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Newly Recognized Mendelian Disorders with Rheumatic Manifestations

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Summary

A number of novel monogenic diseases that present with innate and/or acquired immune dysregulation reveal novel immune pathways that cause human inflammatory diseases and suggest novel targets for treatment.

Keywords

Monogenic autoinflammatory diseases; interferon-mediated diseases; IL-1-mediated autoinflammatory diseases; immune dysregulation; primary immunodeficiencies

Introduction

Over the last 20 years the discovery of monogenic defects that cause excessive activation of innate immune responses and monogenic defects that cause adaptive/acquired immune dysregulation that leads to a break in immune tolerance have helped to not only shape our concepts of “autoinflammation” and “autoimmunity” but revealed targets for therapeutic intervention.

Many currently described monogenic “autoinflammatory conditions” that present with sterile fever, neutrophilic skin rashes and organ–specific inflammation are caused by gain-of-function mutations in innate immune sensors or by loss-of-function mutations in other molecules that can lead to “intracellular stress”. In both instances, an IL-1 cytokine amplification loop is triggered and many diseases can successfully be treated with IL-1 inhibiting drugs [1]*. Recent discoveries described in this review challenge the IL-1 centered view of autoinflammation and suggest abnormal chronic production of Type I interferons as cause for a novel group of predominantly autoinflammatory diseases. Another group of diseases is caused by molecular defects that lead to abnormal cell differentiation,

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Purpose of review

We review newly discovered monogenic immune-dysregulatory disorders that were reported in Pubmed over the last year.

Conflicts of interest

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and mitochondrial and Golgi transport dysfunction as causes for complex clinical phenotypes that include systemic and organ-specific inflammation; the molecular triggers and the inflammatory mediators that lead to the inflammatory disease manifestations remain incompletely understood in the latter disorders.

Novel insights into “autoimmune diseases” have been gained from the discovery of mutated genes that lead to dysregulation of T and B cell function, with or without a loss of regulatory T cell function and ultimately a break in central or peripheral T or B cell tolerance.

The diseases described in this chapter expand the current clinical disease spectrum of monogenic autoinflammatory and autoimmune conditions, illustrate molecular mechanisms that provide explanations for the considerable overlap between clinical features of innate and adaptive immune dysregulation. We have grouped the novel diseases into those that are predominantly leading to innate immune dysregulation (autoinflammation) and those that primarily cause acquired immune dysregulation (autoimmunity).

Table 1 summarizes the newly recognized Mendelian diseases described in the past 12 months.

DISORDERS AFFECTING PREDOMINANTLY THE INNATE IMMUNE SYSTEM

Three immune-dysregulatory diseases described over the past 12 months are caused by gain-of function mutations in cytosolic DNA or RNA innate-immune-sensors or their adaptor molecules. These newly discovered conditions link autoinflammatory phenotypes to innate immune dysregulation of predominatly Type I IFN production and suggest a potent role of Type I IFNs in coordinating innate and adaptive immune responses in these conditions.

1. STING-associated vasculopathy with onset in infancy (SAVI)—SAVI is an ultra-rare autoinflammatory disease caused by *de novo* gain-of-function mutations in *TMEM173*, which encodes the *STimulator of INterferon* (IFN) Genes (STING), an adaptor protein in the cytosolic DNA-sensing pathway [2]**. So far disease-causing missense mutations affect three amino acids, V155, N154 V147 [2-5]. Patients present with early-onset vasculitis/vasculopathy that affects small dermal vessels in mostly acral areas leading to vasoocclusion and gangrene often requiring surgical amputation. Most patients also develop progressive interstitial lung disease (ILD) with variable severity [2-5]. Elevated autoantibody levels are seen in these patients, however the titers do not correlate with the presence or severity of the vascultis and lung disease [2]**.

STING is a dimeric, endoplasmic reticulum (ER) transmembrane adaptor molecule, that coordinates viral immunity [6, 7]. Upon activation it recruits and activates TANK-binding kinase 1 (TBK1), and causes IRF3 phosphorylation/activation and *IFNB1* transcription [7]. The disease-causing STING mutations lead to constitutive transcription of *IFNB1* [2, 3]**,** and to the presence of a strong IFN response-gene-signature in whole-blood RNA of SAVI patients [2]** thus suggesting a critical role of chronic IFN stimulation in the disease pathogenesis. The STING/IFNβ pathway can be directly activated in endothelial cells indicating that the development of vasculitis may be triggered directly by dermal endothelial cell activation [2, 3]**,**. Because STING coordinates signals from multiple upstream

dsDNA sensors, it may be a target for therapeutic interventions not only in SAVI, but also in a wider variety of IFN-mediated diseases [2-4].

2. Aicardi-Goutières syndrome 7 (AGS7)—AGS is a rare disease caused by autosomal recessive mutations in the exonuclease TREX1; the ribonucleases RNASEH2A, RNASEH2B, and RNASEH2C; an enzyme with phosphohydrolase and nuclease activity, SAMHD1; and the double-stranded-RNA-specific adenosine deaminase ADAR1 [8]. In addition, autosomal dominant mutations in *IFIH1*, encoding MDA5, are responisble for another form of AGS. The majority of the patients present with varying severity of spasticity, CNS white matter disease [9]** and variable immune manifestations, including rashes, thrombocytopenia and arthritis [10]. Four of 11 reported subjects had neonatal disease-onset, 5 patients developed disease between 6 and 24 months of age, and 2 mutation-positive carriers remained asymptomatic into adulthood [9]**. Symptomatic patients had severe developmental delay. *In vitro* assays showed that disease-causing *IFIH1* mutations enhance double-stranded RNA binding and baseline or ligand-induced IFN signaling [9]**. Interestingly, one of the AGS7 mutations (p.R779H) was found in a patient with “early-onset juvenile systemic lupus erythematosus (JSLE)”, who presented with arthritis, livedo reticularis, necrotizing cutaneous vasculitis, antiphospholipid syndrome and high-positive anti-dsDNA antibody titers, and lower limb spasticity and selective IgA deficiency [11].

3. Atypical Singleton-Merten Syndrome (atypical SMS)—Mutations in *DDX58* encoding RIG-I, have recently been described in 11 patients from 2 families with glaucoma and skeletal abnormalities [12]*. The musculoskeletal manifestations include arthritis of hands and feet, joint contractures, calcific tendinitis, and, erosive changes in the terminal tufts of the distal phalanges. Four patients had aortic and valvular calcification; psoriasiform rashes were present in 8 individuals and most patients had glaucoma [12]*. Transfection of wildtype and mutant *DDX58* into HEK293T cells showed increased basal reporter gene activity of NF-κB and of the *IFNB1* enhancer region PRDIII-I [12]*. An increased expression of *IFNB1* and *ISG15* in mutant compared to WT-construct transfected cells was further enhanced by poly I:C stimulation [12]*. Additionally, constitutive IRF3 phosphorylation and dimerization were induced by high amounts of mutant *DDX58* [12]*.

Gain-of-function mutations in the innate immune sensor NLRC4, that assembles a caspase-1 activating inflammasome, cause a novel autoinflammatory syndrome and predispose to macrophage activation syndrome.

1. NLRC4-related macrophage-activation syndrome (NLRC4-MAS)/Syndrome of enterocolitis and autoinflammation associated with mutation in NLRC4 (SCAN4)—Activating heterozygous gain-of-function-mutations in the inflammasome component *NLRC4* cause recurrent fevers and predispose to the development of MAS [13, 14]**,**. Two mutations (p.V337S and p.V341A) arose *de novo* in the *NLRC4* NACHT domain in 2 different families. Three of 4 patients, all presenting with enterocolitis, developed MAS flares, two patients soon after infancy and one patient later in life indicating variable disease severity in patients with the same mutation [13, 14]**,**. Another *NLRC4* mutation (p.H443P) resulted in a familial cold autoinflammatory syndrome (FCAS)-like

phenotype in 13 members from a large Japanese kindred [15]* who presented with cold-induced fever episodes, urticaria-like rashes and arthralgia starting between 2 and 3 months of age. Transfection assays demonstrated that the disease causing mutations increase NLRC4 oligomerization and cleavage of procaspase-1 that result in secretion of IL-1β [13-15] and IL-18 (not reported in the Japanese patients). IL-18 levels in the *NLRC4* MAS/SCAN4 patients are several times higher than in CAPS patients with activating *NLRP3* mutations [13, 14]**,**. Although these patients were somewhat responsive to corticosteroid immunosuppression, IL-1 inhibition may provide substantial benefit [13, 14]**,**.

Loss-of-function mutations in intracellular enzymes or transport proteins can generate intracellular stress and lead to inflammatory disease, although the molecular mechanisms that lead to the inflammatory disease manifestations in the diseases described below remain elusive.

1. Deficiency of adenosine deaminase 2 (DADA2)—Autosomal recessive mutations in *CECR1*, encoding the enzyme adenosine deaminase 2 (ADA2), cause an early-onset vasculopathy resembling polyarteritis nodosa [16, 17]**,**. Patients described with DADA2 [16-20] present with early-onset stroke, livedo reticularis, recurrent fever, hepatosplenomegaly, arterial hypertension, ophthalmologic manifestations, and myalgia. Other cutaneous manifestations include leg ulcers, Raynaud phenomenon, subcutaneous nodules, purpura, and digital necrosis. Sixteen pathogenic mutations have been described. *Cecr1b* is essential for vascular integrity and neutrophil development in zebrafish embryos, thus suggesting that ADA2 is a cell growth and differentiation factor for endothelial cells and leukocytes [16, 17]**,**. DADA2 patients have a defect in small vessel endothelial integrity and impaired of M2-like macrophage differentiation, leading to a polarization of macrophage and monocyte subsets towards M1 like cells [16, 17]**,**. Gene-expression-studies showed a marked upregulation of neutrophil-expressed genes, suggesting a potential pathogenic role of activated neutrophils [20]. Therapeutic interventions include anti-TNF agents, fresh-frozen plasma, recombinant ADA2, and hematopoietic stem cell transplantation (HSCT) [16-20].

2. Sideroblastic anemia, immunodeficiency, fevers, and developmental delay (SIFD)—Congenital sideroblastic anemia, B cell immunodeficiency, periodic fevers, and developmental delay is a mitochondrial disease caused by autosomal recessive loss-of-function mutations in *TRNT1* [21]**. Most patients described (n=12) presented in infancy with transfusion-dependent sideroblastic anemia and developed recurrent noninfectious fever episodes, B-cell lymphopenia with hypogammaglobulinemia with recurrent sinopulmonary bacterial infections and progressive developmental delay [22]. Occult multiorgan failure and/or cardiomyopathy were seen in 7 patients; early allogenic bone marrow transplant was curative in one patient [22]. *TRNT1* encodes an enzyme that adds 2 cytosine- and 1 adenosine-(CCA) residues to the 3’ end mitochondrial and cytosolic tRNA molecules, which is necessary for tRNA aminoacylation [23]. The disease-causing mutations lead to a reduction in CCA enzyme activity, defective mitochondrial translation and the inabilty to detect tRNAs with backbone damage [24]. This defect is thought to result

in a “loss of quality-control-mechanisms” that recognize and prevent damaged tRNA from CCA maturation and from entering the ribosome machinery of protein synthesis, thus suggesting a role of CCA addition in intracellular stress responses [25].

3. Interstitial lung disease (ILD) and arthritis caused by *COPA* mutations— Twenty-one patients from five families with an autosomal dominant autoimmune syndrome characterized by high-titer autoantibodies, ILD/pulmonary hemorrhage and arthritis had autosomal-dominant missense mutations in *COPA* [26]**. Of 30 *COPA* mutations carriers, 9 subjects were asympomatic, suggesting incomplete penetrance[26]**. The majority of patients presented with non-erosive arthritis [26]**. Renal biopsies in 4 unrelated patients demonstrated immune complex-mediated renal disease [26]**. Most patients had auto-antibodies to antinuclear (ANA), anti-neutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor (RF). Functional assessment of patient-derived cells and *in vitro* assays showed evidence of increased ER stress and enhanced production of cytokines that promote the expansion of Th17 cells (IL-23 p19, IL-12 p40, IL-12 p35, IL-1β and IL-6) [26]**. Similarities in lung phenotype of COPA-associated disease and SAVI patients may suggest dysregulation in Type I IFN production.

In some of the diseases described in the last year, the mechanisms leading to the inflammatory manifestations remain elusive.

***1. AP1S3*-associated pustular psoriasis—**Fifteen unrelated patients with either generalized pustular psoriasis or palmar plantar pustulosis had heterozygous mutations in the *AP1S3* gene, which encodes the σ1C subunit of the cytosolic transport complex AP1 [27]*. Disease-causing mutations (p.F4C and p.R33W) were predicted to destabilize the 3D structure of the AP-1 complex [27]*. *AP1S3* silencing resulted in disrupted endosomal translocation of TLR3 and in a marked inhibition of its canonical downstream signaling [27]*.

2. TNF-Receptor Associated Periodic Syndrome due to mutations in *TNFRSF11A* (TRAPS11)—Recurrent, long-lasting attacks presenting with fever, abdominal pain, lymphadenopathy and macular rashes were described in 3 patients from 2 families with heterozygous mutations in *TNFRSF11A*, the gene encoding RANK (Receptor Activator of NF-κB) [28]. One patient had a 10Mb genomic duplication of 30 genes followed by a 9.5Mb deletion containing 29 genes that included *TNFRSF11A* [28]. The complex phenotype including congenital heart disease, cleft palate, facial dysmorphism and mental retardation [28], is likely caused by gene duplication or the deletion of other genes in the 29-gene-deletion cluster. Screening for *TNFRSF11A* mutations in 127 patients with similar inflammatory manifestations identified with a frameshift deletion in *TNFRSF11A* (p.M416Cfs*110) in an adolescent and her mother who presented with later-onset (10 and 18 years of age) fever attacks as above, but also had erythema nodosum, anterior uveitis, headaches, elevated CRP and hypergammaglobulinemia [28].

3. Monogenic systemic juvenile idiopathic arthritis (SJIA) caused a mutation in *LACC1*—A homozygous mutation in a conserved cysteine residue at position 284 (p.C284R) in *LACC1*, which encodes the enzyme laccase (multicopper oxidoreductase)

domain-containing 1, causes and inflammatory disease which clinically fulfills criteria for SJIA in 13 patients from 5 Saudi Arabian consanguineous families [29]*. All patients presented with characteristic fever, erythematous maculopapular rashes, chronic polyarthritis, leukocytosis, thrombocytosis and elevated markers of inflammation [29]*. None of the patients had MAS. All patients presented with moderate to severe disease, and were unresponsive to treatment with NSAIDs, systemic corticosteroids, methotrexate, and biological agents, including anti-TNF (all 13 patients) anti-IL-6 (5 patients) or rituximab (3 patients) [29]*.

DISORDERS AFFECTING PREDOMINANTLY THE ACQUIRED/ADAPTIVE IMMUNE SYSTEM

Four monogenic defects described over the last year affect T and B-cell signaling/function that result in loss of central or peripheral immune tolerance.

Three novel monogenic defects that lead to constitutive T cell activation and affect T and B cell homeostasis and have impaired regulatory-T (T_{reg}) cell function are listed below.

1 *STAT3* gain-of-function mediated early-onset lymphoproliferation and autoimmunity—Germline dominant-negative/loss-of-function mutations in *STAT3* cause hyper-IgE syndrome with recurrent infections [30, 31]. Recently, activating (gain-of-function) *STAT3* mutations were found in an early-onset multi-organ autoimmune disease with lymphoproliferation [32]**. Four mutations were identified in 5 patients, who presented with type1 diabetes mellitus, autoimmune enteropathy, autoimmune thyroiditis, ILD and features of SJIA [32]**. Other manifestations were short stature, eczema and dental anomalies [32]**. An additional study expanded the phenotype of the disease and other clinical manifestations were autoimmune cytopenias (hemolytic anemia, neutropenia and/or thrombocytopenia), hepatitis, atopic dermatitis, alopecia, and scleroderma [33]**. Most of these patients (8 out of 13) had recurrent and/or severe infections [33]**. In both studies, increased *STAT3* transcriptional activity and a diminished T_{reg} function were observed [32, 33]**,**.

2. CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI)—In two patient cohorts, heterozygous loss-of-function mutations in the inhibitory receptor, *CTLA4* that is expressed on activated T- and T_{reg} cells cause a complex immune dysregulatory phenotype [34, 35]**,**. Ten *CTLA4* mutations were found in 21 patients from 10 families presenting with diarrhea/enteropathy, granulomatous lymphocytic interstitial lung disease, hepatosplenomegaly, and lymphadenopathy [34, 35]**,**. Autoimmune cytopenias (thrombocytopenia, autoimmune hemolytic anemia), thyroiditis and arthritis and positive serum autoantibodies, including ANA (n=3) and anti-histone (n=2), anti-mitochondrial (AMA), anti-thyroid peroxidase (TPO) and anti-proteinase 3 (PR3) antibodies were observed in one patient each [34, 35]**,**. Constitutively activated CD4+T and reduced numbers of T_{reg} cells were found in peripheral blood [34, 35]**,**. Extensive CD4+T cell infiltrates were also found in intestines, lungs, bone marrow, CNS, kidneys and liver [34, 35]**,**. Progressive loss of circulating B cells, and an increase in predominantly autoreactive CD21(lo) B cells in peripheral blood accompanied the accumulation of B cells in non-lymphoid organs, thus suggesting a critical role for CTLA-4 in T and B lymphocyte

homeostasis [34, 35]**,**. Variable degrees of hypogammaglobulinemia and an increase in the occurrence of lower respiratory infections were also observed [34, 35]**,**.

3. Immunodeficiency with lymphoproliferation caused by a dominant activating mutation in *PIK3R1*—Gain-of-function mutations in *PIK3CD*, encoding the p110δ catalytic subunit of phosphatidylinositol 3-kinase (PI3K) were described to cause an immune dysregulatory disease with autoimmune manifestations and immunodeficiency named PASLI [36] or APDS [37]. More recently, four patients from three families with a similar phenotype had a splice site mutation in another gene in the same pathway, *PIK3R1*, encoding the regulatory protein of PI3K pathway, p85α [38]*. Patients present with recurrent sinopulmonary infections and diffuse lymphadenopathy. Three of four patients had splenomegaly (2 had a splenectomy), and two developed bronchiectasis. Other manifestations included inflammatory bowel disease, autoimmune thrombocytopenia and arthritis and severe juvenile idiopathic arthritis-like disease [38]*. Three out of the four patients had evidence of systemic inflammation with increased inflammatory markers (ESR and CRP) [38]*. Four additional patients with a similar splice site variant presented with recurrent upper and lower respiratory tract infections without any evidence of autoimmunity, splenomegaly or lymphadenopathy [39]*. Disease causing mutations caused skipping of exon 11 of *PIK3R1* and hyperactivity of the PI3K/AKT signaling pathway in both studies [38, 39]*,*.

A central immune tolerance defect similar to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome is observed in the disease below.

4. Immune dysregulatory disease caused by *PRKDC* mutations—Variable disease expression is seen in patients with mutations in *PRKDC*, encoding a catalytic subunit of DNA-dependent protein kinase (DNA-PK), a double-stranded DNA break repair enzyme [40, 41]. Enzymatic activity can vary in patients with the same mutation (p.L3062R). Patients with complete absence of DNA-PK enzymatic activity present with $T^{-}B^{-}NK^{+}$ SCID [40, 41]. Patients with residual enzymatic activity present with autoimmune features, positive ANA, granulomas in skin and spleen, arthritis and recurrent lung infections with bronchiectasis [42]*. Two reported patients had increased numbers of inflammatory CD4+CD16+monocytes, and severely reduced CD4+T, CD8+T and T_{reg} cells [42]*. Mutant DNA-PK impairs AIRE's ability to regulate ectopic expression of tissue specific antigens (TSAs) in medullary thymic epithelial cells [42]*, thus suggesting a critical role of PRKDC in impaired negative selection of autoreactive T cells [43].

Conclusion

The recently discovered monogenic immune-dysregulatory diseases have substantially widened our understanding of pathogenic pathways that cause predominantly innate or adaptive immune response dysregulation.

The discovery of mutations in viral innate immune sensor pathways coupled to chronically increased IFN production introduces Type I IFNs as key cytokines in causing a novel group of autoinflammatory diseases; as potent activators of innate and adaptive immune responses

[44]. Future studies on the release of Type I IFNs will assist in dissecting the contribution of innate and adaptive immune dysregulation in these conditions. Novel disorders caused by mutations in molecules associated with cell differentiation, mitochondrial and Golgi transport provide opportunities to study pathways that cause various forms of cellular stress and their link to proinflammatory pathways. Genetic defects that lead to novel monogenic autoimmune diseases provide insights into pathways that lead to a break in T and B cell tolerance.

Taken together, the study of early-onset immune dysregulatory conditions continues to provide an opportunity to discover and understand the novel molecular pathways that lead to tissue-specific inflammation and provide novel targets to explore for treatment for patients with rare syndomes that present wth excessive inflammation but also for patients with more common inflamamtory disorders.

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Abbreviations

Novel immune dysregulatory diseases described:

SAVI	STING associated vasculopathy with onset in infancy
AGS7	Aicardi-Goutières Syndrome 7
DADA2	Deficiency of adenosine deaminase 2
AP1S3	associated pustular psoriasis
SIFD	Congenital sideroblastic anemia with immunodeficiency, fevers and developmental delay
TRAPS11	TNF-Receptor Associated Periodic Syndrome due mutations in *TNFRSF11A*

Other Abbreviations used in the review

ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
AP1	activator protein 1
APDS	activated PI3K-δ syndrome

CAPS	cryopyrin associated periodic syndrome
CNS	central nervous system
CRP	C-reactive protein
ER	endoplasmic reticulum
ESR	erythrocyte sedimentation rate
FCAS	familial cold autoinflammatory syndrome
HSCT	hematopoietic stem cell transplantation
IFN	interferon
IRF	interferon regulatory factor
MAS	macrophage activation syndrome
MDA5	melanoma differentiation-associated protein 5
NACHT-domain	acronym standing for NAIP (neuronal apoptosis inhibitor protein), C2TA (MHC class 2 transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein)
NF-κB	nuclear factor of kappa light chain gene enhancer in B cells
NSAIDs	nonsteroidal anti-inflammatory drugs
PASLI	*p*110δ*a*ctivating mutations causing *s*enescent T cells, *l*ymphadenopathy, and *i*mmunodeficiency
PRD-III-I	positive regulatory domain III-I element
RANK	Receptor Activator of NF-κB
RF	rheumatoid factor
RIG-I	retinoic acid-inducible gene 1
SCID	severe combined immunodeficiency
SJIA	systemic-onset juvenile idiopathic arthritis
TLR3	Toll-like receptor 3
TREX1	Three prime repair exonuclease 1

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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Recent findings

Ten novel monogenic immune-dysregulatory disorders that present with innate and acquired/adaptive immune dysregulation and inflammatory clinical phenotypes were identified. These include autosomal dominant gain-of function-mutations in viral innate immune sensors or their adaptors, *TMEM173/STING IFIH1/MDA5* and *DDX58/RIG-I* cause complex clinical syndromes distinct from IL-1 mediated diseases and present with a chronic type I interferon (IFN Type I) signature in peripheral blood. Gain-of-function mutations in *NLRC4* add a novel inflammasome disorder associated with predisposition to macrophage-activation syndrome and highly elevated IL-18 levels. Mutations in *ADA2*, *TRNT1* and *COPA*, *AP1S3 and TNFRSF11A* cause complex syndromes; loss of function mutations in enzymes and molecules are linked to the generation of “cellular stress” and the release of inflammatory mediators that likely cause the inflammatory disease manifestations. A monogenic form of systemic-onset juvenile idiopathic arthritis is caused by homozygous mutations in *LACC1*. Lastly, mutations in *PRKDC* (recessive), *STAT3*, *CTLA4* and *PIK3R1* (all dominant) lead to impaired central and peripheral T cell tolerance and present with variable disease manifestations of immunodeficiency and immune dysregulation/autoimmunity.

Key points

1. The monogenic immune-dysregulatory diseases can be caused by defects in molecules involved in either the innate or the adaptive immune reponses.
2. In general, innate immune system dysregulation leads to “autoinflammatory” diseases phenotypes and adaptive immune system dysregulation leads to primary immunodeficiencies with lymphoproliferation with or without autoimmunity.
3. An overlap of clinical and immunological phenotypes is increasingly observed in both groups of immune-dysregulatory diseases.
4. The study of Mendelian immune-dysregulatory disease mechanisms can provide insights into novel inflammatory disease pathways and lead to the discovery of novel therapeutic targets.

Table 1

Newly recognized monogenic disorders of innate and adaptive/acquired immune systems

	OMIM No	Inheritance	Gene (chromosome region)	Protein (UniProtKB)	Number of patients reported	Functional Data	predominant immune cells found in tissues
DISORDERS AFFECTING PREDOMINANTLY THE INNATE IMMUNE SYSTEM							
Type I Interferonopathies							
SAVI	615934	AD	*TMEM173* (5q31.2)	STING	12	Increased expression of ISGs; constitutive *IFNB1* transcription in patients' cells and transfected cell lines, increased serum levels of CXCL10, constitutive STAT1 phosphorylation	Interstitial lymphoid aggregates and macrophage alveolar infiltration in the lung; predominant neutrophil infiltrate in skin tissue
AGS7	615846	AD	*IFIH1* (2q24.2)	IFIH1/MDA5	15	Increased expression of ISGs; increased baseline and ligand-induced *IFNB1* transcription	NR
Singleton-Merten Syndrome 2	616298	AD	*DDX58* (9p21.1)	DDX58/RIG-I	11	Constitutive activation of PRDIII-I and NF-κB; constitutive IRF3 phosphorylation and dimerization	Psoriasiform skin lesions were observed (biopsy in 1 patient).
Macrophage Activation Syndrome							
NLRC4-associated disease	616050 616115	AD	*NLRC4* (2p22.3)	NLRC4	17	Increased serum levels of IL-18; increased NLRC4 oligomerization; increased cleavage of procaspase-1; increased secretion of IL-1β	Intra-epithelial lymphocytes in duodenal tissue; macrophage activation in bone marrow; numerous CD163+ macrophages in CNS tissues
Intracellular stress leading to inflammatory manifestations							
DADA2	615688	AR	*CECR1* (22q11.1)	CECR1/ADA2	38	Increased expression of ISGs and neutrophil-	Mixed inflammatory infiltrate on skin: MPO+ neutrophils and CD68+

	OMIM No	Inheritance	Gene (chromosome region)	Protein (UniProtKB)	Number of patients reported	Functional Data	predominant immune cells found in tissues
						related genes; impairment of M2 macrophage differentiation	macrophages and lymphocytes; impairment of M2 macrophage differentiation
						related genes; impairment of M2 macrophage differentiation	macrophages and lymphocytes; impairment of M2 macrophage differentiation
						related genes; impairment of M2 macrophage differentiation	
						related genes; impairment of M2 macrophage differentiation	
SIFD	616084	AR	*TRNT1* (3p26.2)	TRNT1	16	Deficient CCA-adding to tRNAs	Skin biopsy revealed a perivascular lymphohistiocytic infiltrate within papillary dermis in one patient.
COPA-associated disease	NA	AD	*COPA* (1q23.2)	COPA	21	Increased ER stress, enhanced levels of IL-23 p19, IL-12 p40, IL-12 p35, IL-1β and IL-6	Interstitial infiltrates and germinal center formation with CD20+ B cells (predominant), CD4+ and CD8+ T cells in the lung tissue; immune complex deposition in glomeruli and interstitial chronic inflammation in kidney tissue
Mechanisms leading to inflammatory manifestations not yet elucidated							
AP1S3 associated pustular psoriasis	616106	AD	*AP1S3* (2q36.1)	AP1S3	15	Disrupted endosomal translocation of TLR3	Intra-epidermal spongiform pustules filled with neutrophils
TRAPS11	NA	AD	*TNFRSF11A* (18q21.33)	TNR11	3	Reduced spontaneous activation of NF-κB	NR
Monogenic SJIA caused by *LACC1* mutations	NA	AR	*LACC1* (13q14.11)	LACC1	13	NR	NR
DISORDERS AFFECTING PREDOMINANTLY THE ACQUIRED/ADAPTIVE IMMUNE SYSTEM							
Predominant peripheral tolerance defect							
STAT3 gain-of-function associated disease	615952	AD	*STAT3* (17q21.2)	STAT3	18	Increased STAT3 transcriptional activity and decreased Treg compartment	Lymphocytic interstitial pneumonia
CHAI/ALPS5	616100	AD	*CTLA4* (2q33.2)	CTLA4	21	Defect in the CTLA4-dependent Treg cell suppression	Extensive CD4+ T cell infiltration in intestines, lung, bone marrow, brain, liver, kidneys; follicular hyperplasia in lymph nodes and CD20+ cells in duodenum
Immunodeficiency with lymphoproliferation caused by a dominant activating mutation in *PIK3R1*	616005	AD	*PIK3R1* (5q13.1)	P85A/PIK3R1	8	Constitutive hyperactivation of PI3K and AKT	NR

	OMIM No	Inheritance	Gene (chromosome region)	Protein (UniProtKB)	Number of patients reported	Functional Data	predominant immune cells found in tissues
Predominant central immune tolerance defect							
Immune dysregulatory disease caused by PRKDC mutations	NA	AR	*PRKDC* (8q11.21)	PRKDC	2	Increased expression of ISGs; increased BAFF, TNF-α and IFN-γ mRNA expression; impaired AIRE function	Non-caseating granulomas in skin and caseating granulomas in spleen

SAVI, STING-associated vasculopathy with onset in infancy; AGS7, Aicardi-Goutieres Syndrome 7; DADA2, deficiency of adenosine deaminase 2; SIFD, congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay; TRAPS11, TNF receptor associated periodic syndrome 11; SJIA, systemic-onset juvenile idiopathic arthritis; CHAI, CTLA-4 haploinsufficiency with autoimmune infiltration; ALPS5, autoimmune lymphoproliferative syndrome 5; ISGs, interferon stimulated genes; ER, endoplasmic reticulum; TLR3, Toll-like receptor 3; CCA, cytosine/cytosine/adenine; IRF3, interferon regulatory factor 3; PRDIII-I, positive regulatory domains III-I; Treg, regulatory T cells; AKT, RAC-alpha serine/threonine-protein kinase/protein kinase B; PI3K, phosphoinositide 3-kinase; CNS, central nervous system; MPO, myeloperoxidase; AD, autosomal dominant; AR, autosomal recessive; NA, not available; NR, not reported.