients with ALPS type Ia [14].

Diagnosis is challenging; all patients with ALPS phenotype, elevated serum biomarkers, and no germline mutation should be evaluated for somatic mutations. The identification of somatic mutations is established by sequencing FAS on double-negative T cells (DNT) [13]. DNT cells seem to be originated from activated peripheral single-positive T cells that received a death-inducing signal but cannot go to apoptosis as they harbor a Fas defect [18].

Treatment is similar to ALPS patients with germline mutations. It focuses on treatment of disease manifestations such as lymphoproliferation and autoimmune cytopenias [19]. Patients require steroid therapy and more than 50% immunosuppressive drugs to control autoimmunity. Malignancy can be treated with conventional protocols. As secondary options, intravenous gammaglobulin, plasmapheresis, and bortezomib should be considered [20]. Hematopoietic stem cell transplantation (HSCT) has been used for refractory patients [21].

3.2.2 RALD: Ras-Associated Autoimmune Leukoproliferative Disease (ALPS like)

Ras-associated autoimmune leukoproliferative disorder (RALD) is characterized by autoimmune manifestations, persistent monocytosis, leukocytosis, and non-malignant lymphoproliferation. Clinical and laboratory features overlap with those of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML) [22]. The somatic mutations affect genes of the Ras family, *KRAS*, *NRAS*, and *RAS*, involved in myeloid and lymphoid lineages [23]. Mutations found in RALD patients are also reported in around 25% of JMML patients, suggesting a shared molecular etiology [24]. The presence of autoimmunity supports RALD diagnosis, but these patients can have malignant cell transformation and evolve to JMML [25].

RAS (named for their role in forming rat sarcomas) encodes for GTPases important in cell division, cell differentiation, and apoptosis. Opposite to ALPS, DNT cells or serum vitamin B12 levels are not always increased, and there is no defect in Fas-mediated apoptosis. A key feature of RALD is persistent absolute or relative monocytosis [23, 26]. The autoimmune manifestations can mimic lupus with low complement levels and elevated autoantibodies (dsDNA) [27]. Patients with mutations in *NRAS* may have DNT cells elevation [28]. Restricted clonal expansion of TCR and BCR in one patient has been reported; this might explain the reduce lymphocyte repertoire and immunodeficient state in this disease [29].

There are some reported cases with cutaneous involvement known as RALD cutis. Patients present with panniculitis-like erythematous plaques and sweet syndrome. Usually, they have a benign course [30, 31].

Management is based on corticosteroid therapy and other immunomodulatory agents for the autoimmunity. Rituximab has been published as an effective option in patients with refractory cytopenias [32].

3.2.3 Cryopyrinopathies

NLRP3 auto-inflammatory disorders (*NLRP3*-AIDs) were previously known as cryopyrin-associated periodic syndromes (CAPSs), including overlapping entities with increasing severity: familial cold auto-inflammatory syndrome (FCAS); Muckle-Wells syndrome (MWS); chronic infantile neurological, cutaneous, and articular syndrome (CINCA); and neonatal-onset multisystem inflammatory disease (NOMID) [33].

NLRP3-AIDs are autosomal dominant disorders caused by germline mutations in *NLRP3*. The gene encodes for cryopyrin, which leads to hyperactivation of IL-1β [33]. Somatic mutations have been described. Patients present a late onset of the disease and milder symptoms [34–40]. Clinical manifestations include fever, joint involvement, and skin rash. Laboratory workup reveals neutrophilic leukocytosis, elevated C-reactive protein, and erythrocyte sedimentation rate.

A prompt molecular diagnosis is critical; it requires high-deep next-generation sequencing techniques and specific pipelines [41].

Treatment targets IL-1β, and anti-IL1 (anakinra, rilonacept, and canakinumab) are generally effective [42].

A somatic mutation in *NLRC4*, the caspase recruitment domain-containing 4 gene, was found in a Japanese male child with auto-inflammatory symptoms compatible with neonatal-onset multisystem inflammatory disease. The patient had complete response to anakinra [43].

3.2.4 Hypereosinophilic Syndrome Due to Somatic Mutations in *STAT5b* Gene (*STAT5b* Gain-of-Function Mutation)

Somatic mutations in STAT5b have been described in hematologic malignancies [44–46]. Recently, a somatic mutation in STAT5b was found in two patients with eosinophilia, atopic dermatitis, and urticarial rash. The first one, a 3-year-old girl, presented autoimmunity manifestations (alopecia *totalis*). She had history of one event of pneumonia and measles-like illness 10 days after MMR vaccination. The other patient had a severe clinical presentation with recurrent events of bronchiolitis, worsening eosinophilia, failure to thrive, and delayed speech. Gut biopsy revealed eosinophilic infiltrates. She underwent umbilical cord stem cell transplant but died later. Functional tests in CD3-CD4+ T cells showed increase STAT5B responsiveness [47]. Management was based on steroid therapy.

3.3 Phenocopies of PIDs Caused by Autoantibodies against Various Cytokines

Autoantibodies can be found in healthy individuals; they are mainly IgM and have moderate affinity for self-antigens contributing to the homeostasis of the immune system [48]. In contrast, high-affinity and high-titer autoantibodies reflect the loss of balance in effector functions of the immune system. Clinical presentation is correlated with the affected cytokine pathway. These diseases present as a clinical phenocopy of patients with germline mutations in the same associated pathway [49]. Here, we review current knowledge focusing on diseases with increased susceptibility to infections.

3.3.1 Autoantibodies against IL-17 and/or IL-22

Chronic mucocutaneous candidiasis (CMC) is a disorder characterized by recurrent or persistent candida infections involving the skin, nails, and mucous membrane [50]. When the disease is associated with autoimmune hypoparathyroidism and

primary adrenocortical insufficiency is named APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy). APECED is caused by a loss-of-function mutation in *AIRE*, an essential gene in central immune tolerance [51]. These conditions occur in association with impaired IL-17 and IL-22 immunity [50, 52].

Several genetic mutations lead to impair production of IL-17 and IL-22: *IL17F*, *IL17RA*, IL-*17RC*, and *TRAF3IP2/ACT1* [53–55]. Autoantibodies against IL-17F, IL-17A, and IL-22 have been found in patients with CMC [56]. In one study, high titers of autoantibodies against IL-17A, IL-17F, and/or IL-22 were found in 33 APECED patients; from those 29/33 developed CMC [57]. Along with these findings, autoantibodies against IL-17A (41%), IL-17F (75%), and/ or IL-22 (91%) were detected in more than 150 APECED patients, mainly among the CMC group. Remarkably, in this study, autoantibodies were also found in patients with thymoma who later developed CMC [51].

Diagnosis is based on the detection of autoantibodies by techniques such as western blotting and enzyme-linked immunosorbent assay (ELISA). Management includes antifungal therapy and treatment of associated endocrine and infectious manifestations. Members of the azole family are usually effective for the treatment of CMC [58, 59].

3.3.2 Autoantibodies Against IL12p70

IL-12p70 is a heterodimeric molecule consisting of IL-12p35 and IL-12p40 subunits; it signals through a heterodimeric receptor complex of IL-12Rβ1 and IL-12Rβ2 [60]. The signaling pathway IL-12p40-STAT4-IFNγ is involved in protection against intracellular pathogens, such as mycobacterium [61].

There is just one case of anti-IL-12p70 autoantibodies detected in one Cambodian patient. She presented with severe recurrent *Burkholderia gladioli* lymphadenitis and was demonstrated to have isolated neutralizing anti-IL-12p70 autoantibodies as the only immune defect [62]. Interestingly, patients with myasthenia gravis or thymoma have high titers of autoantibodies against IL12p40, but they do not develop infections [63].

3.3.3 Autoantibodies to Interferon-α (IFN-α)

Type I IFNs include IFN-α, IFN-β, and IFN-ω. IFN-α is involved in the transcription of type 1 interferon genes and acts via phosphorylation of STAT1/2 [64, 65]. Autoantibodies to type I IFNs have been detected in healthy donors [66], autoimmune diseases [67–69], malignancy [70], APECED [71], and thymoma [72, 73]. Infections have been reported in a patient with dermatomal varicella zoster reactivation. IFN-α was given as treatment with good response [74].

3.3.4 Autoantibodies to IFN-γ and Susceptibility to Intracellular Pathogens

Interferon-gamma (IFN-γ) is produced by type 1 helper T lymphocytes and NK cells and is crucial for immunity against intracellular pathogens. The IFN-γ receptor is composed of two subunits IFNγR1 and IFNγR2, which combine in duplicate, to form a tetramer, and bind IFN-γ. IFN-γ downstream signaling is mainly through the JAK-STAT1 pathway [52, 75]. Autoantibodies against IFN-γ may impair the production of IL-12. Mendelian susceptibility to mycobacterial disease (MSMD) is a condition that predisposes to infections by low pathogenicity mycobacteria such as nontuberculous mycobacteria (NTM) or bacille Calmette-Guérin (BCG) [76]. Patients are also susceptible to *Salmonella*, *Candida*, and *Mycobacterium tuberculosis*. Genetic defects along these pathways confer similar infection susceptibility [77].

The first cases reporting an association between anti-IFN-γ autoantibodies with severe atypical NMT infection were published in 2004 [78, 79]. Supporting these data, several cases are published, including one study in which 85 patients were enrolled [78–88]. Other opportunistic infections have been reported, including *Salmonella*, *Burkholderia*, *Penicillium*, *Histoplasma*, *Cryptococcus*, and viruses, in particular *varicella zoster virus (VZV)* [89]; these infections resemble those observed in patients with germline mutations in the IFN-γ-IL12 axis.

A high prevalence rate among patients from South East Asia was observed; this was later explained by the discovery of a strong HLA association: HLA-DQB1*05:01/05:02 and DRB1*15:02/16:02. In addition, a major epitope, P12-131, located at the C-terminus of IFN-γ was identified [90, 91].

Patients with opportunistic infections and neutrophilic dermatosis (Sweet syndrome) were reported to have anti-IFN-γ autoantibodies [92]. Lymph nodes are the main site of involvement [93], and 80% of patients have skin manifestations such as reactive dermatoses, erythema nodosum, pustular psoriasis, and exanthematous pustulosis [89, 94].

Laboratory workup reveals features of chronic inflammation including anemia, leukocytosis, elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and elevated C-reactive protein (CRP) and/or β2-microglobulin. Other immunological parameters are normal [89]. Undetectable levels or low levels of IFN-γ suggest the presence of autoantibodies. Autoantibodies can be measured using particle-based technology or ELISA [95, 96]. For screening, QuantiFERON-TB Gold In-Tube (QFT-GIT) test can be useful [97].

Management is based on antimicrobial therapy. NTM are usually refractory to first-line therapy and often require second-line drugs for months to years. If the response is poor, immunomodulatory agents can help to decrease autoantibody production. Rituximab has been used in four cases; all patients had a decrease in anti-IFN-γ autoantibody levels. Use of rituximab was reported in a series of four cases, all of which responded clinically, with commensurate decrease in neutralizing capacity [98]. Plasmapheresis and cyclophosphamide were used in one patient [99].

3.3.5 Autoantibodies Against Granulocyte Macrophage Colony Stimulation Factor (GM-CSF)

Granulocyte macrophage colony stimulation factor (GM-CSF) is a growth factor which promotes the immune activation, proliferation, and differentiation of neutrophils, dendritic cells, erythrocyte progenitors, macrophages, and megakaryocytes [100]. In the lung, it is essential for function and differentiation of alveolar macrophages. GM-CSF induces phosphorylation of STAT5, nuclear translocation, and induction of transcription factor PU.1. Together, GM-CSF and PU.1 are essential for surfactant catabolism in the pulmonary alveoli [101–104].

High titers of neutralizing autoantibodies against GM-CSF are associated with pulmonary alveolar proteinosis (PAP) [105]. PAP is a disease linked to congenital or acquired defects in the GM-CSF signaling pathway, causing the impairment of GM-CSF-dependent catabolism of surfactant and leading to accumulation in pulmonary alveoli [106]. PAP is classified in different types according to the underlying pathogenesis: primary PAP characterized by the disruption of GM-CSF signaling which can be autoimmune [107] or hereditary (mutations in CSF2RA or CSF2RB) [108, 109], secondary PAP in patients on immunosuppressive therapy or malignancies [110], and congenital PAP caused by mutations in genes involved in surfactant production [86–88]. Histopathological findings are alveolar filling with acellular periodic acid-Schiff (PAS)-positive proteinaceous material [111].

Autoimmune PAP is the most common, representing approximately 90% of cases [112]. Autoimmune PAP can cause respiratory failure, and it presents between 20 and 50 years of age. The presentation is heterogeneous; it can range from asymptomatic to progressive respiratory failure. Autoantibodies can be detected in the bronchoalveolar lavage (BAL) fluid [113]. It has been suggested its levels may correlate with disease severity and predict the need for additional treatment.

Patients with autoimmune PAP can present defects in neutrophil functions, manifesting as infections by *Nocardia* [114, 115], *nontuberculous mycobacteria (NMT)* [116], *Histoplasma* [117], and *Cryptococcus* [118]. Pulmonary and extrapulmonary infections do not always develop in the same patient. To date, it remains unknown why some patients have just PAP and others just infections.

Useful tools for the diagnostic are pulmonary function tests, which may reveal a restrictive pattern [119]; high-resolution computed tomography (HRCT) of the lungs, which could show a “crazy paving” pattern [120]; and levels of autoantibodies in BAL lavage [121].

The first-line treatment in PAP are whole-lung lavage to remove the proteinaceous material contained in the alveoli and long-term antimicrobial agents for patients with infections [122]. Inhaled and subcutaneous GM-CSF were effective in some studies [123–125]. Rituximab has been used in a small number of patients [126, 127].

3.3.6 Antibodies to Interleukin-6

IL-6 is a cytokine involved in the acute-phase response and in chronic inflammation. It is produced by B and T lymphocytes, macrophages, endothelial cells, hepatocytes, and synovial cells. It regulates the acute phase response in the liver with induction of serum C-reactive protein (CPR) and elevated erythrocyte sedimentation rate [128–130].

Autoantibodies to IL-6 have been found in healthy controls [131, 132] and in four patients associated with severe bacterial infections. The first patient was a 4-year-old boy with a history of recurrent staphylococcal cellulitis and abscesses [133]. The second case was detected in a 20-month-old female with severe septic shock [134]. The third was a 67-year-old man with fatal thoracic empyema by *Escherichia coli* and *Streptococcus intermedius*, and the fourth was a 56-year-old woman with multiple abscesses by *Staphylococcus aureus* [135]. Management included supportive care and antibiotic treatment.

All patients had undetectable levels of CRP despite severity of infections, suggesting impaired IL-6 activity. Functional assays with plasma of patients showed block of activity of IL-6 in vitro. However, IL-6 production from peripheral blood monocytes was normal. Hence, patients with autoantibodies against IL-6 have increased susceptibility to staphylococcal infections; a hint toward the diagnosis is low levels of CRP, despite severity of infection.

3.3.7 Autoantibodies in Good Syndrome

Good syndrome is defined as the triad of thymoma, immunodeficiency, and hypogammaglobulinemia [136]. Clinical manifestations are increased susceptibility to bacterial infections with encapsulated organisms and opportunistic viral and fungal infections. Patients have combined B and T cell immunodeficiency [137, 138]. Anti-cytokine autoantibodies have been identified in these patients and are a potential cause of immunodeficiency [139, 140]. This disorder should be treated by resection of the thymoma and immunoglobulin replacement to maintain adequate trough IgG values. Anti-cytokine autoantibodies have been also associated with infection in patients with thymoma [63]. These need to be further studied.

References

1. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W et al (2018) The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol 38:129–143
2. Youssoufian H, Pyeritz RE (2002) Mechanisms and consequences of somatic mosaicism in humans. Nat Rev Genet 3(10):748–758. https://doi.org/10.1038/nrg906
3. Gottlieb B, Beitel LK, Trifiro MA (2001) Somatic mosaicism and variable expressivity. Trends Genet 17(2):79–82. https://doi.org/10.1016/S0168-9525(00)02178-8
4. King DA, Sifrim A, Fitzgerald TW et al (2017) Detection of structural mosaicism from targeted and whole-genome sequencing data. Genome Res 27(10):1704–1714. https://doi.org/10.1101/gr.212373.116

5. Dou Y, Gold HD, Luquette LJ, Park PJ (2018) Detecting somatic mutations in Normal cells. Trends Genet 34(7):545–557. https://doi.org/10.1016/j.tig.2018.04.003
6. George LA, Teachey DT (2016) Optimal management of autoimmune lymphoproliferative syndrome in children. Pediatr Drugs 18(4):261–272. https://doi.org/10.1007/s40272-016-0175-3
7. DeNicola DB (2011) Autoimmune lymphoproliferative syndrome: new approaches to diagnosis and management. Top Companion Anim Med 26(2):52–61. https://doi.org/10.1053/j.tcam.2011.02.001
8. Arends MJ, Wyllie AH, Schwartz LM et al (1995) The fas death factor. Science 267(5203):1449–1456
9. Nagata S, Suda T (1995) Fas and Fas ligand: Ipr and gld mutations. Immunol Today 16(1):39–43
10. Fisher GH, Rosenberg FJ, Straus SE et al (1995) Dominant interfering fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 81(6):935–946. https://doi.org/10.1016/0092-8674(95)90013-6
11. Le Deist F, Emile J, Rieux-laucat F et al (1996) Clinical, immunological, and pathological consequences of Fas-deficient conditions. Lancet 348:719–723
12. Sneller BMC, Wang J, Dale JK et al (1997) Clinical, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Blood 89:1341–1348
13. Holzelova E, Vonarbourg C, Stolzenberg MC et al (2004) Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med 351(14):1409–1418. https://doi.org/10.1056/NEJMoa040036
14. Dowdell KC, Niemela JE, Price S et al (2010) Somatic FAS mutations are common in patients with genetically undefined autoimmune lymphoproliferative syndrome. Blood 115(25):5164–5169. https://doi.org/10.1182/blood-2010-01-263145
15. Martínez-Feito A, Melero J, Mora-Díaz S et al (2016) Autoimmune lymphoproliferative syndrome due to somatic FAS mutation (ALPS-sFAS) combined with a germline caspase-10 (CASP10) variation. Immunobiology 221(1):40–47. https://doi.org/10.1016/j.imbio.2015.08.004
16. Neven B, Magerus-Chatinet A, Florkin B et al (2011) Asurvey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood 118(18):4798–4807. https://doi.org/10.1182/blood-2011-04-347641
17. García García GM, Bureo Dacal JC, Pineda SS-V, Izaguirre RE (2015) Adult onset autoimmune lymphoproliferative syndrome due to somatic FAS mutation. Intern Med J 45(4):461–462. https://doi.org/10.1111/imj.12711
18. Bleesing JJH, Brown MR, Dale JK et al (2001) TcR-α/β+ CD4-CD8- T cells in humans with the autoimmune lymphoproliferative syndrome express a novel CD45 isoform that is analogous to murine B220 and represents a marker of altered O-glycan biosynthesis. Clin Immunol 100(3):314–324. https://doi.org/10.1006/clim.2001.5069
19. Teachey DT, Lambert MP (2013) Diagnosis and management of autoimmune cytopenias in childhood. Pediatr Clin N Am 60(6):1489–1511. https://doi.org/10.1016/j.pcl.2013.08.009
20. Rao VK (2015) Approaches to managing autoimmune cytopenias in novel immunological disorders with genetic underpinnings like autoimmune lymphoproliferative syndrome. Front Pediatr 3(July):1–6. https://doi.org/10.3389/fped.2015.00065
21. Sleight BJ, Prasad VS, DeLaat C et al (1998) Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. Bone Marrow Transplant 22(4):375–380. https://doi.org/10.1038/sj.bmt.1701306
22. Calvo KR, Price S, Braylan RC et al (2015) JMML and RALD (Ras-associated autoimmune leukoproliferative disorder): common genetic etiology yet clinically distinct entities. Blood 125(18):2753–2758. https://doi.org/10.1182/blood-2014-11-567917
23. Niemela JE, Lu L, Fleisher TA et al (2011) Somatic KRAS mutations associated with a human nonmalignant syndrome of autoimmunity and abnormal leukocyte homeostasis. Blood 117(10):2883–2886. https://doi.org/10.1182/blood-2010-07-295501

24. Miyauchi BJ, Asada M, Sasaki M, Tsunematsu Y, Kojima S, Mizutani S (1994) Mutations of the N-ras gene in juvenile chronic myelogenous leukemia. Blood 83(8):2248–2254
25. Herman SEM, Butchar JP, Cheney C, Johnson AJ, Byrd JC (2019) RAS-associated lymphoproliferative disease evolves into severe juvenile myelo-monocytic. Blood 123(12):2–4
26. Oliveira JB, Bidère N, Niemela JE et al (2007) NRAS mutation causes a human autoimmune lymphoproliferative syndrome. Proc Natl Acad Sci U S A 104(21):8953–8958. https://doi.org/10.1073/pnas.0702975104
27. Wang W, Zhou Y, Zhong L et al (2019) RAS-associated autoimmune Leukoproliferative disease (RALD) manifested with early-onset SLE-like syndrome: a case series of RALD in Chinese children. Pediatr Rheumatol 17(1):1–8. https://doi.org/10.1186/s12969-019-0346-1
28. Picard C, Bobby Gaspar H, Al-Herz W et al (2018) International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol 38(1):96–128. https://doi.org/10.1007/s10875-017-0464-9
29. Levy-Mendelovich S, Lev A, Rechavi E et al (2017) T and B cell clonal expansion in Ras-associated lymphoproliferative disease (RALD) as revealed by next-generation sequencing. Clin Exp Immunol 189(3):310–317. https://doi.org/10.1111/cei.12986
30. Tran TAN, Grow C-CC WB (2019) Superficial and deep cutaneous involvement by RAS-associated autoimmune Leukoproliferative disease (RALD cutis): a histologic mimicker of Histiocytoid sweet syndrome. Am J Dermatopathol 41(8):606–610
31. Giacaman A, Bauzá Alonso A, Salinas Sanz JA et al (2018) Cutaneous involvement in an 8-year-old boy with Ras-associated autoimmune leucoproliferative disorder (RALD). Clin Exp Dermatol 43(8):913–916. https://doi.org/10.1111/ced.13668
32. Toyoda H, Deguchi T, Iwamoto S et al (2018) Weekly rituximab followed by monthly rituximab treatment for autoimmune disease associated with RAS-associated autoimmune leukoproliferative disease. J Pediatr Hematol Oncol 40(8):e516–e518. https://doi.org/10.1097/MPH.0000000000001276
33. Neven B, Prieur AM, dit Maire PQ (2008) Cryopyrinopathies: update on pathogenesis and treatment. Nat Clin Pract Rheumatol 4(9):481–489. https://doi.org/10.1038/ncprheum0874
34. Rowczenio DM, Gomes SM, Aróstegui JI et al (2017) Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism-UK single center experience. Front Immunol 8(OCT). https://doi.org/10.3389/fimmu.2017.01410
35. Lasigliè D, Mensa-Vilaro A, Ferrera D et al (2017) Cryopyrin-associated periodic syndromes in Italian patients: evaluation of the rate of somatic NLRP3 mosaicism and phenotypic characterization. J Rheumatol 44(11):1667–1673. https://doi.org/10.3899/jrheum.170041
36. Zhou Q, Aksentijevich I, Wood GM et al (2015) Late-onset Cryopyrin-associated periodic syndrome due to myeloid-restricted somatic NLRP3 mosaicism. Arthritis Rheum 67(9):2482–2486
37. Omoyinmi E, Gomes SM, Standing A et al (2014) Whole-exome sequencing revealing somatic NLRP3 mosaicism in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheumatol 66(1):197–202. https://doi.org/10.1002/art.38217
38. Tanaka N, Izawa K, Saito MK et al (2011) High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an international multicenter collaborative study. Arthritis Rheum 63(11):3625–3632. https://doi.org/10.1002/art.30512
39. Aróstegui JI, Saldaña MDL, Pascal M et al (2010) A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease novel: evidence of the role of low-level mosaicism as the pathophysiologic mechanism unde. Arthritis Rheum 62(4):1158–1166. https://doi.org/10.1002/art.27342
40. Nakagawa K, Gonzalez-Roca E, Souto A et al (2015) Somatic NLRP3 mosaicism in muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes. Ann Rheum Dis 74(3):603–610. https://doi.org/10.1136/annrheumdis-2013-204361

41. Louvrier C, Assrawi E, El Khouri E et al (2020) NLRP3-associated autoinflammatory diseases: phenotypic and molecular characteristics of germline versus somatic mutations. J Allergy Clin Immunol 145(4):1254–1261. https://doi.org/10.1016/j.jaci.2019.11.035
42. Sag E, Bilginer Y, Ozen S (2017) Autoinflammatory diseases with periodic fevers. Curr Rheumatol Rep 19(7):1–10. https://doi.org/10.1007/s11926-017-0670-8
43. Kawasaki Y, Oda H, Ito J et al (2017) Identification of a high-frequency somatic NLRC4 mutation as a cause of autoinflammation by pluripotent cell–based phenotype dissection. Arthritis Rheumatol 69(2):447–459. https://doi.org/10.1002/art.39960
44. Kiel MJ, Velusamy T, Rolland D et al (2014) Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood 124(9):1460–1472. https://doi.org/10.1182/blood-2014-03-559542
45. Kontro M, Kuusanmäki H, Eldfors S et al (2014) Novel activating STAT5B mutations as putative drivers of T-cell acute lymphoblastic leukemia. Leukemia 28(8):1738–1742. https://doi.org/10.1038/leu.2014.89
46. Rajala HLM, Eldfors S, Kuusanmäki H et al (2013) Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood 121(22):4541–4550. https://doi.org/10.1182/blood-2012-12-474577
47. Lee LY, Hernandez D, Rajkhowa T, Smith SC, Raman JR, Nguyen B (2017) Somatic STAT5b gain-of-function mutations in early onset nonclonal eosinophilia, urticaria, dermatitis, and diarrhea. Blood 129(2):257–261
48. Elkon KCP (2008) Nature and functions of autoantibodies. Nat Clin Pract Rheumatol 4(9):491–498. https://doi.org/10.1038/jid.2014.371
49. Ludwig RJ, Vanhoorelbeke K, Leypoldt F et al (2017) Mechanisms of autoantibody-induced pathology. Front Immunol 8(MAY). https://doi.org/10.3389/fimmu.2017.00603
50. Okada S, Puel A, Casanova J-L, Kobayashi M (2016) Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. Clin Transl Immunol 5(12):e114. https://doi.org/10.1038/cti.2016.71
51. Kisand K, Bøe Wolff AS, Podkrajšek KT et al (2010) Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 207(2):299–308. https://doi.org/10.1084/jem.20091669
52. Browne SK, Holland SM (2010) Anticytokine autoantibodies in infectious diseases: pathogenesis and mechanisms. Lancet Infect Dis 10(12):875–885. https://doi.org/10.1016/S1473-3099(10)70196-1
53. Lim HK, Migaud M, Israel L et al (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 332:65–69
54. Boisson B, Wang C, Pedergnana V et al (2013) An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 39(4):676–686. https://doi.org/10.1016/j.immuni.2013.09.002
55. Ling Y, Cypowyj S, Aytekin C, Galicchio M, Camcioglu YNS et al (2015) Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis. J Exp Med 212:619–631
56. Sarkadi AK, Taskó S, Csorba G, Tóth B, Erdos M, Maródi L (2014) Autoantibodies to IL-17A may be correlated with the severity of mucocutaneous candidiasis in APECED patients. J Clin Immunol 34(2):181–193. https://doi.org/10.1007/s10875-014-9987-5
57. Puel A, Döffinger R, Natividad A et al (2010) Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 207(2):291–297. https://doi.org/10.1084/jem.20091983
58. Horsburgh CR, Kirkpatrick CH (1983) Long-term therapy of chronic mucocutaneous candidiasis with ketoconazole: Experience with twenty-one patients. Am J Med 74(1 PART 2):23–29. https://doi.org/10.1016/0002-9343(83)90511-9
59. Levo Y (2001) Chronic mucocutaneous candidiasis. Pediatr Infect Dis J 20:197–206. https://doi.org/10.1136/bmj.2.5914.334
60. Presky DH, Yang H, Minetti LJ et al (1996) A functional interleukin 12 receptor complex is composed of two β-type cytokine receptor subunits. Proc Natl Acad Sci U S A 93(24):14,002–14,007. https://doi.org/10.1073/pnas.93.24.14002

61. Hölscher C, Atkinson RA, Arendse B et al (2001) A protective and agonistic function of IL-12p40 in mycobacterial infection. J Immunol 167(12):6957–6966. https://doi.org/10.4049/jimmunol.167.12.6957
62. Sim BTT, Browne SK, Vigliani M et al (2013) Recurrent burkholderia gladioli suppurative lymphadenitis associated with neutralizing anti-IL-12p70 autoantibodies. J Clin Immunol 33(6):1057–1061. https://doi.org/10.1007/s10875-013-9908-z
63. Burbelo PD, Browne SK, Sampaio EP et al (2010) Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. Blood 116(23):4848–4858. https://doi.org/10.1182/blood-2010-05-286161
64. Lavoie TB, Kalie E, Crisafulli-Cabatu S et al (2011) Binding and activity of all human alpha interferon subtypes. Cytokine 56(2):282–289. https://doi.org/10.1016/j.cyto.2011.07.019
65. DA Szabo G (2008) The role of plasmacytoid dendritic cell–derived IFNα in antiviral immunity. Crit Rev Immunol 28(1):61–94
66. Ross C, Hansen MB, Schyberg T, Berg K (2008) Autoantibodies to crude human leucocyte interferon (IFN), native human IFN, recombinant human IFN-alpha 2b and human IFN-gamma in healthy blood donors. Clin Exp Immunol 82(1):57–62. https://doi.org/10.1111/j.1365-2249.1990.tb05403.x
67. Morimoto AM, Flesher DT, Yang J et al (2011) Association of endogenous anti-interferon-α autoantibodies with decreased interferon-pathway and disease activity in patients with systemic lupus erythematosus. Arthritis Rheum 63(8):2407–2415. https://doi.org/10.1002/art.30399
68. Baechler EC, Batliwalla FM, Karypis G et al (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A 100(5):2610–2615. https://doi.org/10.1073/pnas.0337679100
69. Slavikova M, Schmeisser H, Kontsekova E, Mateička F, Borecky L, Kontsek P (2003) Incidence of autoantibodies against type I and type II interferons in a cohort of systemic lupus erythematosus patients in Slovakia. J Interf Cytokine Res 23(3):143–147. https://doi.org/10.1089/107999003321532475
70. Trown PW, Dennin RA, Kramer MJ, Connell EV, Palleroni AV, Gutterman JU (1983) Antibodies to human leucocyte interferons in cancer patients. Lancet 8316(1):81–84
71. Meager A, Visvalingam K, Peterson P et al (2006) Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med 3(7):1152–1164. https://doi.org/10.1371/journal.pmed.0030289
72. Meager A, Wadhwa M, Dilger P, Bird C, Thorpe R et al (2003) Anti-cytokine autoantibodies in autoimmunity preponderance. Clin Exp Immunol 132:128–136
73. Shiono H, Wong YL, Matthews I et al (2003) Spontaneous production of anti-IFN-α and anti-IL-12 autoantibodies by thymoma cells from myasthenia gravis patients suggests autoimmunization in the tumor. Int Immunol 15(8):903–913. https://doi.org/10.1093/intimm/dxg088
74. Pozzetto B, Mogensen KE, Tovey MG, Gresser I (1984) Characteristics of autoantibodies to human interferon in a patient with varicella-zoster disease. J Infect Dis 150(5):707–713. https://doi.org/10.1093/infdis/150.5.707
75. Bhat MY, Solanki HS, Advani J, Khan AA, Prasad TSK (2018) Comprehensive network map of interferon gamma signaling. J Cell Commun Signal 12(4):745–751
76. Bustamante J, Boisson-dupuis S (2014) Mendelian susceptibility to mycobacterial disease: Genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol 26(6):454–470. https://doi.org/10.1016/j.smim.2014.09.008
77. Al-muhsen S, Casanova J, Arabia S (2008) The genetic heterogeneity of Mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol 122(6):1043–1051. https://doi.org/10.1016/j.jaci.2008.10.037
78. Doffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S et al (2004) Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis 38(1):e10–e14
79. Hoflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H et al (2004) Naturally occurring anti—IFN-gamma autoantibody and severe infections with Mycobacterium chelo-

neae and Burkholderia cocovenenans. Blood 103(2):673–675. https://doi.org/10.1182/blood-2003-04-1065.Reprints
80. Browne SK, Zaman R, Sampaio EP et al (2012) Anti-CD20 (rituximab) therapy for anti-IFN-γ autoantibody-associated nontuberculous mycobacterial infection. Blood 119(17):3933–3939. https://doi.org/10.1182/blood-2011-12-395707
81. Chi CY, Chu CC, Liu JP, Lin CH, Ho MW et al (2012) Anti-interferon-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and DQB1*05:02 and the reactivation of latent varicella-zoster virus infection. Blood 121:1357–1366
82. Kampitak T, Suwanpimolkul G, Browne S, Suankratav C (2010) Anti-interferon-γ autoantibody and opportunistic infections case series and review of the literature. Infection 39:65–71
83. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A et al (2005) Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-γ. J Clin Investig 115:2480–2488
84. Koya T, Tsubata C, Kagamu H et al (2009) Anti-interferon- g autoantibody in a patient with disseminated Mycobacterium avium complex. J Infect Chemother 15(2):118–122. https://doi.org/10.1007/s10156-008-0662-8
85. Patel SY, Ding L, Brown MR, Lantz L, Gay T et al (2005) Anti-IFN-γ autoantibodies in disseminated nontuberculous mycobacterial infections. J Immunol 175:4769–4776
86. Poulin S, Corbeil C, Nguyen M et al (2013) Fatal Mycobacterium colombiense/cytomegalovirus coinfection associated with acquired immunodeficiency due to autoantibodies against interferon gamma: a case report. BMC Infect Dis:1–6. Published online. https://doi.org/10.1186/1471-2334-13-24
87. Tanaka Y, Hori T, Ito K, Fujita T, Ishikawa T et al (2007) Disseminated Mycobacterium avium complex infection in a patient with autoantibody to interferon-γ. Intern Med 46:1005–1009
88. Tang BS, Chan JF, Chen M et al (2010) Disseminated penicilliosis, recurrent bacteremic nontyphoidal salmonellosis, and burkholderiosis associated with acquired immunodeficiency due to autoantibody against gamma interferon. Clin Vaccine Immuno 17(7):1132–1138. https://doi.org/10.1128/CVI.00053-10
89. Browne SK, Burbelo PD, Chetchotisakd P et al (2012) Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med 367(8):725–734. https://doi.org/10.1056/NEJMoa1111160
90. Lin C-H, Chi C-Y, Shih H-P, Ding J-Y, Lo C-C, Wang S-Y, Kuo C-Y, Yeh C-F, Tu K-H, Liu S-H, Chen H-K, Ho C-H, Ho M-W, Lee C-H, Lai H-C, Ku C-L (2016) Identification of a major epitope by anti-interferon-γ autoantibodies in patients with mycobacterial disease. Nat Med 22:994–1001. https://www.nature.com/articles/nm.4158
91. Ku C-L, Lin C-H, Chang S-W, Chu C-C, Chan JFW, Kong X-F, Lee C-H, Rosen EA, Ding J-Y, Lee W-I, Bustamante J, Witte T, Shih H-P, Kuo C-Y, Chetchotisakd P, Kiertiburanakul S, Suputtamongkol Y, Yuen K-Y, Casa C-Y (2016) Anti-IFN-γ autoantibodies are strongly associated with HLA-DR*15:02/16:02 and HLA-DQ*05:01/05:02 across Southeast Asia. J Allergy Clin Immunol 137:945–948
92. Chan JFW, Trendell-Smith NJ, Chan JCY et al (2013) Reactive and infective dermatoses associated with adult-onset immunodeficiency due to anti-interferon-gamma autoantibody: Sweet's syndrome and beyond. Dermatology 226(2):157–166. https://doi.org/10.1159/000347112
93. Wongkulab P, Wipasa J, Chaiwarith R, Supparatpinyo K (2013) Autoantibody to interferon-gamma associated with adult-onset immunodeficiency in non-HIV individuals in northern Thailand. PLoS One 8(9):e76371. https://doi.org/10.1371/journal.pone.0076371
94. Jutivorakool K, Sittiwattanawong P, Kantikosum K, Hurst CP, Kumtornrut C, Asawanonda P, Klaewsongkram J, Rerknimitr P (2018) Skin manifestations in patients with adult-onset immunodeficiency due to anti-interferon-gamma autoantibody: a relationship with systemic infections. Acta Derm Venereol 98(8):742–747. https://doi.org/10.2340/00015555-2959
95. Ding L, Mo A, Jutivorakool K, Pancholi M, Holland SM, Browne SK (2012) Determination of human anticytokine autoantibody profiles using a particle-based approach. J Clin Immunol 32(2):238–245. https://doi.org/10.1007/s10875-011-9621-8

96. Browne SK (2014) Anticytokine autoantibody–associated immunodeficiency. Annu Rev Immunol 32(1):635–657. https://doi.org/10.1146/annurev-immunol-032713-120222
97. Wu UI, Chuang YC, Sheng WH et al (2018) Use of QuantiFERON-TB gold in-tube assay in screening for neutralizing anti-interferon-γ autoantibodies in patients with disseminated nontuberculous mycobacterial infection. Clin Microbiol Infect 24(2):159–165. https://doi.org/10.1016/j.cmi.2017.06.029
98. Browne SK, Zaman R, Sampaio EP, Jutivorakool KRL (2012) Anti-CD20 (rituximab) therapy for anti-interferon-γ autoantibody-associated nontuberculous mycobacterial infection. Blood 119:3933–3939. https://www.annualreviews.org/servlet/linkout?suffix=B68&dbid=16&doi=10.1146%2Fannurev-immunol-032713-120222&key=10.1086%2F605581
99. Baerlecken N, Jacobs R, Stoll M, Schmidt REWT (2009) Recurrent, multifocal Mycobacterium avium-intercellulare infection in a patient with interferon-γ autoantibody. Clin Infect Dis 49:e76–e78
100. Becher B, Tugues S, Greter M (2016) Review GM-CSF: from growth factor to central mediator of tissue inflammation. Immunity 45(5):963–973. https://doi.org/10.1016/j.immuni.2016.10.026
101. Akagawa KS, Kamoshita KTT (1988) Effects of granulocyte-macrophage colony-stimulating factor and colony-stimulating factor-1 on the proliferation and differentiation of murine alveolar macrophages. J Immunol:3383–3390. Published online
102. Shibata Y, Berclaz P, Chroneos ZC, Yoshida M, Whitsett JA, Trapnell BC (2001) GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU. 1. Immunity 15:557–567
103. Bonfield TL, Raychaudhuri B, Malur A et al (2003) PU.1 regulation of human alveolar macrophage differentiation requires granulocyte-macrophage colony-stimulating factor. Am J Physiol Lung Cell Mol Physiol 285:1132–1136. https://doi.org/10.1152/ajplung.00216.2003
104. Chen BD, Mueller M, Chou T (1988) Role of granulocyte/macrophage colony-stimulating factor in the regulation of murine alveolar macrophage proliferation and differentiation. J Immunol 141:139–144. Information about subscribing to The Journal of Immunology is online at the regulation of murine alveolar macr
105. Factor GMC, Kitamura BT, Tanaka N, Watanabe J (1999) Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against. J Exp Med 190(6):875–880
106. Trapnell BC, Whitsett JA, Nakata K (2003) Pulmonary alveolar proteinosis. N Engl J Med 349(26):2527–2539
107. Seymour JF, Presneill JJ (2002) Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 166:7–9. https://doi.org/10.1164/rccm.2109105
108. Suzuki T, Sakagami T, Young LR et al (2010) Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Respir Crit Care Med 182:1292–1304. https://doi.org/10.1164/rccm.201002-0271OC
109. Tanaka T, Motoi N, Tsuchihashi Y et al (2011) Adult-onset hereditary pulmonary alveolar proteinosis caused by a single-base deletion in CSF2RB. J Med Genet 48(3):205–209. https://doi.org/10.1136/jmg.2010.082586
110. Fieury-feith J (1996) Secondary alveolar proteinosis in cancer patients. Support Care Cancer 4(6):420–426
111. Carey B, Trapnell BC (2010) The molecular basis of pulmonary alveolar proteinosis. Clin Immunol 135(2):223–235. https://doi.org/10.1016/j.clim.2010.02.017
112. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N (2008) Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 177:752–762. https://doi.org/10.1164/rccm.200708-1271OC
113. Kitamura T, Uchida K, Tanaka N et al (2000) Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 162:658–662. https://doi.org/10.1164/ajrccm.162.2.9910032
114. Wgh O, Enh J, Rl P (1998) Primary EMMM. Primary cerebellar nocardiosis and alveolar proteinosis. Acta Neurol Scand:138–141. Published online

115. Andersen BR, Eclund REKW (1960) Pulmonary alveolar proteinosis with systemic nocardiosis. JAMA 3(174):28–31
116. Witty LA, Tapson VFPC (1994) Isolation of mycobacteria in patients with pulmonary alveolar proteinosis. Medicine (Baltimore) 73:103–109
117. Hartung MSK (1975) Pulmonary alveolar proteinosis and histoplasmosis: report of three cases. Virchows Arch A Pathol Anat Histol 368(4):281–287
118. Rosen LB, Freeman AF, Yang LM et al (2013) Anti–GM-CSF autoantibodies in patients with cryptococcal meningitis. J Immunol 190(8):3959–3966. https://doi.org/10.4049/jimmunol.1202526
119. Borie R, Danel C, Debray M, Taille C, Dombret M, Aubier M (2011) Pulmonary alveolar proteinosis. Eur Respir Rev 20(120):98–107. https://doi.org/10.1183/09059180.00001311
120. Holbert JM, Costello P, Hoffman RM, Rogers RM (2001) CT features of pulmonary alveolar. Am J Roentgenol 176:1287–1294
121. Campo I, Kadija Z, Mariani F et al (2012) Pulmonary alveolar proteinosis: diagnostic and therapeutic challenges. Multidiscip Respir Med 7:4
122. Griese M (2017) Pulmonary alveolar proteinosis: a comprehensive clinical perspective. Pediatrics 140(2):e20170610
123. Kavuru MS, Sullivan EJ, Piccin R, Thomassen MJ, Stoller JK (2000) Exogenous granulocyte-macrophage colony-stimulating factor administration for pulmonary alveolar proteinosis. Am J Respir Crit Care Med Care Med 161:1143–1148
124. Seymour JF, Presneill JJ, Schoch OD et al (2001) Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med 163:524–531
125. Tazawa R, Trapnell BC, Inoue Y et al (2010) Inhaled granulocyte/macrophage—colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respir Crit Care Med 181:1345–1354. https://doi.org/10.1164/rccm.200906-0978OC
126. Kavuru MS, Malur A, Marshall I et al (2011) An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J 38(6):1361–1367. https://doi.org/10.1183/09031936.00197710
127. Borie R, Debray MP, Laine C, Aubier M, Crestani B (2009) Rituximab therapy in autoimmune pulmonary alveolar proteinosis. Eur Respir J 33:1503–1506. https://doi.org/10.1183/09031936.00160908
128. Jones SA (2005) Directing transition from innate to acquired immunity: defining a role for IL-6. J Immunol 175:3463–3468. https://doi.org/10.4049/jimmunol.175.6.3463
129. Majello B, Arcone R, Toniatti C (1990) Constitutive and IL-6-induced nuclear factors that interact with the human C-reactive protein promoter. EMBO 9(2):457–465
130. Heinrich PC, Castellt JV (1990) Interleukin-6 and the acute phase response. Biochem J 265:621–636
131. Galle P, Svenson M, Bendtzen K, Hansen MB (2004) High levels of neutralizing IL-6 autoantibodies in 0.1% of apparently healthy blood donors. Eur J Immunol 34:3267–3275. https://doi.org/10.1002/eji.200425268
132. Hansen MB, Diamant M, Svenson M, Bendtzen K (1991) Anti-interleukin-6 antibodies in normal human serum. Scand J Immunol 33:777–781
133. Puel A, Picard C, Lorrot M et al (2008) Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. J Immunol 180:647–654. https://doi.org/10.4049/jimmunol.180.1.647
134. Bloomfield M, Parackova Z, Cabelova T, Pospisilova I (2019) Anti-IL6 autoantibodies in an infant with CRP-less septic shock. Front Immunol 10:1–6. https://doi.org/10.3389/fimmu.2019.02629
135. Nanki T, Onoue I, Nagasaka K, Takayasu A, Ebisawa M et al (2013) Suppression of elevations in serum C reactive protein levels by anti-IL-6 autoantibodies in two patients with severe bacterial infections. Rheum Dis 72(6):1100–1102
136. Kelleher P, Misbah SA (2003) What is Good's syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol 56:12–16

137. Trober WAS, Undles CHCU, Ucey DARL (2001) Infections in patients with immunodeficiency with thymoma (Good Syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) 80(2):123–133
138. Agarwal S, Cunningham-Rundles C (2007) Thymoma and immunodeficiency (good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 98(2):185–190. https://doi.org/10.1016/S1081-1206(10)60695-3.Thymoma
139. Meager A, Vincent A, Willcox N (1997) Spontaneous neutralising antibodies to interferon--alpha and interleukin-12 in thymoma-associated autoimmune disease. Lancet 350:1996–1997
140. Jansen A, Van Deuren M, Miller J, Litzman J, De Gracia J, Sáenz-cuesta M (2016) Prognosis of Good syndrome: mortality and morbidity of thymoma associated immunodeficiency in perspective. Clin Immunol 171:12–17. https://doi.org/10.1016/j.clim.2016.07.025