NIH Public Access
Author Manuscript
Curr Opin Rheumatol. Author manuscript; available in PMC 2010 January 1.

Published in final edited form as:
Curr Opin Rheumatol. 2009 January ; 21(1): 78–84. doi:10.1097/BOR.0b013e32831cb939.

Rheumatologic and Autoimmune Manifestations of Primary Immunodeficiency Disorders

Ramona Goyal[1], **Ariel C. Bulua**[4], **Nikolay P. Nikolov**[2], **Pamela L. Schwartzberg**[3], and **Richard M. Siegel**[4,*]

[1] Office of the Clinical Director, NIDCD, NIH

[2] Autoimmunity Branch, NIAMS, National Institutes of Health, NIDCD, NIH

[3] Genetic Disease Research Branch, National Human Genome Research Institute, NIDCD, NIH

[4] Molecular Physiology and Therapeutics Branch, NIDCD, NIH

Abstract

Purpose of Review—Although it may seem paradoxical, Primary Immunodeficiency Disorders (PID) are frequently complicated by autoimmune and inflammatory conditions. These conditions pose significant diagnostic and therapeutic challenges for clinicians caring for these patients. There have been a number of new insights into how Rheumatologists should understand the basis for and manifestations of autoimmunity in PID to more effectively care for these patients.

Recent Findings—A number of mechanisms have recently been proposed to link primary immunodeficiencies and autoimmunity, including increased homeostatic proliferation and defects in regulatory T cells.

Summary—The realization that Primary Immunodeficiencies can also impair negative regulation of immune responses has provided a new framework for the understanding of autoimmunity associated with these conditions, and may lead to new, more targeted therapies for these clinically challenging patients.

Primary Immunodeficiencies and Autoimmunity: the clinical challenge

The primary immunodeficiency disorders (PID) are a heterogeneous group of diseases resulting from inherited defectsin the development and maturation of immune cells. PID can involve defects in adaptive immunity, with involvement of either or both B and T cells, and PID can also affect the innate immune system [1] PID are inevitably associated with increased susceptibility to infections, with the type of infection determined by which immune cells are affected by each disorder. Although it may at first seem paradoxical, autoimmunity and abnormal inflammation in the apparent absence of infection has often been observed clinically in association with PID. In a PID patient presenting with symptoms consistent with autoimmune or autoinflammatory disease, subclinical and clinical infections must always be considered. However, autoimmune complications of PID are often independent of any known infection, and persuasive evidence has come from animal models showing that the underlying immunodeficiency can directly predispose to autoimmune or autoinflammatory disease by disrupting mechanisms that normally negatively regulate immune responses. Just as specific PID are often linked to characteristic opportunistic infections, different forms of PID have been linked to specific autoimmune complications at various frequencies (Table 1). We will review

Address correspondence to Richard M. Siegel, Building 10 Rm 13C103, NIH Bethesda, MD, 20892, USA, rsiegel@nih.gov.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

autoimmune complications of primary immunodeficiencies and discuss recent findings that have uncovered cellular and molecular mechanisms linking PID to autoimmune disease.

Primary Immuodeficiencies affecting lymphocyte development

A number of PID affect lymphocyte development, resulting in severely decreased numbers of peripheral T and/or B cells. These disorders are part of the spectrum of Severe Combined Immunodeficiecies (SCID). Although these are among the most clinically severe immunodeficiencies, autoimmune complications have been noted [2]. Omenn Syndrome (MIM #603554) is SCID subtype associated with a number of specific autoimmune complications. This syndrome is characterized by severely decreased circulating T and B cells, some cases of which are caused by mutations in recombination-activating genes (RAG) 1 and 2, proteins that are critical in catalyzing the DNA recombination that generates the T and B cell repertoire. In addition to increased susceptibility to infections from birth, patents with Omenn syndrome can develop autoimmune complications including lymphadenopathy, splenomegaly, erythroderma, and autoimmune hepatic dysfunction. These complications are associated with eosinophilia and elevated IgE, suggesting involvement of the Th2 subset of T cells that produces IL-4, IL-6 and other cytokines that drive plasma cell differentiation and IgE production by B cells[3]. Patients with these complications have been treated with high-dose steroids, antithymocyte globulin, and cyclosporin A. Bone marrow transplantation remains the only definitive treatment.

Immunodeficiencies resulting in severe lymphopenia may result in autoimmunity through an immunological process termed homeostatic proliferation. While normal naïve T and B cells turn over very slowly, much more rapid T and B cell proliferation is seen in the setting of severe lymphopenia. In animal models, it has been found that T cells in a lymphopenic environment can divide as rapidly as every two days without any external stimulus [4,5]. Homeostatic proliferation can be seen after therapies that deplete lymphocytes, bone marrow transplantation, transfer of cells into a lymphopenic environment, and during the physiological lymphopenia of the neonatal period [6]. Homeostatic proliferation is thought to be driven by the functional excess of cytokines such as Interleukin-7 that normally are limiting in a replete lymphocyte compartment due to binding and uptake by specific receptors [7] Originally thought to be a benign process that simply reconstitutes a damaged immune system, T cells that proliferate through this mechanism have been more recently shown to acquire properties of memory cells including effector cytokine production and cytotoxicity. Because homeostatically proliferating lymphocytes are presumably reactive against self-antigens, potent autoreactive effector cells may be produced [8]. In the NOD mouse model of type I diabetes, homeostatic proliferation secondary to lymphopenia was found to be integral to the development of anti-islet autoimmunity [9]. Less is known about the autoreactive potential of B cells expanded through homeostatic proliferation, but some of the same principals may apply. Notably, mice engineered to have RAG1 mutations similar to those in Omenn syndrome developed the eosinophila, hypergammaglobulinemia and T cell infiltration seen in humans with this disease, and homeostatically proliferating memory–phenotype T cells producing effector cytokines were isolated from these animals. [10,11]. Homeostatic proliferation may predispose to autoimmunity in any PID involving severe lymphopenia. Conceivably, therapies that could increase lymphocyte numbers in these patients may ameliorate autoimmune manifestations as well as treat the underlying immunodeficiency.

Primary Immunodeficiencies and failure of self-tolerance

Two genetic immunodeficiency/dysregulation syndromes specifically affecting mechanisms of T cell tolerance illustrate how PID can affect checkpoints that govern both positive and negative regulation of immunity. Autoimmune polyendocrinopathy-candidasis-ectodermal

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

dystrophy(APECED) (autoimmune polyglandular syndrome type 1) is an autosomal recessive disorder with a genetic mutation of the AIRE gene whose product is expressed in the thymus, lymph nodes, pancreas, adrenal cortex and fetal liver. Primary manifestations include hypoparathyroidism (89%), chronic mucocutaneous candidiasis (75%), adrenal insufficiency (60%), primary hypogonadism (45%), and malabsorption (25%). Other non-endocrine and autoimmune manifestations include alopecia, pernicious anemia, chronic hepatitis, and vitiligo [12]. The gene mutated in APECED, termed the autoimmune regulator (AIRE) gene, is a nuclear transcription factor that functions in the thymus to upregulate expression of tissue-specific genes in thymic epithelial cells. Developing thymocytes with a TCR that recognize these antigens undergo apoptosis during development, creating central immune tolerance to these antigens. Central tolerance fails in AIRE deficient mice, which recapitulate many features of APECED [13–15]. Defective AIRE expression in the thymus has also been seen in two patients with Omenn's syndrome [16], suggesting that feedback from normal T cell development may be necessary in some cases for proper expression of AIRE and central tolerance.

Genetic deficiency in the FoxP3 transcription factor that is essential for the development of $CD25^+$ regulatory T cells produces the syndrome of Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX), providing dramatic proof that regulatory T cells are necessary for immunological self-tolerance in humans. Clinical features include early onset type 1 diabetes mellitus, severe enteropathy, autoimmune hepatitis, eczema, anemia, thrombocytopenia, and hypothyroidism [17]. Mutations in the FoxP3 gene that encodes the protein scurfin has been identified in most IPEX patients [18]. FoxP3 deficient mice recapitulate many of the symptoms of IPEX patients. Immunosuppressive therapy including tacroliums, cyclosporine, methotrexate, infliximab, and rituximab has been used to treat this syndrome, but bone-marrow transplanation remains the only curative therapy [19]. Interestingly, lymphoproliferation during the neonatal period has recently been identified as another possible contributor to autoimmunity in FoxP3 deficient mice [20]

In some cases, autoimmunity itself may contribute to immunodeficiency. Although not strictly a primary immunodeficiency disorder, idiopathic CD4 Lymphopenia (ICL) shares some features with SCID and in some cases appears to be linked to autoimmunity. ICL is diagnosed in patients who develop CD4 T-lymphocytopenia with CD4 counts <300 cell/uL without HIV infection or other known viral cause. Increased susceptibility to infections, particularly Cryptococci, has been noted in these patients. The lymphopenia associated with Sjogren's syndrome can become severe enough in some cases for patients to be classified as having ICL; in a study of 214 Sjögren's patients, (3.7%) were found to have ICL [21], with lymphocytopenia associated with antibodies directed against CD4 lymphocytes. Decreased numbers of CD4 lymphoctyes and a low CD4:CD8 ratio were associated with severe renal disease or thrombocytopenia [22,23]. Lymphopenia in SLE patients may have a related pathogenesis. These observations suggest the interesting possibility that autoantibodies against immune cells may play a role in functional immunodeficiency and susceptibility to infections seen clinically in patients with systemic autoimmune conditions.

Immunodeficiencies affecting B cells and mixed immune defects

Patients with defects in humoral immunity can also suffer from autoimmune complications. Since autoantibody production is limited by the B cell defects in these patients, other mechanisms likely contribute. X-linked agammaglobulinemia (XLA or Bruton's agammaglobulenemia) is due to mutations in Bruton's tyrosine kinase, a signal transduction molecule essential for B cell maturation. Btk-deficient B cells do not differentiate into antibody-producing plasma cells, and patients have pan-hypogammaglobulinema. Clinical manifestations include recurrent bacterial sinopulmonary infections, eczema, and diarrhea.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Interestingly, XLA patients have an elevated incidence of juvenile rheumatoid arthritis, aspetic polyarthritis, cytopenias, IBD, and dermatomyositis [24]. Hyper-IgM (HIGM) is a primary immunodeficiency from a genetic defect in the CD40 ligand pathway (X-linked HIGM) or in other proteins required for immunoglobulin class switch recombination. (MIM #308230). Consequently, HIGM patients have selective IgG deficiency with normal or elevated IgM levels, and are prone to recurrent sinopulmonary and gastrointestinal infections. Autoimmunity has often been described in HIGM patient series. In a cohort of 56 X-linked HIGM patients, IBD was seen in 6%, seronegative arthritis in 11%, chronic neutropenia in 45% [25]. In another study of 79 patients, 60% were found to have neutropenia, with anemia and thrombocytopenia in 15% and 4%, respectively [26]. Parvovirus B19 infection was only detected in 4% of the patients raising the suspicion of an autoimmune etiology independent of known infections.

Primary immunodeficiencies affecting CD8 and Natural killer (NK) cell cytotoxicity such as perforin deficiency (MIM #603553) and Griscelli Syndrome (MIM #607624) are associated with development of the hemophagocytic syndrome HLH (Hemophagocytic lymphocytic histiocytosis). In HLH, abnormal activation of both lymphocytes and innate cells, especially macrophages, can lead to immune cell infiltration into a number of organs, including the bone marrow, which leads to the complication of aplastic anemia and other features [27]. Another immunodeficiency associated with HLH is X-linked Immunoproliferative Syndrome (XLP1, MIM #308240), a disorder characterized by fulminant mononucleosis, lymphomas and other lymphoproliferative syndromes and dysgammaglobulinemias. XLP1 results from mutations in the gene encoding SAP, an adapter protein that transduces signals from SLAM family receptors [28] [29]. This family of cell surface molecules is important in mediating homotypic lymphocyte interactions that are necessary for CD8 T and NK cell-mediated killing of EBV-infected targets, for development of the NKT cell lineage, as well as for T:B cell interactions required for germinal center formation and long-term humoral immunity[28]. Abnormal cytolytic activity towards EBV infected B cells is a hallmark of this disorder, and like other disorders with abnormal cytolytic activity, HLH-type complications, including development of aplastic anemia, can develop in a small percentage of patients. Other rare complications include lymphocytic vasculitis and other lymphocytic tissue infiltration, which have on occasion been treated successfully with steroids. Whether these features result from inappropriate lymphocyte interactions, a lack of NKT cells or other alterations in lymphocyte homeostasis (including abnormal cell death that is observed in this syndrome) is unknown. The only definitive treatment for XLP is bone marrow transplantation.

Common variable immunodeficiency (CVID) is a heterogeneous group of diseases characterized by defective antibody production and underlying T cell defects. About 10% of CVID cases have been linked to autosomal dominant mutations in the TNF-receptor family member TACI [30,31]. Clinical manifestations include recurrent sinopulmonary and gastrointestinal infections, with chronic bronchiectasis. Autoimmune diseases, particularly chronic inflammatory bowel disease, autoimmune cytopenias such as thrombocytopenia and hemolytic anemia, and rheumatoid arthritis are common in patients with CVID [32,33]. Interestingly, mice engineered to lack TACI have a partial deficiency in B cell class-switching, but also develop splenomegaly and accumulate B cells that hyper-produce immunoglobulins, reproducing some features of CVID. [34,35]

Wiskott - Aldrich syndrome (WAS) is a single gene PID that affects many aspects of immune cell function and is associated with a remarkably high prevalence of autoimmunity, as high as 70% in retrospective cohorts [36,37] with some patients developing multiple autoimmune manifestations. The mutated gene in WAS encodes a multidomain protein called Wiskott - Aldrich syndrome protein (WASp). WASp is expressed exclusively in cells of the hematopoietic lineage and is critical for cytoskeletal remodeling via actin polymerization. Its role in cell and organelle motility, immune cell polarization, immunological synapse formation

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and T cell receptor (TCR) signaling was found from studies in WAS patients and WASp deficient mice [38]. WASP deficiency can affect NK and T cell cytolytic function and T cell help for B cells. WAS patients have reduced antibody responses to polysaccharide vaccines and increased susceptibility to a wide variety of bacterial, viral and fungal infections. Mast Cell, NK cell, platelet and neutrophil function are also affected in WAS [39–41]. WASp deficient mice were found to develop immune-mediated colitis and other autoimmune manifestations[42,43], but how WASp deficiency predisposes to autoimmunity remained obscure until recently.

WASp deficient T cells are defective in their production of Interleukin-2, a cytokine known to be required for survival of regulatory T cells. Several groups have recently investigated the role of WASp in the development and function of regulatory T cells, which are essential in the control of T-cell mediated autoimmunity [43,44,45] Humblet-Baron et al. reported normal thymic development but compromised peripheral survival and function of WASp-deficient murine Tregs. Maillard et al. found decreased numbers of both thymic and peripheral Tregs along with impaired homing and suppressive function of the WASp-deficient Treg cells, partly resulting from deficient production of IL-2 and IL-10. Adriani et al. described defective Treg function in WASp deficient T cells from mice and humans and restoration of Treg function by addition of IL-2, reinforcing the concept that defective IL-2 production in WAS may compromise Treg function and lead to autoimmunity. Defective Treg function may not be the only mechanism contributing to autoimmunity in WAS. Our own work has also suggested a role for defective production of Fas Ligand, a TNF-family member that enforces self-tolerance through inducing apoptosis via its receptor (Fas/CD95) in the pathogenesis of autoimmunity in WAS (Nikolov et al, manuscript submitted). Defective clearance of apoptotic cells, which can contribute to autoimmunity, was also suggested to play a role in the pathogenesis of autoimmunity in WAS [46]. These findings illustrate how even in a single-gene PID, multiple mechanisms may contribute to autoimmune complications.

Primary Immunodeficiencies affecting innate immunity

It is being increasingly recognized that the activation of innate immune cells such as macrophages, neutrophils and dendritic cells is regulated independently from lymphocytes. The autoinflammatory diseases, genetic syndromes resulting from mutations that affect negative regulators of inflammation or hyperactivate components of the ‘inflammasome’ responsible for the generation of the active form of the pro-inflammatory cytokine IL-1, offer clear clinical evidence that molecular mechanisms regulating innate immune responses exist and are relevant to human disease. Autoinflammatory diseases often result in arthralgias, arthritis, periodic fevers, and like other chronic rheumatic diseases, can predispose to secondary amyloidosis. The discovery that uric acid crystals and other particulate compounds can activate the inflammasome has linked many of the purely inflammatory disorders seen by rheumatologists to the same pathway. Interestingly, genetic autoinflammatory syndromes and acquired autoinflammatory diseases such as gout do not predispose to the development of antibody and T cell-mediated autoimmunity, suggesting that these types of inflammatory conditions do not prime the adaptive immune system in ways that predispose to autoimmunity.

Conversely, diseases that impair innate immunity have been associated with chronic inflammation that can mimic rheumatic conditions. A good example of this is chronic granulomatous disease (CGD), which is linked to mutations in the genes coding for the multisubunit phagocytic NADPH oxidase complex. Two thirds of patients have an x-linked mutation in $gp91^{phox}$, a subunit of the NAPDH oxidase enzyme complex, while the rest possess mutations in other NOX subunits[47,48]. Phagocytic NADPH oxidase generates the ‘respiratory burst’ in macrophages and neutrophils that facilitates bacterial killing, adhesion and other functions. [49]. With the exception of a few cases in which low levels of ROS

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

generation have been detected, patients with the disease have a total failure of respiratory burst activity [47,48]. Patients with CGD present with chronic recurrent infections, but inflammatory complications are prominent, including the development of granulomas and severe inflammatory bowel disease [50].

The finding that CGD patients present with hyperinflammation seems at first to be paradoxical, since ROS have been shown to induce activation of the NF-κB transcription factor complex which facilitates production of proinflammatory cytokines such as TNF, IL-6 and IL-1β. One would expect a defect in ROS production to result in decreased production of inflammatory cytokines; however, studies of leukocytes from CGD patients and mouse models consistently show hyperresponsiveness to a number of proinflammatory stimuli in terms of cytokine prodction, and enhanced infiltration of neutrophils in the peritoneum in sterile peritonitis. [51] Gene expression profiling results from PMNs of 8 CGD patients showed upregulation of numerous proinflammatory molecules[52]. In addition, it has been shown that the inflammatory manifestations of CGD are not due to increased cell survival, and CGD cells are capable of executing normal NF-κB signaling in the absence of NOX2- generated ROS. These results suggest that another NOX family member or a parallel NOX-independent pathway is responsible for NF-kB activation and inflammatory sequelae in CGD. The hyperinflammation in CGD shows that in addition to an important function in pathogen clearance, ROS appear provide a signal for cessation of the inflammatory response, which is absent in CGD. Leukocyte adhesion deficiency 1 (LAD-1) is another primary innate immune system PID in which neutrophils lack expression of β2 integrin (CD18), an adhesion molecule essential in the process of neutrophil extravasation from blood vessels. Despite this block in what would seem to be a critical pathway for generating an inflammatory response, LAD-1 patients have been reported to develop inflammatory bowel disease[53].

Approach to therapy of autoimmune complications in patients with PID

Given that PID patients are by definition immunocompromised, a thorough exclusion of infections coincident with or possibly causative of autoimmune complications should be undertaken before initiating specific treatments for autoimmune complications in these patients. In the absence of any trial data for these rare diseases, most therapies are empirical. Nevertheless, one valuable approach is to consider the clinical severity of any particular autoimmune complication and need for treatment, as one would do in a patient without underlying immunodeficiency. Specific therapy can then be tailored to avoid those known to predispose to infections to which a patient may already be susceptible given the specific immunodeficiency involved. In cases where it is clinically indicated, non-immunosuppressive therapeutics such as Intravenous Immunoglobulin (IV-Ig) would be preferable. Targeted therapies that affect specific immune cell subsets, such as Rituximab for B-cell mediated pathologies, CTLA4-Ig for T cells, or anti-TNF for inflammatory bowel disease, may be preferable over the broad immunosuppressive activity of glucocorticoids. With the recent advances uncovering molecular causes of PID and specific pathways responsible for the development of autoimmune complications, it is hoped that more rational treatment will evolve for these challenging patients.

References

1. Rosen FS, Cooper MD, Wedgwood RJ. The primary immunodeficiencies. N Engl J Med 1995;333:431–440. [PubMed: 7616993]
2. Elhasid R, Bergman R, Etzioni A. Autoimmunity in severe combined immunodeficiency (SCID). Blood 2002;100:2677–2678. [PubMed: 12360982]author reply 2678–2679
3. Honig M, Schwarz K. Omenn syndrome: a lack of tolerance on the background of deficient lymphocyte development and maturation. Curr Opin Rheumatol 2006;18:383–388. [PubMed: 16763459]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

4. Surh CD, Sprent J. Homeostatic T cell proliferation: how far can T cells be activated to self-ligands? J Exp Med 2000;192:F9–F14. [PubMed: 10952731]
5. Cabatingan MS, Schmidt MR, Sen R, Woodland RT. Naive B lymphocytes undergo homeostatic proliferation in response to B cell deficit. J Immunol 2002;169:6795–6805. [PubMed: 12471111]
6. Min B, McHugh R, Sempowski GD, Mackall C, Foucras G, Paul WE. Neonates support lymphopenia-induced proliferation. Immunity 2003;18:131–140. [PubMed: 12530982]
7. Goldrath AW, Sivakumar PV, Glaccum M, Kennedy MK, Bevan MJ, Benoist C, Mathis D, Butz EA. Cytokine requirements for acute and Basal homeostatic proliferation of naive and memory CD8+ T cells. J Exp Med 2002;195:1515–1522. [PubMed: 12070279]
8. Baccala R, Theofilopoulos AN. The new paradigm of T-cell homeostatic proliferation-induced autoimmunity. Trends Immunol 2005;26:5–8. [PubMed: 15629402]
9. King C, Ilic A, Koelsch K, Sarvetnick N. Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell 2004;117:265–277. [PubMed: 15084263]An important paper showing that lymphopenia can exacerbate autoimmunity through stimulation homeostatic expansion
10. Khiong K, Murakami M, Kitabayashi C, Ueda N, Sawa S, Sakamoto A, Kotzin BL, Rozzo SJ, Ishihara K, Verella-Garcia M, et al. Homeostatically proliferating CD4 T cells are involved in the pathogenesis of an Omenn syndrome murine model. J Clin Invest 2007;117:1270–1281. [PubMed: 17476359] Another link between lymphopenia and homeostatic expansion of T cells in a mouse model of Omenn syndrome
11. Marrella V, Poliani PL, Casati A, Rucci F, Frascoli L, Gougeon ML, Lemercier B, Bosticardo M, Ravanini M, Battaglia M, et al. A hypomorphic R229Q Rag2 mouse mutant recapitulates human Omenn syndrome. J Clin Invest 2007;117:1260–1269. [PubMed: 17476358]
12. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 1990;322:1829–1836. [PubMed: 2348835]
13. Liston A, Lesage S, Wilson J, Peltonen L, Goodnow CC. Aire regulates negative selection of organ-specific T cells. Nat Immunol 2003;4:350–354. [PubMed: 12612579]
14. Ramsey C, Winqvist O, Puhakka L, Halonen M, Moro A, Kampe O, Eskelin P, Pelto-Huikko M, Peltonen L. Aire deficient mice develop multiple features of APECED phenotype and show altered immune response. Hum Mol Genet 2002;11:397–409. [PubMed: 11854172]
15. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science 2002;298:1395–1401. [PubMed: 12376594]
16. Cavadini P, Vermi W, Facchetti F, Fontana S, Nagafuchi S, Mazzolari E, Sediva A, Marrella V, Villa A, Fischer A, et al. AIRE deficiency in thymus of 2 patients with Omenn syndrome. J Clin Invest 2005;115:728–732. [PubMed: 15696198]
17. Moraes-Vasconcelos D, Costa-Carvalho BT, Torgerson TR, Ochs HD. Primary immune deficiency disorders presenting as autoimmune diseases: IPEX and APECED. J Clin Immunol 2008;28 (Suppl 1):S11–19. [PubMed: 18264745]
18. Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol 2003;15:430–435. [PubMed: 12819471]
19. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 2002;39:537–545. [PubMed: 12161590]
20. Chang X, Zheng P, Liu Y. Homeostatic proliferation in the mice with germline FoxP3 mutation and its contribution to fatal autoimmunity. J Immunol 2008;181:2399–2406. [PubMed: 18684929]An interesting paper implicating homeostatic proliferation in the genesis of autoimmunity in foxP3 mutatnt mice.
21. Henriksson G, Manthorpe R, Bredberg A. Antibodies to CD4 in primary Sjogren's syndrome. Rheumatology (Oxford) 2000;39:142–147. [PubMed: 10725063]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

22. Yamada A, Cohen PL, Winfield JB. Subset specificity of antilymphocyte antibodies in systemic lupus erythematosus. Preferential reactivity with cells bearing the T4 and autologous erythrocyte receptor phenotypes. Arthritis Rheum 1985;28:262–270. [PubMed: 3884018]

23. Morimoto C, Reinherz EL, Distaso JA, Steinberg AD, Schlossman SF. Relationship between systemic lupus erythematosus T cell subsets, anti-T cell antibodies, and T cell functions. J Clin Invest 1984;73:689–700. [PubMed: 6231307]

24. Lee AH, Levinson AI, Schumacher HR Jr. Hypogammaglobulinemia and rheumatic disease. Semin Arthritis Rheum 1993;22:252–264. [PubMed: 8484132]

25. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 1997;131:47–54. [PubMed: 9255191]

26. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 2003;82:373–384. [PubMed: 14663287]

27. Arceci RJ. When T cells and macrophages do not talk: the hemophagocytic syndromes. Current Opinion in Hematology 2008;15:359–367. [PubMed: 18536575]

28. Nichols KE, Ma CS, Cannons JL, Schwartzberg PL, Tangye SG. Molecular and cellular pathogenesis of X-linked lymphoproliferative disease. Immunol Rev 2005;203:180–199. [PubMed: 15661030]

29. Coffey AJ, Brooksbank RA, Brandau O, Oohashi T, Howell GR, Bye JM, Cahn AP, Durham J, Heath P, Wray P, et al. Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. Nat Genet 1998;20:129–135. [PubMed: 9771704]

30. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 2005;37:829–834. [PubMed: 16007086]

31. Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 2005;37:820–828. [PubMed: 16007087]The above two papers link CVID to dominant mutations in the TNF-receptor family member TACI

32. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92:34–48. [PubMed: 10413651]

33. Uluhan A, Sager D, Jasin HE. Juvenile rheumatoid arthritis and common variable hypogammaglobulinemia. J Rheumatol 1998;25:1205–1210. [PubMed: 9632087]

34. Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS. TACI and BAFF-R mediate isotype switching in B cells. J Exp Med 2005;201:35–39. [PubMed: 15630136]

35. Yan M, Wang H, Chan B, Roose-Girma M, Erickson S, Baker T, Tumas D, Grewal IS, Dixit VM. Activation and accumulation of B cells in TACI-deficient mice. Nat Immunol 2001;2:638–643. [PubMed: 11429549]

36. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 1994;125:876–885. [PubMed: 7996359]

37. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, et al. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 2003;111:e622–627. [PubMed: 12728121]

38. Zhang J, Shehabeldin A, da Cruz LA, Butler J, Somani AK, McGavin M, Kozieradzki I, dos Santos AO, Nagy A, Grinstein S, et al. Antigen receptor-induced activation and cytoskeletal rearrangement are impaired in Wiskott-Aldrich syndrome protein-deficient lymphocytes. J Exp Med 1999;190:1329–1342. [PubMed: 10544204]

39. Snapper SB, Meelu P, Nguyen D, Stockton BM, Bozza P, Alt FW, Rosen FS, von Andrian UH, Klein C. WASP deficiency leads to global defects of directed leukocyte migration in vitro and in vivo. J Leukoc Biol 2005;77:993–998. [PubMed: 15774550]

40. Orange JS, Ramesh N, Remold-O'Donnell E, Sasahara Y, Koopman L, Byrne M, Bonilla FA, Rosen FS, Geha RS, Strominger JL. Wiskott-Aldrich syndrome protein is required for NK cell cytotoxicity

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and colocalizes with actin to NK cell-activating immunologic synapses. Proc Natl Acad Sci U S A 2002;99:11351–11356. [PubMed: 12177428]

41. Pivniouk VI, Snapper SB, Kettner A, Alenius H, Laouini D, Falet H, Hartwig J, Alt FW, Geha RS. Impaired signaling via the high-affinity IgE receptor in Wiskott-Aldrich syndrome protein-deficient mast cells. Int Immunol 2003;15:1431–1440. [PubMed: 14645152]
42. Snapper SB, Rosen FS, Mizoguchi E, Cohen P, Khan W, Liu CH, Hagemann TL, Kwan SP, Ferrini R, Davidson L, et al. Wiskott-Aldrich syndrome protein-deficient mice reveal a role for WASP in T but not B cell activation. Immunity 1998;9:81–91. [PubMed: 9697838]
43. Humblet-Baron S, Sather B, Anover S, Becker-Herman S, Kasprowicz DJ, Khim S, Nguyen T, Hudkins-Loya K, Alpers CE, Ziegler SF, et al. Wiskott-Aldrich syndrome protein is required for regulatory T cell homeostasis. J Clin Invest 2007;117:407–418. [PubMed: 17218989]
44. Adriani M, Aoki J, Horai R, Thornton AM, Konno A, Kirby M, Anderson SM, Siegel RM, Candotti F, Schwartzberg PL. Impaired in vitro regulatory T cell function associated with Wiskott-Aldrich syndrome. Clin Immunol 2007;124:41–48. [PubMed: 17512803]
45. Maillard MH, Cotta-de-Almeida V, Takeshima F, Nguyen DD, Michetti P, Nagler C, Bhan AK, Snapper SB. The Wiskott-Aldrich syndrome protein is required for the function of CD4(+)CD25(+) Foxp3(+) regulatory T cells. J Exp Med 2007;204:381–391. [PubMed: 17296786]The above three papers implicate defective Treg homeostasis and function to the autoimmunity seen in the Wiskott-Aldrich syndrome
46. Lorenzi R, Brickell PM, Katz DR, Kinnon C, Thrasher AJ. Wiskott-Aldrich syndrome protein is necessary for efficient IgG-mediated phagocytosis. Blood 2000;95:2943–2946. [PubMed: 10779443]
47. Royer-Pokora B, Kunkel LM, Monaco AP, Goff SC, Newburger PE, Baehner RL, Cole FS, Curnutte JT, Orkin SH. Cloning the gene for an inherited human disorder--chronic granulomatous disease--on the basis of its chromosomal location. Nature 1986;322:32–38. [PubMed: 2425263]
48. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000;79:155–169. [PubMed: 10844935]
49. Lambeth JD. NOX enzymes and the biology of reactive oxygen. Nat Rev Immunol 2004;4:181–189. [PubMed: 15039755]
50. Heyworth PG, Cross AR, Curnutte JT. Chronic granulomatous disease. Curr Opin Immunol 2003;15:578–584. [PubMed: 14499268]
51. Pollock JD, Williams DA, Gifford MA, Li LL, Du X, Fisherman J, Orkin SH, Doerschuk CM, Dinauer MC. Mouse model of X-linked chronic granulomatous disease, an inherited defect in phagocyte superoxide production. Nat Genet 1995;9:202–209. [PubMed: 7719350]
52. Kobayashi SD, Voyich JM, Braughton KR, Whitney AR, Nauseef WM, Malech HL, DeLeo FR. Gene expression profiling provides insight into the pathophysiology of chronic granulomatous disease. J Immunol 2004;172:636–643. [PubMed: 14688376]
53. Uzel G, Kleiner DE, Kuhns DB, Holland SM. Dysfunctional LAD-1 neutrophils and colitis. Gastroenterology 2001;121:958–964. [PubMed: 11606509]
54. Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, Oksenhendler E, Schaeffer A, Bierling P, Godeau B. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore) 2004;83:254–263. [PubMed: 15232313]
55. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 2005;25:57–62. [PubMed: 15994061]
56. Milner JD, Fasth A, Etzioni A. Autoimmunity in severe combined immunodeficiency (SCID): lessons from patients and experimental models. J Clin Immunol 2008;28 (Suppl 1):S29–33. [PubMed: 18193342]
57. Arimura Y, Goto A, Yamashita K, Endo T, Ikeda H, Tanaka K, Tsutsumi H, Shinomura Y, Imai K. Intractable colitis associated with chronic granulomatous disease. J Med Microbiol 2006;55:1587–1590. [PubMed: 17030921]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Association of Primary Immunodeficiency Diseases with Autoimmunity and Autoinflammation

Disease or Syndrome	Mutant gene	Immunologic defect	1* manifestations	Autoimmune Manifestations
Common Variable Immunodeficiency (CVID)	TACI (TNFRSF13B) and others	hypogammaglobulinemia, humoral and T-lymphocyte dysfunction	recurrent chronic infections, particularly respiratory	inflammatory bowel disease autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis, and pernicious anemia [54,55]
Severe Combined Immunodeficiciency (SCID)	Multiple	Lymphocyte Development	failure to thrive, chronic mucocutaneous fungal infections, and/or opportunistic infections	alopecia, autoimmune thrombocytopenia[2,56]
Bruton Agammaglobulinemia	Bruton's tyrosine kinase	X-linked agammaglobulinemia	recurrent bacterial infections of the respiratory tract	juvenile rheumatoid arthritis, aseptic polyarthritis, dermatomyositis[24]
Hyper IgM syndrome (HIgM)	CD40 ligand and others	Ig Class switching defect leading to decreased IgG with normal to elevated IgM	sinopulmonary and GI infections with encapsulated bacteria. and lymphoid hyperplasia	diabetes mellitus, autoimmune hepatitis, rheumatoid arthritis, inflammatory bowel disease, and uveitis
Omenn Syndrome	Rag1; Rag2	T-B-NK+	exudative skin rash, lymphadenopathy, hepatosplenomegaly, eosinophilia, and hyper-IgE levels	part of primary syndrome[2,56]
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)	AIRE	nuclear transcription factor?	Hypoparathyroidism, chronic mucocutaneous candidiasis, adrenal insufficiency, primary hypogonadism, alopecia, vitiligo, pernicious anemia	part of primary syndrome
immunodysregulation polyendocrinopathy enteropathy X-linked syndrome(IPEX)	Foxp3	regulatory T-cells	Autoimmune thyroid diseae, excema, type I diabetes, eosinophilia, hyper IgE	Part of primary syndrome
Leukocyte Adhesion Deficiency (LAD1)	CD18; ITGB2	monocyte and neutrophil adhesion	recurrent bacterial infections	inflammatory bowel disease[53]
Wiskott-Aldrich Syndrome (WAS)	WASP	CD4 T-lymphocytes; regulatory T-cells	micro- thrombocytopenia with bleeding diathesis, eczema, recurrent infections	autoimmune hemolytic anemia, artirits, vasculitis, inflammatory bowel disease, glomerulonephritis
Chronic Granulomatous Disease (CGD)	CYBB and other components of the NOX2 NADPH oxidase complex	NADPH Oxidase	recurrent suppurative microbial infections, granuloma formation	chronic inflammation with granuloma formation, inflammatory bowel disease[57]