Monogenic autoinflammatory diseases

Ricardo A. G. Russo and Paul A. Brogan

Abstract

During the past 15 years, a growing number of monogenic inflammatory diseases have been described and their respective responsible genes identified. The proteins encoded by these genes are involved in the regulatory pathways of inflammation and are mostly expressed in cells of the innate immune system. Diagnosis remains clinical, with genetic confirmation where feasible. Although a group of patients exhibit episodic systemic inflammation (periodic fevers), these disorders are mediated by continuous overproduction and release of pro-inflammatory mediators, such as IL-1 and IL-6, and TNF and are best considered as autoinflammatory diseases rather than periodic fevers. Treatment with biologic agents that block these cytokines, particularly IL-1, has proved to be dramatically effective in some patients. Still, in many cases of autoinflammation no genetic abnormalities are detected and treatment remains suboptimal, raising the question of novel pathogenic mutations in unexplored genes and pathways.

Key words: autoinflammatory, periodic fevers, familial Mediterranean fever, genetic, biologic agents.

Introduction

The monogenic autoinflammatory diseases are genetic disease orders characterized by episodic or persistent, seemingly unprovoked inflammation, without evidence of high-titre autoantibodies or antigen-specific T lymphocytes [1]. The concept of autoinflammation was introduced in the late 1990s, when the genetic causes of familial Mediterranean fever (FMF) and the TNF receptor-associated periodic syndrome (TRAPS) were identified [2,3]. In contrast to autoimmune diseases, in autoinflammatory diseases most abnormalities occur in the innate immune system components [5]. That said, the arbitrary distinction between dysregulation of the innate and adaptive immune systems and immunodeficiency is increasingly blurred with the discovery of novel monogenic autoinflammatory diseases. Typically these disorders result from dysregulation of the physiological alarm responses to foreign or endogenous danger signals, leading to abnormally increased inflammation, predominantly mediated by cells (neutrophils, monocytes) and molecules (IL-1β, IL-6 and TNF-α) of the innate immune system.

Significant advances in the knowledge of genetics, pathogenesis and treatment have occurred in the last few years. Autoinflammatory mechanisms (i.e. involving altered pathways in the innate immune system physiology) have been described in multifactorial, polygenic acquired inflammatory diseases such as gout and SLE [5]. Thus a new view of immune-mediated inflammatory diseases has arisen since the concept of autoinflammatory diseases was introduced [6]. This article will focus on the monogenic autoinflammatory diseases that are most relevant clinically to the rheumatologist.

Classification and generic clinical features

Different classifications have been attempted for this group of disorders. While a classification based on clinical features is useful for the practising physician (Table 1), a pathogenetically structured classification is mandatory for the conceptual understanding of the genetics and pathways involved in each entity (Table 2; see also http://fmf.igh.cnrs.fr/ISSAID/infevers/) [5].

Chronic, systemic inflammation is the common background for all autoinflammatory diseases. While patients with episodic diseases will typically experience recurrent bouts of fever followed by symptom-free periods (periodic fevers), individuals with autoinflammatory diseases may exhibit severe, continuous acute phase response, sometimes with periodic exacerbation. While the frequency, length and periodicity of the episodes are variable according to the mutated gene(s) and diagnosis, many other as
yet poorly defined host and environmental factors contribute to the clinical phenotype of individual patients.

Due to their genetic nature, most individuals with a monogenic autoinflammatory disease start exhibiting manifestations of the disease early in life, although these may be dismissed initially as recurrent infections in early childhood. Inflammation usually manifests as fever; headache; abdominal, chest and limb pain and elevated acute phase responses such as elevated CRP, serum amyloid A (SAA), ESR, leucocytosis and thrombocytosis. While these features are common to most autoinflammatory diseases, there is wide clinical heterogeneity among the different disorders, and even between individuals with the same disease. Cold exposure, immunizations, concurrent infections, exposure to drugs and physical or emotional stress may precipitate an inflammatory episode. Often, no trigger is identified.

Finally, although many patients with autoinflammatory diseases have a normal life expectancy, their quality of life may be significantly hampered by recurrent/persistent inflammatory symptoms. Moreover, reactive systemic AA amyloidosis may develop in some individuals. The risk of amyloidosis is influenced by the diagnosis, type of mutation within disease subsets, environment (including the frequency of concurrent infections) and probably other undefined host factors [7].

Familial Mediterranean fever
FMF is considered the prototypical and most common monogenic autoinflammatory disease, and the first for which a genetic cause was identified [2, 3]. Individuals with FMF suffer from repeated, self-limiting acute attacks lasting 12–72 h, characterized by fever, peritoneal abdominal pain and/or pleuritic chest pain, arthritis,

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<th>Clinical classification of autoinflammatory diseases</th>
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<td><strong>Group</strong></td>
<td><strong>Disease</strong></td>
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<tr>
<td>Hereditary periodic fevers</td>
<td>FMF</td>
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<td>TRAPS</td>
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<td>HIDS</td>
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<td></td>
<td>CAPS</td>
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<td></td>
<td>NAPS</td>
</tr>
<tr>
<td>Granulomatous disorders</td>
<td>BS/EOS</td>
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<tr>
<td>Pyogenic disorders</td>
<td>PAPA</td>
</tr>
<tr>
<td></td>
<td>DIRA</td>
</tr>
<tr>
<td>Autoinflammatory bone disorders</td>
<td>Majeed</td>
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<tr>
<td>Psoriasis-related monogenic disorders</td>
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<tr>
<td></td>
<td>Cherubism</td>
</tr>
<tr>
<td></td>
<td>DITRA</td>
</tr>
<tr>
<td></td>
<td>CAMPS</td>
</tr>
<tr>
<td>Miscellaneous disorders</td>
<td>CANDLE</td>
</tr>
<tr>
<td></td>
<td>APLAID</td>
</tr>
<tr>
<td></td>
<td>Early IBD</td>
</tr>
<tr>
<td></td>
<td>SLC29A3 related</td>
</tr>
<tr>
<td></td>
<td>HOIL deficiency</td>
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</table>

AR: autosomal recessive; AD: autosomal dominant; FMF: familial Mediterranean fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; HIDS: hyperimmunoglobulin D and periodic fever syndrome; CAPS: cryopyrin-associated periodic syndromes; NAPS: NALP12-associated periodic syndrome; BS: Blau syndrome; EOS: early onset sarcoidosis; PAPA: pyogenic sterile arthritis, pyoderma gangrenosum and acne; DIRA: deficiency of the IL-1 receptor antagonist; DITRA: deficiency of IL-36 receptor antagonist; CAMPS: CARD-14-mediated pustular psoriasis; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; APLAID: autoinflammation and PLC\(\gamma\)2-associated antibody deficiency and immune dysregulation.
factors may also have an impact on the risk for amyloidosis (such as M694V homozygosity) [8, 16]. Environmental laxis, in those with severe attacks from childhood or in patients who are non-compliant with prophylactic colchicine at 1/C150 mg/day is an important diagnostic clue [15]. Amyloidosis may occur more frequently in patients who are non-compliant with prophylaxis, in those with severe attacks from childhood or in certain individuals who carry particular genetic variants (such as M694V homozygosity) [8, 16]. Environmental factors may also have an impact on the risk for amyloidosis [17].

TRAPS
TRAPS is an autosomal dominant disorder caused by mutations in the TNF receptor superfamily 1A (TNFRSF1A) gene coding for the p55TNF receptor [4, 18]. Although onset usually occurs in childhood, low suspicion and clinical mimicry of other more common entities may lead to late diagnosis in adult life. During febrile episodes, which may last from 5 days to several weeks, patients complain of myalgia, peri-orbital swelling, conjunctivitis, headache, abdominal and chest pain (secondary to pleuritis), scrotal pain, erythematous macular or serpiginous skin rash (often migratory), swollen plaques simulating cellulitis, lymphadenopathy and arthralgia or arthritis of the large joints [19-20]. The duration of symptom-free intervals is variable. Although no clear genotype-phenotype correlation exists, mutations leading to amino acid substitutions in the cysteine-rich domains of the protein have a higher penetrance and are associated with a more aggressive phenotype than mutations not related to cysteine substitutions [21, 22]. The R92Q variant (the most frequently observed) is associated with later onset and milder disease, sometimes resembling the periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome [23]. Healthy individuals without clinical features of TRAPS may also harbour this variant and therefore the diagnosis of TRAPS cannot be made purely by the finding of this variant in the absence of clinical features. Amyloidosis may develop in up to 25% of untreated patients, particularly in individuals with cysteine substitutions. Diagnostic indicators for the disorder have been proposed [19]. Recently the largest series of TRAPS patients has been described, providing a robust clinical description of the full spectrum of the disease [22].

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
<th>Gene</th>
<th>Mutation</th>
<th>Protein</th>
<th>Physiopathology</th>
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</thead>
<tbody>
<tr>
<td>IL-1 activation disorders</td>
<td>FMF</td>
<td>MEFV</td>
<td>LF (GF)</td>
<td>Pyrin</td>
<td>Inflammasome activation</td>
</tr>
<tr>
<td></td>
<td>HIDS</td>
<td>MKV</td>
<td>LF</td>
<td>MKV</td>
<td>Inflammasome activation</td>
</tr>
<tr>
<td></td>
<td>CAPS</td>
<td>NLRP3</td>
<td>GF</td>
<td>Cryopyrin</td>
<td>Inflammasome activation</td>
</tr>
<tr>
<td></td>
<td>PAPA</td>
<td>PSTPIP1</td>
<td>GF</td>
<td>PSTPIP1</td>
<td>Inflammasome activation</td>
</tr>
<tr>
<td></td>
<td>Majeed</td>
<td>LPIN2</td>
<td>LF</td>
<td>Lipin2</td>
<td>Unknown</td>
</tr>
<tr>
<td>Misfolded protein disorders</td>
<td>TRAPS</td>
<td>TNFRSF1A</td>
<td>GF</td>
<td>TNFR1 (p55)</td>
<td>Cellular stress</td>
</tr>
<tr>
<td>Proteasomopathies</td>
<td>CANDLE</td>
<td>PSMB8</td>
<td>LF</td>
<td>PSMB8</td>
<td>Cellular stress</td>
</tr>
<tr>
<td>Miscellaneous disorders</td>
<td>MAJED</td>
<td>LPIN2</td>
<td>LF</td>
<td>Lipin2</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Cherubism</td>
<td>SH3BP2</td>
<td>GF</td>
<td>SH3BP2</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>DITRA</td>
<td>IL36RN</td>
<td>LF</td>
<td>IL-36Ra</td>
<td>Absence of IL-36 antagonism</td>
</tr>
<tr>
<td></td>
<td>CAMPS</td>
<td>CARD14</td>
<td>GF</td>
<td>CARD14</td>
<td>Increased IL-36 k activation</td>
</tr>
<tr>
<td></td>
<td>HOIL-1 deficiency</td>
<td>HOIL-1</td>
<td>LF</td>
<td>HOIL-1</td>
<td>Increased NF-k activation</td>
</tr>
<tr>
<td></td>
<td>Early IBD</td>
<td>IL10R, IL10RB, IL-10</td>
<td>LF</td>
<td>IL-10R</td>
<td>Absence of IL-10 signalling</td>
</tr>
<tr>
<td></td>
<td>SLC29A3-related</td>
<td>SLC29A3</td>
<td>LF</td>
<td>SLC29A3</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>APLAID</td>
<td>PLCγ2</td>
<td>GF</td>
<td>PLCγ2</td>
<td>Unknown</td>
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</tbody>
</table>
Mevalonate kinase deficiency (hyperimmunoglobulinaemia D and periodic fever syndrome)

Mevalonate kinase deficiency (MKD), also known as hyperimmunoglobulin D and periodic fever syndrome (HIDS), is an autosomal recessive condition caused by mutations in the mevalonate kinase (MVK) gene resulting in deficiency of mevalonate kinase enzyme, involved in the isoprenoid biosynthesis pathway [24-26]. Initially thought to be predominantly a disease of individuals of Dutch ancestry, it is now recognized in many other ethnic groups. The clinical severity depends on the residual activity of the enzyme. Profound enzymatic deficiency leads to the severe metabolic disease, mevalonic aciduria, which shares some features with the periodic fever, MKD, at the milder end of the clinical spectrum. Genotype-phenotype correlation has been described: some variants are associated with a severe (V310M) or milder (V377I) phenotype [27, 28]. The disease usually manifests in the first months of life, with fever attacks typically characterized by abrupt onset, painful cervical lymphadenopathy and abdominal pain with vomiting and diarrhoea. Attacks usually last 4–7 days and are often precipitated by vaccination, minor physical trauma or stress. Arthralgia, headaches, irritability, erythematous or urticaria-like skin rash, hepatomegaly, splenomegaly and aphthous stomatitis may also occur during the attacks [29-31]. Urinary mevalonic acid is strongly elevated during the crisis, but may be normal when asymptomatic. Serum IgA is elevated in most patients, but despite its previous name of HIDS, IgD may be elevated or normal (very young patients do not usually exhibit high levels) [32, 33]. Decreased MVK enzymatic activity is a diagnostic clue, but its determination is confined to specialized laboratories. Although symptoms tend to ameliorate in adult life, a significant proportion of patients continue to suffer frequent febrile attacks into adulthood and may (rarely) develop amyloidosis [34]. Interestingly, individuals with MKD and hypogammaglobulinaemia [35] or macrophage activation syndrome [36] have been reported.

Cryopyrin-associated periodic syndromes

The cryopyrin-associated periodic syndromes (CAPS or cryopyrinopathies) comprise a group of autoinflammatory diseases classified as different clinical entities but have a common genetic defect. Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease (CINCA/NOMID), Muckle-Wells syndrome (MWS) and familial cold-induced autoinflammatory syndrome (FCAS) are autosomal dominant conditions that represent particular phenotypic expressions on a clinical continuum, with CINCA/NOMID at the severe end, FCAS at the milder end, and MWS with moderate severity [37-39] (Table 3). Individuals with intermediate clinical pictures (CAPS overlap) have been reported [40]. Mutations in the NLRP3 gene, encoding cryopyrin, are the cause for all three of these clinical syndromes [41-44]. However, mutations in NLRP3 can be found in only 60% of patients with the CINCA/NOMID phenotype using conventional Sanger sequencing. Somatic mosaicism, reported in patients with CAPS, may partly explain the mutation-negative cases [45, 46]; such patients have NLRP3 mutations affecting a proportion of their leucocytes, enough to cause the disease, but too low to be detected by Sanger sequencing (used in standard genetic testing) [47]. While patients with the CINCA or severe CAPS phenotype exhibit a continuous inflammatory state, patients with milder MWS and FCAS usually have an episodic course. Common clinical features are fever, urticaria-like rash, conjunctivitis, arthralgia or arthritis and myalgia. Patients with CINCA/NOMID present an early disease onset (often at birth) and usually develop a severe, disabling arthropathy, bony overgrowth in the patellae and epiphyses of the long bones, facial dysmorphic features, short stature, hepatosplenomegaly and chronic meningitis leading to cerebral atrophy, progressive visual and sensorineural hearing loss and developmental delay [48]. Generalized exposure to cold frequently triggers inflammatory bouts, most strikingly in patients with FCAS. Amyloidosis may develop in individuals with MWS or CINCA/NOMID [49].

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>FCAS</th>
<th>MWS</th>
<th>CINCA/NOMID</th>
</tr>
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<tbody>
<tr>
<td>Onset</td>
<td>Neonatal/infancy</td>
<td>Infancy/adolescence</td>
<td>Neonatal period/infancy</td>
</tr>
<tr>
<td>Fever/rash duration</td>
<td>12-24 h</td>
<td>1-3 days</td>
<td>Continuous</td>
</tr>
<tr>
<td>Skin</td>
<td>Cold-induced urticaria-like rash</td>
<td>Urticaria-like rash</td>
<td>Urticaria-like rash</td>
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<tr>
<td>Articular</td>
<td>Arthralgia</td>
<td>Episodic arthritis</td>
<td>Progressive, deforming arthropathy with tumour-like bony and cartilaginous growth</td>
</tr>
<tr>
<td>Neurological</td>
<td>—</td>
<td>—</td>
<td>Chronic meningitis leading to cerebral atrophy, mental retardation</td>
</tr>
<tr>
<td>Deafness</td>
<td>—</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctivitis</td>
<td>Conjunctivitis</td>
<td>Conjunctivitis, uveitis, progressive visual loss</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>1-2%</td>
<td>25%</td>
<td>Present in some individuals</td>
</tr>
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</table>

FCAS: familial cold-induced autoinflammatory syndrome; MWS: Muckle-Wells syndrome; CINCA/NOMID: chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease.
Pyogenic sterile arthritis, pyoderma gangrenosum and acne

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA syndrome) is a rare autosomal dominant disorder caused by mutations in the gene coding for CD2-binding protein 1 (CD2BP1), also known as proline serine threonine phosphatase interacting protein 1 (PSTPIP1) [50, 51]. Patients usually exhibit episodic, sterile arthritis beginning in childhood, which may resemble septic arthritis; repeated bouts of joint inflammation may lead to destructive cartilaginous and bony changes [52]. Recurrent ulcerative skin lesions, pyoderma gangrenosum, severe cystic acne and abscesses at the site of injections are less frequent manifestations. Mutations in the PSTPIP1 gene can also cause a clinical picture of pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa (PAPASH) [53].

Deficiency of the IL-1 receptor antagonist

Patients with deficiency of the IL-1 receptor antagonist (DIRA) were first described in unrelated families in 2010 [54–56]. Autosomal recessive mutations in the IL-1RN gene encoding the IL-1 receptor antagonist (IL-1Ra) are the cause of DIRA. Affected individuals exhibit a severe picture characterized by a chronic psoriasiform, pustular or ichthyosiform rash, oral mucosal lesions and bone involvement with multifocal osteolytic lesions, epiphyseal overgrowth, widening of the rib ends and clavicles and periostitis. Presentation occurs in the neonatal period, with death in the first decade of life reported.

Deficiency of IL-36 receptor antagonist

Deficiency of IL-36 receptor antagonist (DITRA) is an autosomal recessive autoinflammatory disease caused by mutations in the IL-36 receptor antagonist gene [57]. Patients exhibit repeated bouts of generalized pustular psoriasis, fever, geographic tongue, nail dystrophy, arthritis and cholangitis. The disease may be life threatening.

Blau syndrome/early onset sarcoidosis

Since the discovery of a common genetic background, Blau syndrome (BS) and early onset sarcoidosis (EOS) are considered to be the familial and sporadic forms, respectively, of the same disorder. It is an autosomal dominant inherited autoinflammatory disease characterized by chronic intermediate or panuveitis, ichthyosiform tanscoloured skin rash, symmetrical polyarthritis with exuberant synovitis, tenosynovitis, camptodactyly and evidence of non-caseating epithelioid cell and giant cell granulomata [58]. Defects occurring in exon 4 of the gene NOD2 (CARD15) are related to the disease [59–61]. Patients usually present in the first years of life with the classic triad of synovitis, uveitis and skin rash, but may also exhibit more severe manifestations such as large vessel vasculitis, interstitial lung disease, pericarditis, splenic involvement or hepatic granulomatous infiltration [58].

Guadeloupe-type fever syndrome (FCAS2)

Guadeloupe-type fever syndrome, also known as NALP12-associated periodic syndrome (NAPS) or FCAS2, is an autosomal dominant autoinflammatory disease with some clinical similarities to FCAS. Patients usually exhibit attacks of fever, urticaria-like rash, arthralgia and headaches upon generalized cold exposure [62]. Sensorineural hearing loss, aphthous stomatitis and abdominal pain may also occur. Mutations in the NALP12 gene [encoding for a protein acting as a negative regulator of inflammation through suppression of nuclear factor κB (NF-κB)] are associated with this syndrome [63].

Majeed syndrome

Majeed syndrome is a form of hereditary autoinflammatory disease of the bone considered to be a rare monogenic form of chronic recurrent multifocal osteomyelitis (CRMO) [64] (Table 4). Originally described in 1989, it is an autosomal recessive disorder caused by mutations in the LPIN2 gene [65–67]. The role of LPIN2 in the regulation of inflammation is unknown. Patients exhibit recurrent fever episodes, sterile multifocal osteomyelitis (persistent rather than recurrent), microcytic congenital dyserythropoietic anaemia, inflammatory neutrophilic dermatosis, pustulosis and growth failure. Unlike CRMO, Majeed syndrome usually starts in the very early years of life. Radiographs show large osteolytic areas in the metaphyses of the long bones, and joint deformities may occur.

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

The syndrome chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) has been recently described [68]. CANDLE and other similar entities (such as Nakajo-Nishimatsu syndrome, and the joint contractures, muscle atrophy, microcytic anaemia, lipodystrophy and panniculitis syndrome) are now known to be caused by mutations in the same gene [68–70]. It is

<table>
<thead>
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<th>Table 4 Autoinflammatory diseases of bone</th>
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<tr>
<td>Genetics</td>
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</tr>
<tr>
<td>Predominantly bone disorders</td>
</tr>
<tr>
<td>Monogenic</td>
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<tr>
<td>Polygenic</td>
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PAPA: pyogenic sterile arthritis, pyoderma gangrenosum and acne; DIRA: deficiency of the IL-1 receptor antagonist; CAPS: cryopyrin-associated periodic syndromes; CINCA/NOMID: chronic infantile neurological cutaneous and articular/neonatal ony multisystem inflammatory disease; CRMO: chronic recurrent multifocal osteomyelitis; SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis.
an autosomal recessive disorder caused by mutations in genes encoding proteins of the immunoproteasome, with proteasome subunit type 8 (PSMB8) being the most frequently mutated gene. Other genes in the proteasome/immunoproteasome pathway can also cause CANDLE syndrome (P. Brogan et al., unpublished results). The clinical picture includes fever, fixed purple plaques, arthritis, dactylitis, joint contractures, panniculitis, lipodystrophy, myositis, accumulation of abdominal fat, interstitial keratitis, intracranial calcification and intermittent cytopenias. The disorder usually develops in the first decade of life, but may be present from birth; severe anaemia and the presence of high-titre autoantibodies may occur.

**Other recently described monogenic autoinflammatory syndromes**

In the past few years, new syndromes have been added to the growing list of monogenic autoinflammatory diseases (http://fmf.igh.cnrs.fr/SSAID/fevers/). Excellent reviews on the subject have recently been published [71–74]; a full description of all disorders is beyond the scope of this review. The following is a brief summary.

A gain of function mutation in CARD14 is associated with the autosomal dominant syndrome of pustular psoriasis (CARD-14-mediated pustular psoriasis or CAMPS) [75].

Two recently described dominant monogenic disorders are related to gain of function defects in the phospholipase Cγ2 (PLCγ2) gene, expressed in B cells, natural killer cells and mast cells. Deletions in the gene lead to a clinical picture of cold-induced urticaria-like lesions, atopy, granulomatous rash, autoimmune thyroiditis, sinuspulmonary infections, antinuclear antibodies and common variable immunodeficiency called PC2-associated antibody deficiency and immune dysregulation (PLAID), also known as FCAS type 3 [76]. On the other hand, missense mutations in the same gene cause a syndrome characterized by blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies and mild immunodeficiency. This syndrome has been named autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID) [77].

HOIL-1 [a component of the linear ubiquitination chain assembly complex (LUBAC)] deficiency provokes a clinical picture of immunodeficiency, autoinflammation and amylopectinosis [78].

A group of patients with mutations in the SLC29A3 gene (causing a wide spectrum of clinical pictures spanning from the H syndrome to a Rosai Dorfman’s-like histiocytosis) may carry an autoinflammatory phenotype [79–80].

Finally, mutations in the genes encoding the IL-10 receptors (IL-10RA and IL-10RB) [81] or the IL-10 gene itself [82] cause early IBD.

**Pathogenesis**

Although increased production and release of pro-inflammatory mediators is a final common abnormality, different mechanisms are involved in the pathogenesis of these conditions (Table 2). It is suggested that different levels of increased cellular stress and inflammatory signalling may be involved in most disorders [83]. The following is a short description of the main proposed pathogenic pathways (Table 2) [5].

**IL-1 activation disorders**

Description and characterization of the constituent and regulatory proteins of the NLRP3 inflammasome has shed light on the inflammatory pathways of the innate immune system cells, both in physiological and pathological settings [84, 85]. The inflammasome is a cytosolic multimolecular complex that links the innate immune system’s ability to sense danger to the activation of the pro-inflammatory cytokine IL-1β as a rapid response [86]. Different proteins such as cryopyrin, pyrin or PSTPIP1 integrate or modulate the inflammasome [5, 87].

Gain of function mutations in the NLRP3 gene (occurring in patients with CAPS) cause spontaneous oligomerization of cryopyrin and assembly of the inflammasome, resulting in activation of IL-1-converting enzyme (caspase 1) and subsequent cleavage of pro-IL-1β into active IL-1β [88].

The precise molecular mechanism by which MVK deficiency leads to inflammation remains obscure. A shortage of isoprenoid end products, such as the geranylgeranyl groups, could lead to inflammation through activation of caspase 1 in circulating monocytes and the consequent activation and liberation of IL-1β [89, 90]. In DIRA, competitive inhibition of the assembly of IL-1 and its receptor is deficient due to constitutive absence of IL-1Ra [54].

**NF-κB activation disorders**

The NF-κB disorders (BS and NAPS) do not seem to be as strongly related to increased activation of IL-1 as the previous entities, but more to activation of NF-κB [91, 92]. In CAMPS, mutations in CARD14, expressed mostly in keratinocytes, lead to up-regulation of NF-κB and transcription of pro-inflammatory proteins (i.e. CCL20, IL-8, and IL-36) [75].

**Misfolded protein disorders**

Various mechanisms have been proposed for the pathogenesis of TRAPS, including a shedding defect of TNFR1 due to the inability of metalloproteases to cleave it from the cell membrane, a defect of TNF-induced apoptosis, a defect in TNFR1 trafficking to the cell membrane and retention within the endoplasmic reticulum of mutant misfolded receptors that may lead to enhanced signalling [92–96]. Retained TNFR1 would lead to increased activation of pro-inflammatory mitogen-activated protein kinases secondary to stress-induced overproduction of mitochondrial reactive oxygen species.

**Proteasomopathies**

In CANDLE, mutations in the PSMB8 gene lead to deficient assembly and activity of the immunoproteasome. The resulting intracellular accumulation of polyubiquitinated proteins results in a cell stress response with up-regulation of IFN-regulated genes and products [70].
Thus, unlike other autoinflammatory diseases, CANDLE is an interferonopathy associated with an IFN signature on microarray profiles [67].

Still unknown, possibly complex mechanisms are involved in other autoinflammatory diseases. Moreover, recent investigations have shed new light on the pathogenesis of FMF and other autoinflammatory diseases, with defects in autophagy as likely additional pathogenic abnormalities [97, 98].

**Diagnosis**

The clinical diagnosis of autoinflammatory diseases may be guided by the recognition of symptoms, disease course pattern (recurrent or persistent), presence of acute phase reactants, pattern of inheritance and age at onset of symptoms. A question clinicians must ask themselves when faced with a patient with possible autoinflammatory disease is: Is the immune system overactive or underactive? In other words, is there autoinflammation/autoimmunity or immunodeficiency with or without immune dysregulation? Clinical history taking and investigations can then be tailored with these questions in mind.

The clinician must also assess if acute phase responses are truly periodic (i.e. only coincident with fever attacks) or if there is evidence of subclinical inflammation between fever attacks, usually by measuring CRP or SAA when the patient is well.

Diagnostic criteria have been designed for FMF in countries where the disease is more prevalent, but their clinical utility in populations where the disease is less common remains uncertain [15, 99, 100]. There are no validated diagnostic criteria for the other monogenic autoinflammatory diseases. Therefore genetic testing is clearly of utmost importance for the monogenic autoinflammatory diseases, but is not always feasible, affordable or straightforward. Even in countries where genetic testing is widely available, it will usually only (routinely) cover a minority of the known genetic mutations. In fact, at least 50% of patients with a clinical picture of an autoinflammatory disease will show normal genetic results for the available tests. Diagnostic scores and decision trees may aid in selecting candidate individuals for a diagnostic genetic test and to differentiate them from polygenic autoinflammatory diseases such as PFAPA syndrome [99, 101–103]. Dedicated laboratories with accreditation in molecular biology and gene sequencing should be consulted for gene analysis. Techniques for gene analysis may vary, but standard recommendations for indications, strategy, interpretation and reporting of testing have been formulated to diminish variability [104, 105]. Certain gene variants have a high allelic frequency in the normal healthy population and should be treated cautiously, as they may represent coincidental bystanders: E148Q and R408Q for the MEVF gene, R92Q and P46L for the TNFRSF1A gene, and Q703K and V198M for the NLRP3 gene [105]. Some patients with recessive diseases may exhibit only one mutated allele. Finally, genes related to a particular autoinflammatory disease may unexpectedly show pathogenic variants in patients with a clinical picture corresponding to another autoinflammatory disease. Different theories have been postulated to explain such findings [106–111]. Therefore diagnosis of the autoinflammatory diseases usually remains a clinically based one, sometimes confirmed by the genetic findings.

International registries and databases provide rich information about gene variants and associated phenotypes [112–114]. They may be consulted to compare the clinical and genetic picture of a given patient with others that have already been genotyped and described, keeping in mind that ethnic and environmental factors may impact the clinical expression of the same genetic defect.

**Treatment**

The objectives of treatment of the autoimmune inflammatory diseases are to prevent acute flares, reduce chronic inflammation, normalize growth where possible for children and prevent amyloidosis and other late end-organ sequelae that result in impairment of patient quality of life. While most published reports are based on single cases or experience in an open-label fashion, controlled clinical trials have demonstrated the efficacy of some agents in these conditions. For many patients, most therapeutic interventions are still based on the experience of the treating physician. Colchicine, the prophylactic therapy of choice in FMF, reduces (or abolishes) both the recurrence of attacks and the risk of developing amyloidosis [115–118]. Systemic corticosteroid therapy may be effective in the management of fever attacks in patients with TRAPS, MKD and Blau/EOS, but its continuous use frequently leads to unacceptable toxicity [119]. Simvastatin may decrease fever attacks in adult individuals with MKD [120].

Since the beginning of the last decade, biologics have been used in the treatment of patients with autoinflammatory diseases, delivering striking improvements in clinical symptoms, quality of life and long-term clinical course. Demonstration of a pivotal role of IL-1β in a number of autoinflammatory diseases has led to the introduction of anti-IL-1 strategies in the management of patients with autoinflammatory diseases. Patients with CAPS and DIRA benefit from therapy with anakinra, the recombinant receptor antagonist for IL-1β (blocking IL-1α and β), canakinumab, a longer-acting monoclonal antibody against IL-1β, and rilonacept (IL-1 trap), as reported in small case series and controlled trials, leading to approval of these latter drugs for the treatment of patients with CAPS [59, 121–140]. However, research into the safety and efficacy of anti-IL-1 agents in other autoinflammatory diseases is continuing. Case reports of their effectiveness in patients with TRAPS, MKD, refractory FMF, Blau and PAPA syndromes have increased optimism among physicians and patients [141–151].

However, a significant group of individuals do not respond to IL-1 blockade. In these cases, anti-TNF agents may be efficacious [152–159]. Tocilizumab, an IL-6 receptor antagonist, has been successfully used in the treatment of TRAPS [160]. IFN-α has been proposed as an alternative therapy for colchicine-resistant patients with FMF [161–164]. Lastly, the efficacy of Janus kinase
(JAK) inhibitors in patients with CANDLE is being tested in clinical trials [67, 165]. All these old and new therapies are associated with side effects, and clinicians must remain ever vigilant regarding opportunistic infection. We also advocate participation in registries of biologic therapy, where available, for ongoing prospective monitoring for potential toxicity.

Conclusions

The monogenic autoinflammatory diseases are rare, genetic diseases resulting in constitutive innate immune activation leading to dysregulation of inflammation pathways and excessive release of pro-inflammatory cytokines, notably IL-1β. Diagnosis remains clinical and is based on the different phenotypic features. Genetic diagnosis is of utmost importance, but must be performed judiciously and interpreted cautiously. IL-1β blocking agents and other biologic therapies are efficacious treatments for these patients. New therapies on the horizon for autoinflammatory diseases include JAK inhibitors. Challenges for the future include understanding the clinical significance of low-penetrance variants, the genetics and physiopathology of different autoinflammatory diseases and the long-term safety and efficacy of anti-IL-1 therapies. Additional yet unidentified genetic defects will continue to expand the horizons of autoinflammatory diseases, and will highlight novel therapeutic targets in this exciting and ever-expanding field.

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Rheumatology key messages

- The monogenic autoinflammatory diseases are rare inherited disorders resulting in constitutive innate immune activation.
- IL-1 is a central mediator in autoinflammatory diseases and IL-1β blocking agents have proved efficacious.
- Diagnosis of monogenic autoinflammatory diseases remains largely clinical, based on the phenotypic features, and genetic findings must be interpreted in the context of clinical features.

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