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An Integrated Classification of Pediatric Inflammatory Diseases, Based on the Concepts of Autoinflammation and the Immunological Disease Continuum

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ABSTRACT: Historically, pediatric inflammatory diseases were viewed as autoimmune but developments in genetics of monogenic disease have supported our proposal that "inflammation against self" be viewed as an immunologic disease continuum (IDC), with genetic disorders of adaptive and innate immunity at either end. Innate immune-mediated diseases may be associated with significant tissue destruction without evident adaptive immune responses and are designated as autoinflammatory due to distinct immunopathologic features. However, the majority of pediatric inflammatory disorders are situated along this IDC. Innate immunity has been demonstrated in polygenic disorders, particularly Crohn's disease (CD). A genetic overlap exists between CD and some major histocompatability complex (MHC) class I-associated diseases, including psoriasis; these diseases seem to represent a true intermediate between autoinflammation and autoimmunity. Conversely, classical autoimmune diseases, with autoantibody and MHC class II associations, including celiac disease and rheumatoid arthritis (RA), have adaptive immune genetic associations, including *Cytotoxic T-Lymphocyte Antigen-4* (*CTLA4*) and *PTPN22*. This proposed classification is clinically relevant, because innate immune-mediated disorders may respond to cytokine antagonism whereas autoimmune-mediated diseases respond better to anti-T and B cell therapies. Furthermore, the etiopathogenesis of poorly defined "autoimmune" diseases, such as juvenile idiopathic arthritis, may be inferred to have substantial innate immune involvement, based on response to IL-1 antagonism. (***Pediatr Res* 65: 38R–45R, 2009**)

Traditionally, the pediatric inflammatory noninfectious diseases have been classified and viewed through the scientific monocle of autoimmunity. The autoimmunity concept pertains to aberrant adaptive immune responses, which are dependent on classical major histocompatability complex (MHC) based antigen-dependent T cell responses. These involve CD4-mediated activation of other effector cells, including macrophages, via interferon gamma production, as well as tissue destruction, mediated directly by cytotoxic CD8 T cells, in addition to T cell dependent B cell autoantibody production. However, in the past decade this autoimmune-centric view of immune-mediated disease has undergone a fundamental shift that was ushered in by an improved understanding of a range of monogenic human inflammatory disorders, typically afflicting the pediatric population. Specifically, mutations in proteins associated with innate immune cells, such as monocytes/macrophages and neutrophils, have firmly implicated innate immune dysregulation in the pathogenesis of many of these disorders, which have been collectively termed the autoinflammatory diseases (1,2). The term autoinflammation is now used interchangeably with the term innate immune-mediated inflammation, and so it is becoming the accepted term to describe innate immune-mediated disease (3).

Originally, the autoinflammatory diseases were designated as a category of disorders quite distinct from the well-recognized MHC and autoantibody-associated disorders that were clearly linked, both genetically and immunologically, to adaptive immunity. This approach tended toward a two-tiered classification of inflammation against self and failed to explain obvious overlaps between these two types of inflammation, especially concerning MHC class I-associated disorders. We have proposed an immunologic disease continuum (IDC) (4), whereby diseases could be classified as driven by adaptive or innate immune responses, with the majority of conditions involving variable degrees of interaction between these two systems. The IDC concept hinges on the notion that tissue perturbations at the target sites of inflammation, rather than the immune system *per se*, is the key to disease expression (4,5).

The purpose of this article is to develop this classification further in relationship to pediatric inflammatory diseases and to emphasize the utility of the IDC concept, particularly with regard to autoinflammation, not only for a mechanistic classification of inflammatory disease but also its implications for therapy development. Given that inflammation against self generally starts with activation of the innate immune system, we will first consider diseases with a predominantly innate

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Abbreviations: ALPS, autoimmune lymphoproliferative syndrome; **BD,** Behçet's disease; **BS,** Blau syndrome; **CD,** Crohn's disease; **CINCA,** chronic infantile neurological cutaneous and articular syndrome; **FMF,** familial Mediterranean fever; **HPFS,** hereditary periodic fever syndrome; **IBD,** inflammatory bowel disease; **IDC,** immunological disease continuum; **MHC,** major histocompatability complex; **MWS,** Muckle-Wells syndrome; **NALP3,** nacht domain-, leucine rich repeat-, and pyrin domain-containing protein 3, **NOD2,** nucleotide-binding oligomerisation domain 2; **NOMID,** neonatal onset multisystem inflammatory disease; **PAPA,** pyogenic arthritis, pyoderma gangrenosum and acne syndrome; **PSTPIP1,** proline-serine-threonine phosphatase-interacting protein 1; **RA,** rheumatoid arthritis; **SLE,** systemic lupus erythematosus; **T1D,** type 1 diabetes; **UC,** ulcerative colitis

immune component and then discuss disorders in the autoimmunity category, followed by a range of intermediate diseases, before finally discussing the relevance and implications of an IDC for therapy development.

PEDIATRIC DISEASE CLASSIFICATION-INNATE IMMUNITY

Collectively, most of the pediatric autoinflammatory diseases, or innate immunopathologies, are fairly uncommon but are immensely informative with regards to mechanisms of tissue immunopathology and destruction.

Monogenic Innate Immune Diseases

Over the past 10 years a group of monogenic diseases, termed the hereditary periodic fever syndromes (HPFS), which include recurrent inflammation and unexplained fevers as part of their phenotype, have been classified as autoinflammatory in nature and typically manifest in the pediatric population (1,6,7). These conditions are linked at the functional level, in which the described mutations are manifested in cells and proteins of the innate immune system. At least seven distinct inherited HPFS are currently listed in this category of disorders; there are two autosomal recessive conditions, familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), in addition to a group of autosomal dominant diseases, including tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (8), pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) (1), and three related conditions, collectively termed the cryopyrinopathies (9) or cryopyrin-associated periodic syndromes (CAPS). The cryopyrinopathies include familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome (NOMID/CINCA). Genes responsible for these autoinflammatory HPFS have been identified in the past 10 years, and they include *MEFV* (encoding marenostrin/pyrin) (10,11) responsible for FMF, *TNFRSF1A* for TRAPS (8), mevalonate kinase for HIDS (12,13), nacht domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (*NLRP3/CIASI/NALP3*) gene encoding NALP3 (cryopyrin/NLRP3) for cryopyrin-associated periodic syndromes (14–16), and proline-serine-threonine phosphatase-interacting protein 1 (*PSTPIP1*) gene encoding CD2 binding protein (CD2BP1/PSTPIP), responsible for PAPA syndrome (17).

NALP3 and pyrin belong to the same family of pyrin domain-containing proteins, and the CD2-binding protein 1 (CD2BP1), mutated in PAPA patients, binds pyrin (18). Recent studies have shown that activation of the IL-1β pathway, which is a common mechanism in the pathogenesis of autoinflammatory diseases, is a unifying factor in these diseases (19). Constitutive increases in the secretion of IL-1β and IL-18 have been shown in macrophages from NOMID/CINCA and MWS patients (20–22), suggesting that mutations in *NLRP3* increase production of these proinflammatory cytokines. Lipopolysaccharide (LPS) stimulation was shown to enhance monocytic cell death in peripheral blood mononuclear cells of a patient with a mild phenotype of NOMID/CINCA (23). Impaired pyrin-mediated IL-1β regulation is also implicated in the pathogenesis of PAPA syndrome, as mutations in the *PSTPIP1* gene lead to an increased interaction between PSTPIP1 and pyrin, resulting in reduced modulation of the NALP3 inflammasome by pyrin (17). Thus, there is a biochemical pathway common to both FMF and PAPA, although the precise mechanisms have not been elucidated (19). The activation of the NALP3 inflammasome leads directly to IL-1β and IL-18 production, and so collectively, some of the autoinflammatory disorders can be therapeutically targeted by IL-1 receptor antagonist (IL-1Ra) or other agents including MAb and soluble receptors that block IL-1β.

Mutations in other components of the NALP3 inflammasome platform have also been shown to perpetuate excessive IL-1β production. Pyrin interacts with both the NALP3 and apoptosis-associated speck-like protein containing a CARD (ASC) proteins, and it has been proposed that pyrin negatively regulates caspase-1 by competing for binding with ASC (24). Both the *NALP3* and *MEFV* genes have also been associated with psoriatic juvenile idiopathic arthritis (JIA) (25), suggesting the potential for shared disease mechanisms between various autoinflammatory syndromes, involving abnormal production of IL-1β.

Nucleotide-binding oligomerization domain-containing 2 (NOD2/NLRC2), like NALP3, is another member of the NLR family of intracellular proteins, involved in innate immune responses by recognition of bacterial components and activation of NF-κB transcription factor. *NOD2* mutations are implicated in a number of autoinflammatory disorders, including Crohn's disease (CD), a polygenic autoinflammatory disorder, as outlined below (26,27). The discovery that Blau syndrome (BS), a rare autosomal dominant disorder, was also associated with NOD2 mutations, arose from clinical observations that granulomata formation, reminiscent of CD were observed in BS patients (28). This causes inflammation of the skin, arthritis, uveitis, and lymphadenopathy. BS has been associated with early-onset sarcoidosis, but it is more likely that such granulomatous pediatric inflammation is part of the intrinsic BS phenotype (29,30).

IMPLICATIONS FOR NOVEL MECHANISMS OF TISSUE IMMUNOPATHOLOGY IN MAN

Although tissue destruction in chronic non-infectious diseases has traditionally been viewed in relationship to autoimmunity, in particular to the five classically described hypersensitivity reactions, it is also clear that disorders of innate immunity may culminate in severe end-organ damage, leading to a range of serious complications including destructive arthropathy as well as possible blindness and mental retardation, without ostensible involvement of the adaptive system (31). The neurologic and ocular features of both NOMID/CINCA and BS, as well as the joint manifestations of BS, which may manifest as end-stage joint destruction, attest to genetic perturbations of the innate immune system as being sufficient of themselves to lead to severe organ involvement.

Although secondary involvement of the adaptive immune system cannot be excluded in man, there is compelling evidence that joint destruction may be the sole result of innate immune-mediated pathology, because it occurs in RAG-deficient mice, which harbor mutations in the proline-serine-threonine phosphatase-interacting protein 2 (PSTPIP2) protein (32). PSTPIP2 is a protein closely related to PSTPIP1, which is mutated in the PAPA syndrome. Observations such as these provide a strong rationale for antagonism of key innate immune cytokine pathways in autoinflammatory disease and also help to explain the striking success of such strategies, as outlined later.

Polygenic Innate Immune Diseases With a prominent Autoinflammatory Component

Inflammatory bowl disease (IBD) is well recognized in childhood and the etiology of CD has been strongly linked to mutations in *NOD2/NLRC3*, originally reported in 2001 (26,27), and subsequently replicated in several independent studies, although not found to be a major contributor to CD susceptibility in the Japanese population (33). This was the first evidence of a link between the innate immune system and underlying inflammatory processes in CD, which, until that point, was widely accepted to be Th1-driven autoimmune disease, and, therefore, a disease of the adaptive immune system (34). Recent genome-wide association studies (GWAS) have indicated that sequence variants at multiple other loci contribute to IBD susceptibility, in both CD and ulcerative colitis (UC), although not necessarily the same genes. The raft of additional single nucleotide polymorphisms (SNPs) in CD susceptibility, that are associated with proteins involved in innate immunity, includes the Interleukin-23 receptor subunit (IL23R) and neutrophil cytosolic factor 4 (*NCF4*) (35–37).

Of these new candidates, multiple replication studies have confirmed the association of IL-23R with both CD and UC. Although IL-23R has usually been viewed in relationship to Th17 differentiation, as IL-23 acts as a survival/proliferation signal for Th17 committed cells, the IL-23 pathway also plays a key role in effector cytokine production within the innate intestinal immune system (38), and the principle pathways affected in IBD remain to be determined. The NOD2 association with CD susceptibility has been replicated in many studies, whereas no association of this locus has been reported in UC. This finding points to an essential difference in the immunopathology of these two disorders. There is increasing evidence that CD has a combined environmental, immunogenic, and genetic etiology, which, acting in concert, cause a breach in stability of mucosal barrier defenses, thereby causing abnormal handling of commensal luminal bacteria. An association has been found between a coding SNP in the *ATG16L1* gene and CD susceptibility (39). The *ATG16L1* gene encodes a protein involved in the autophagic mechanism, whereby intracellular bacteria are processed by lysosomal degradation. Thus, a defect in this pathway may produce an inappropriate response to gut bacteria, thereby increasing the risk of CD. The frequency of this susceptibility variant was not increased in UC.

The situation is more complex with respect to UC susceptibility in that the described genetic associations may point less strongly toward innate immunity. SNPs in the IL-10 locus have been associated with UC in man (37) and the phenotype of the IL-10 knockout mouse involves colonic inflammation reminiscent of lesions seen in UC (30,41). Strong support for a key role for IL-10 in innate immunity, including its ability to modulate gut flora has been reported (37). Although the aforementioned pathway points predominantly toward an innate immune-mediated pathology, the potential involvement of adaptive immunity at the genetic level in UC could be supported by possible associations with the MHC region (36). However, the MHC genetic association of UC seems to be mainly with the butyrophylin-like 2 gene (*BTNL2*), an MHC class II-associated gene, whose function remains poorly defined and may turn out not to act predominantly on adaptive immunity pathways. Further clues to the possibility that UC susceptibility may lie closer to the adaptive end of the immune spectrum come from the observed remissions to severe colitis, in an appreciable number of cases, by treatment using i.v. cyclosporin, a drug whose major target is still thought to be T lymphocytes (40). The *MEFV* gene is also mutated in a significant proportion of UC patients, with a number of these having an associated inflammatory arthritis (42,43), indicating that genes involved in innate immune diseases, in this case FMF, may significantly modulate the expression of UC. Of course, *MEFV* mutations are also associated with Behçet's disease (BD), which is characterized by prominent neutrophilic inflammation and colitis that may be clinically indistinguishable from UC (44).

PEDIATRIC DISEASE CLASSIFICATION—AUTOIMMUNITY

The aforementioned inflammatory diseases seem to be genetically distinct from autoimmunity, but may demonstrate some evidence of adaptive immune responses. However, the purely pediatric autoimmune diseases, associated with the presence of autoantibodies, which may be multiple, can be split into three distinct categories—monogenic autoimmune disease (three main conditions, which are all very rare, as described later), transplacental (neonatal) autoimmunity, and polygenic autoimmune diseases, of which there are several. Although very rare, the monogenic autoimmune diseases are highly informative with respect to pediatric immunopathology because they are the diametric opposites of autoinflammation (Fig. 1).

Monogenic Autoimmune Disease

Autoimmune lymphoproliferative syndrome. Autoimmune lymphoproliferative syndrome (ALPS) is an inherited disorder of the immune system, mainly affecting the pediatric population (45). The ALPS phenotype is due to a failure of programmed cell death (apoptosis), resulting in both lymphoproliferation and autoimmunity. Most patients are carriers of a heterozygous mutation affecting either the TNFRSF6 (Fas)

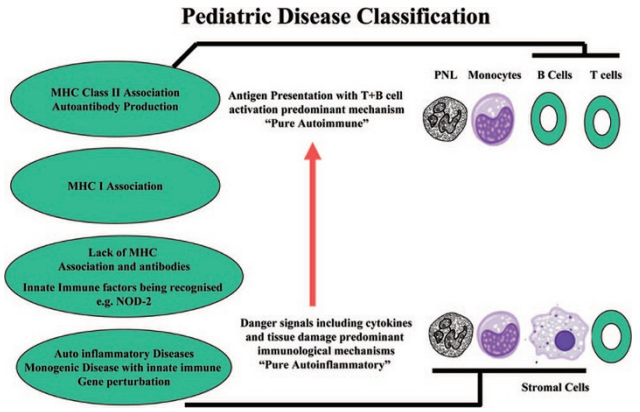

Figure 1. In the classical autoimmune diseases, the phenotypic expression of disease is crucially dependent on B and T cells. However, stromal cell genetic abnormalities, including FOXP3 dysregulated expression in the thymus could drive disease at distant sites via autoantibody production. In the autoinflammatory diseases, it is the neutrophils and monocytes, both innate immune cells, that may be key to phenotypic expression. Furthermore, stromal cell dysregulation or functional perturbations might explain the propensity for regional inflammation and disease localization at sites like the peritoneum in FMF and TRAPS. The tissue specific factors that lead to autoinflammation at characteristic sites await formal identification but could include tissue microtrauma, with microinflammation. The figure represents clinical heterogeneity of inflammatory disorders and especially the fact that MHC class I-associated diseases are intermediates between innate and adaptive immunity.

cell surface protein or in its ligand, FASL. Hypergammaglobulinemia G may be present, with numerous autoimmune problems, such as hemolytic anemia, thrombocytopenia, and neutropenia. However, Fas mutations are only found in approximately 70% of ALPS patients, indicating that alterations of other molecules in the Fas signaling pathway may cause an ALPS-like syndrome (46).

Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX). This X-linked immune disorder is caused by mutations in the *FOXP3* gene (47) and has an animal model equivalent in the scurfy mouse (48). Symptoms generally appear in infancy and include protracted diarrhea, secondary to intestinal autoimmune inflammation and reminiscent of celiac disease (49), ichthyosiform dermatitis, type 1 diabetes (T1D), hemolytic anemia, and thyroiditis. There may be massive skin and gastrointestinal tract T cell infiltration, with high serum levels of autoantibodies against blood, thyroid, and pancreatic cells.

Autoimmune polyglandular syndrome type I (APS1). APSI is a very rare systemic autosomal recessive disorder caused by mutations in the autoimmune regulator (*AIRE*) gene (49) and is immunologically characterized by multiple autoantibodies and clinically masquerading as Addison's disease, and/or hypoparathyroidism, and/or chronic mucocutaneous candidiasis. APSI patients present during childhood with multiple organ failure, such as hypoparathyroidism, T1D, Addison's disease, hepatitis, and pernicious anemia. Malabsorption and diarrhea, which may be diagnosed in the presence or absence of signs of celiac disease, can be very striking. These patients may also present with chronic mucocutaneous candidiasis that has been recently attributed to autoantibodies against gamma interferon (50). The first manifestation usually occurs in childhood, and the complete evolution of the three main diseases takes place in the first 20 years of life, whereas other accompanying diseases continue to appear until at least the fifth decade.

Transplacental Autoimmunity

All of the aforementioned monogenic diseases are associated with the presence of autoantibodies, but direct pathogenicity of these autoantibodies has not yet been demonstrated. Perhaps, the strongest vindication for the autoimmunity concept comes from pediatric diseases where maternal autoantibodies, that in themselves are not clearly pathogenic, are found to be the sole necessity for induction of several fetal or neonatal autoimmune diseases, including idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), myasthenia gravis (MG), and hyperthyroidism (51,52). Disease abates with physiologic clearance of the maternal antibodies (53).

Collectively, the genetic and immunologic features of both the monogenic autoimmune diseases and transplacental autoimmunity powerfully vindicate the autoinflammatory concept because expression of these diseases are the diametric opposite, in which their phenotypic expression is absolutely dependent on functional perturbations of tissues and cells of the primary and secondary lymphoid organs. Transplacental passage of innate immune-mediated diseases, either monogenic or polygenic, has not been recognized. Furthermore, it has proved difficult, if not impossible, to generate robust and reliable animal models, and we have attributed this to the fact that tissue-specific factors are critical for the expression of innate immune mediated pathology (5).

Polygenic Autoimmune Disease

The purpose of this article is not to provide an exhaustive list of polygenic pediatric autoimmune diseases but to provide a framework for improved classification of these conditions. Although many genetic associations have recently been described in autoimmunity, our main focus is on genetic associations that have been independently replicated. Generally, classical autoimmunity is associated with autoantibody production that predates clinical evidence of end-organ damage and such diseases are usually associated with certain MHC class II alleles. CTLA-4 has been associated with Graves' disease, T1D, Addison's disease, celiac disease, and RA (54). This protein plays a key role in costimulation reaction blockade and can powerfully modulate adaptive immune responses, and hence it is obvious link to the autoimmunity concept. In addition, a missense SNP in the *PTPN22* gene has been shown to be a risk factor for several autoimmune diseases, including RA, T1D, autoimmune thyroid disease (AITD), and SLE, whereas variants of the third intron of the transcription factor *STAT4* have been associated with the risk of both RA and SLE (55). *PTPN22* encodes a T cell protein-tyrosine phosphatase and is thought to be a negative regulator of inflammatory responses. We will specifically discuss celiac disease, the most common pediatric gastrointestinal autoimmune condition, as an example of a polygenic autoimmune disease, because, at the genetic level, it contrasts significantly with

IBD, where innate immune genetic perturbations predominate. When we originally proposed the IDC (4), we designated celiac disease as being toward the adaptive immune end of the spectrum (despite the fact that the causative antigen is a wheat peptide and not a true autoantigen), and we placed IBD near the innate immune end (4). The basis for this was the strong association of celiac disease with particular MHC class II alleles of human leukocyte antigen (HLA-DQA1 and DQB1) and autoantibodies [anti-tissue transglutaminase (tTGA) and IgA antiendomysium antibodies (AEA)], plus the absence of HLA associations and antibodies, in the case of IBD, and the NOD2 association with CD. Since that time, several GWAS have appeared, which show strong genetic associations of celiac disease and T1D with molecules related to adaptive immunity, including the IL2-IL21 region (56). Both of these molecules are known to play key roles in adaptive immune responses. In keeping with the IDC concept, it must also be pointed out that several putative genetic associations in the common autoimmune diseases may be associated with molecular pathways not specific to adaptive immune responses (57).

INTERMEDIATE DISEASES AND HITHERTO POORLY CLASSIFIED DISEASES—CONTRASTING STORIES OF THE *IL23R* AND *PTPN22* GENETIC ASSOCIATIONS

We have previously noted that the MHC class I-associated diseases that include psoriasis, ankylosing spondylitis, reactive arthritis, and BD show strong clinical overlaps with polygenic innate immune diseases, especially CD and UC (58). The disease associations of the *IL23R* gene thus far show an association with MHC class I-related autoinflammation and have been reported in both psoriasis and AS. Stated in another way, the inflammatory diseases associated with *IL23R* variants reported here lie toward the autoinflammatory end of the spectrum; CD and AS are classified as autoinflammatory diseases, whereas psoriasis is proposed to have a mixed pattern of both autoimmune and autoinflammatory characteristics. Also, psoriasis has been associated with the *IL12B* gene that has polyfunctional roles in both innate and adaptive immunity (59). In contrast, RA is primarily autoimmune in nature and generally not associated with *IL23R* (57,60). RA and several other classic autoimmune diseases, such as SLE and T1D, are associated with the R620W variant in *PTPN22*, whereas AS, psoriasis, and other autoinflammatory diseases are not (54). Thus, the emerging common genetic threads in immunology tend to support the IDC concept (Fig. 2).

EMERGING LESSONS FROM THERAPY

The IDC classification is directly relevant, not only for the classification of inflammation against self, but also for appropriate therapeutic options/choices and possibly even for predicting the true nature of poorly classified inflammatory disorders. It must be pointed out that the mainstay of therapy for all these inflammatory disorders has been corticosteroids that have diverse effects on many innate and adaptive immune cell types, whereas new specific targeted therapies usually have

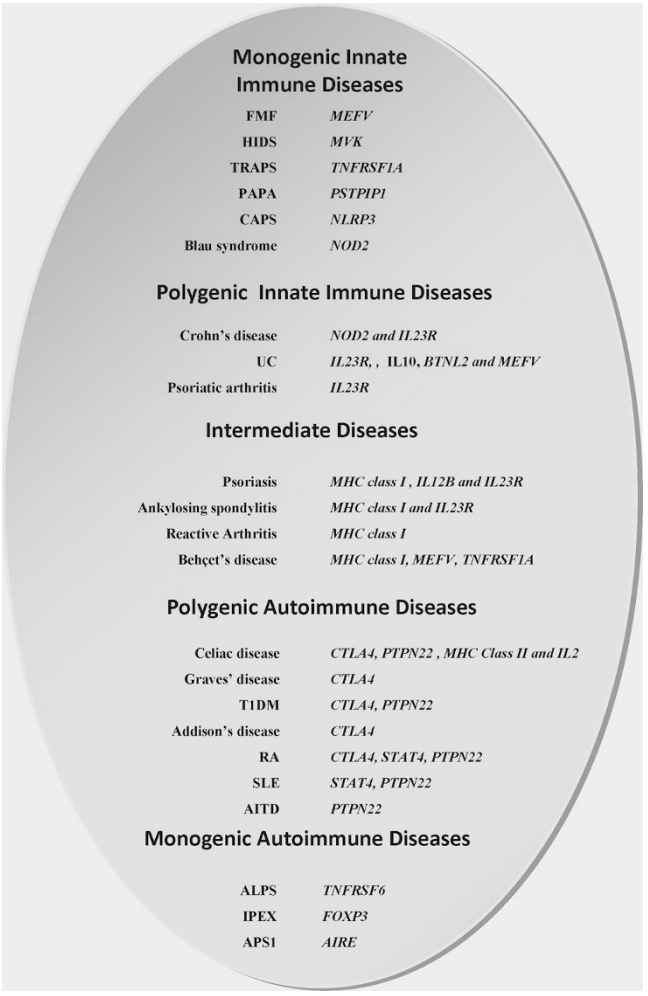

Figure 2. Genetic basis of the IDC. The susceptibility genes (on the right) for monogenic innate immune diseases, also known as "autoinflammatory" diseases, are quite distinct to those for rare monogenic "autoimmune" conditions. Genes encoding proteins involved in innate immune responses, such as members of the NLR family of intracellular proteins (NALP3 and NOD2), are associated with polygenic innate immune diseases, and the *IL23R* gene, thus far, has shown an association with MHC class I-related conditions or innate immune related disorders. T cell related proteins, such as CTLA-4 and PTPN22, are generally associated with the more common autoimmune diseases and not MHC class I-associated or innate immune-mediated diseases.

predominant actions on either innate or adaptive immunity. The emerging evidence supporting strategies that target autoinflammation and autoimmunity respectively in the pediatric setting are briefly discussed.

Given the aforementioned critical involvement of IL-1 and the NALP3 inflammasome in NOMID/CINCA pathogenesis, it is not surprising that anakinra and rilonacept have also been used therapeutically in a number of diseases, which are associated with excessive IL-1β production, including MWS (61–68), FCAS (64,69–73), NOMID/CINCA (74–76), and Schnitzler's syndrome (77–79). Not surprisingly, these lessons from pediatric arthritis/inflammation have been successfully applied to adult patients with NALP3 inflammasome-related diseases, including gout and pseudogout (80,81).

At the other end of the IDC spectrum, evidence is gradually emerging that good clinical outcomes in monogenic autoim-

mune pediatric disease can be achieved by blockade of the T and B cell autoantibody axis. For example, the successful use of rituximab has recently been reported in IPEX (82). Although we are not aware of the use of rituximab in man in APS1, it certainly has a dramatic effect in animal models of this condition. AIRE-deficient mice only developed severe manifestations in the absence of B cells (83). Likewise, there is some evidence for the successful use of rituximab to correct the severe thrombocytopenia associated with ALPS (84,85). With respect to the adult polygenic autoimmune diseases, a considerable amount of evidence has already accumulated on the successful use of B and T cell-directed therapies including rituximab, Campath-1h, and mycophenolate moefitil.

This use of drug therapy to aid in inflammatory disease classification is novel and has implications for the evaluation of pediatric inflammatory disease in a mechanistic light. JIA and Schnitzler's disease are cases in point. The dramatic response sometime seen with anakinra in these conditions points to prominent autoinflammatory mechanisms in the respective disease pathogenesis. This is further mirrored by other innate immune features of disease, including high fevers and the lack of autoantibodies. Not only is the response of pediatric disease to immune-based therapies relevant for disease control but it could also provide focus for future immunopathological and genetic studies.

NEW DIRECTIONS AND CONCLUSIONS

This is truly an exciting time in research into the pediatric inflammatory disorders. However, several questions remain unanswered, particularly the function of associated molecules, including pyrin and NALP3, and specifically how these modulate IL-1β activity (86). The genetic or environmental factors that orchestrate the clinical presentation in these patients are barely understood. We have argued that the identification of site-specific factors that trigger regional inflammation in the autoinflammatory disorders could be a key to a better appreciation of disease mechanisms (4). Such tissue specific factors are likely to include microdamage at sites of movement and local commensal bacteria (4). Intensive investigations are also underway to discover additional genes that may either modify these disorders or result in similar phenotypes. Elucidation of these pathways could have important implications for understanding the specific disease mechanisms and for applying this knowledge in other settings in common polygenic diseases. Understanding autoinflammatory diseases will further our knowledge of cutaneous as well as systemic inflammation.

Recognition that the autoinflammatory disorders define one end of an IDC and that innate immunity likely plays a major role in other pediatric diseases hitherto designated as autoimmune has important consequences for disease classification. For example, the pediatric inflammatory arthropathies are currently designated in seven categories (87). This classification is based on clinical patterns of joint swelling; we propose that this could be greatly refined if these conditions were designated along an IDC to determine the principal immunopathological mechanisms which could be highly relevant for therapy development.

Although the recognition of autoinflammation and the development of an IDC seem to provide new insights into understanding the full spectrum of inflammation against self, it is clear that human polygenic inflammatory diseases may be both clinically and immunologically heterogeneous. This means that predominantly innate immune related diseases may have adaptive immune associations and vise versa. The PTPN22 gene, originally associated with classical autoimmune diseases, including RA, and T1D, has also been linked to CD in a recent GWAS (37); however, it is interesting that the R602W risk allele of *PTPN22* for both RA and T1DM, offers protection from CD, not susceptibility. These interesting findings await confirmation. Conversely, diseases that are predominantly adaptive immune based, such as SLE, may have strong genetic associations with molecules involved in innate immunity, such as the complement pathway proteins. Whether these findings represent clinically defined but heterogeneous subgroups awaits further assessment.

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