



Periodic fever syndromes and the autoinflammatory diseases (AIDs)

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ABSTRACT

Innate immune system represents the ancestral defense against infectious agents preserved along the evolution and species; it is phylogenetically older than the adaptive immune system, which exists only in the vertebrates. Cells with phagocytic activity such as neutrophils, macrophages, and natural killer (NK) cells play a key role in innate immunity. In 1999 Kastner et al. first introduced the term “autoinflammation” describing two diseases characterized by recurrent episodes of systemic inflammation without any identifiable infectious trigger: Familial Mediterranean Fever (FMF) and TNF Receptor Associated Periodic Syndrome (TRAPS). Autoinflammatory diseases (AIDs) are caused by self-directed inflammation due to an alteration of innate immunity leading to systemic inflammatory attacks typically in an on/off mode. In addition to inflammasomopathies, nuclear factor (NF)- κ B-mediated disorders (also known as Relopathies) and type 1 interferonopathies are subjects of more recent studies.

This review aims to provide an overview of the field with the most recent updates (see “Most recent developments in...” paragraphs) and a description of the newly identified AIDs.

1. Introduction

Innate immune system represents the ancestral defense against infectious agents preserved along the evolution and species; it is phylogenetically older than the adaptive immune system, which exists only in the vertebrates. Cells with phagocytic activity such as neutrophils, macrophages, and natural killer (NK) cells play a key role in innate immunity. Phagocytes can recognize highly conserved structures of external pathogens, called pathogen-associated molecular patterns (PAMPs), and endogenous molecules released by injured cells, called danger-associated molecular patterns (DAMPs). These molecules are recognized by pattern recognition receptors (PRRs) present on the surface of phagocytes [1]. The activation of PRRs fosters intracellular signaling cascades inducing the production of molecules (pro-inflammatory cytokines and interferon) in order to eliminate the infectious agents. The consequent transduction cascade involves different possible pathways (phosphorylation, ubiquitination and proteins interplay) leading to the induction of transcription factors of genes involved in inflammation [2]. Some PRRs are transmembrane proteins such as Toll-like receptors (TLRs) and stimulator of interferon genes (STING) [3,4], whereas others like

nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are cytosolic receptors [5–9].

In 1999 Kastner et al. first introduced the term “autoinflammation” describing two diseases characterized by recurrent episodes of systemic inflammation without any identifiable infectious trigger: Familial Mediterranean Fever (FMF) and TNF Receptor Associated Periodic Syndrome (TRAPS) [10]. Moreover, the absence of autoantibodies and of self-reactive T cells confirms the different nature of the immune dysregulation involved in these disorders.

Autoinflammatory diseases (AIDs) are caused by self-directed inflammation due to an alteration of innate immunity leading to systemic inflammation attacks in on/off mode (although it may rarely be persistent) [11].

In addition to inflammasomopathies, nuclear factor (NF)- κ B-mediated disorders (also known as Relopathies) and type 1 interferonopathies are subjects of more recent studies [12,13].

This review aims to provide an overview of the field with the most recent updates (see “Most recent developments in ...” paragraphs) and the newest identified AIDs (Table 1). It must be highlighted that since autoinflammatory field is quickly expanding and new genes as well as

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Table 1
List of autoinflammatory diseases (AIDs).

	MUTATION	PROTEIN	PATHOGENESIS
Inflammasomopathies/Monogenic recurrent fevers			
FMF	<i>MEFV</i> , autosomal recessive	Pyrin	Gain of function mutation leads to excessive inflammasome activation driven by pyrin
MKD/HIDS	<i>MVK</i> , autosomal recessive	Mevalonate kinase	Loss of function mutation leading to alteration into cholesterol and non-sterol isoprenoid pathway
TRAPS	<i>TNFRSF1A</i> , autosomal dominant	TNF receptor super-family member 1 A	Altered intracellular TNF receptor trafficking fostering ROS production and subsequent NLRP3 inflammasome activation
CAPS	<i>NLRP3</i> , autosomal dominant	Cryopyrin	Gain of function mutation, leading to overactivation of IL-1 β through caspase 1 cryopyrin-induced activation
PAPA	<i>PSTPIP1</i> , autosomal dominant	Proline-serine-threonine phosphatase-interacting protein 1	Pyrin inflammasome activation through direct interaction between PSTPIP1 and pyrin
New Inflammasomopathies			
NLRC4-inflammasomopathies	<i>NLRC4</i> , autosomal dominant	NLRC4	Gain of function mutation, overproduction of IL-1 β and IL-18 through de-inhibition of NLRC4 inflammasome
NAIAD	<i>NLRP1</i> , Autosomal dominant and autosomal recessive	NLR containing a pyrin domain 1	Caspase-1 and IL-18 overproduction induced by NLRP1 inflammasome
NLRP12 periodic fever syndrome	<i>NALP12</i> , autosomal dominant	Monarch-1	Alteration of constitutive NF- κ B inhibition and elevated ROS production
PAAND	S242R autosomal dominant mutation of <i>MEFV</i> gene	Pyrin	Loss of pyrin inhibition by 14-3-3 protein, resulting in inflammasome assembling
APLAID	<i>PLCG2</i>	Phospholipase C gamma 2	PLC γ 2 de-inhibition leading to NLRP3 inflammasome activation
PFIT	<i>WDR1</i>	WD40 repeat protein 1	T-cell and megacaryocyte dysfunction due to actin accumulation
Relopathies/Nuclear factor Kappa-B (NF-κB) related AIDs			
Blau Syndrome (Early Onset Sarcoidosis)	<i>NOD2</i> , Autosomal dominant	NOD2/CARD15	Activation of NF- κ B signaling with activation of proinflammatory transcriptional genes
Familial pityriasis rubra pilaris	<i>CARD14</i> , autosomal dominant	CARD14	Activation of NF- κ B driven inflammation in the skin
Autoinflammation/Immunodeficiency Associated with Mutations in LUBAC Proteins	<i>HOIP</i> , Autosomal Recessive <i>HOIL</i> , Autosomal Dominant	LUBAC proteins	Defective deubiquitination and constitutive activation of NF- κ B pathway
A20 haploinsufficiency	<i>TNFAIP3</i> , Autosomal Dominant	A20	Defective deubiquitination and constitutive activation of NF- κ B pathway
ORAS	<i>FAM105B</i> , Autosomal Recessive	Otulin	Defective deubiquitination and constitutive activation of NF- κ B pathway
Interferonopathies			
Aicardi Goutières Syndrome	<i>TREX1</i> , <i>NASEH2</i> , <i>SAMHD1</i> , <i>ADAR1</i> , Autosomal Recessive <i>IFIH1</i> , Autosomal Dominant	Exonuclease, Ribonuclease, Phosphohydrolase dsRNA-specific adenosine deaminase dsRNA sensor	Possible role of accumulation of nucleic acids
SAVI	<i>TMEM173</i> , Autosomal Dominant	STING	Gain of function mutation leading to hyperactivation of type I IFN pathway
PRAAS	<i>PSMB8</i> , <i>PSMB4</i> <i>PSMA3</i> , <i>PSMB9</i> , <i>POMP</i> Autosomal Dominant	Proteasome ring proteins Proteasome maturation Protein	Loss of function mutations of immunoproteasome components causes upregulation of type I IFN pathway
Singleton-Merten Syndrome	<i>IFIH1</i> <i>DDX58</i> , Autosomal Dominant	MDA5 RIG-I	Gain of function mutation of dsRNA sensors leading to upregulation of IFN I pathway
Other monogenic AIDs			
ADA2 Deficiency	<i>ADA2</i> , autosomal recessive	ADA2	Macrophage differentiation towards pro-inflammatory activity (M1 subsets), prominent IFN 1 signature
SIFD	<i>TRNT1</i> , autosomal recessive	TRNT1	Altered maturation of cytosolic and mitochondrial transfer RNAs
DITRA	<i>IL36RN</i> , autosomal recessive	IL-36 receptor antagonist	Loss of NF- κ B pathway inhibition leading to inflammation in keratinocytes
Autoinflammatory diseases without an identified monogenic etiology			
Systemic-onset Juvenile Idiopathic Arthritis	Polygenic Monogenic early onset associated to mutation of <i>LACC1/FAMIN</i>		
Idiopathic pericarditis	Polygenic		
Autoinflammatory bone disorders			
CRMO	Polygenic		
Majeed syndrome	<i>LPIN2</i>	Lipin-2	Alteration of cytosolic potassium with the final result of NLRP3 inflammasome hyperactivity
DIRA	<i>IL1RN</i> , autosomal recessive	IL-1 receptor antagonist	Loss of IL-1 β and IL-1 α physiological inhibition resulting in pro-inflammatory imbalance
Cherubism	<i>SH3BP2</i> , autosomal dominant	SH3 binding protein 2	Alteration of immune and adaptive immune cells function; alteration of bone resorption

new pathogenic pathways are constantly discovered, this review has not the presumption to be exhaustive.

2. Inflammasomopathies/monogenic recurrent fevers

2.1. Familial Mediterranean Fever (FMF)

FMF is an autosomal recessive disease characterized by recurrent systemic inflammatory attacks with fever and serositis. It is the most common monogenic AID. FMF originates from the Middle East with the highest prevalence among Sephardic Jews, Armenians, Turks and Arabs; it later spreads towards the Mediterranean area, and towards the “new world” more recently following migrations [14]. In 1997, two different groups identified the underlying genetic cause of FMF in mutations of *MEFV* gene located on chromosome 16, encoding for a protein called pyrin [15,16]. So far, more than 340 *MEFV* sequence variants have been reported (<https://infervers.umai-montpellier.fr/web/search.php?n=1>), although many of those have no clear pathogenic role; thus, a careful interpretation of genetic results is advocated [17,18]. Clinical phenotype of FMF may be present also in subjects harboring heterozygous mutations of *MEFV* gene and those patients typically show a good response to colchicine treatment [19,20].

The involvement of other genes encoding for proteins implicated into FMF pathogenesis may influence clinical expression and severity. Serum amyloid A (SAA; particularly SAA1a allele) and MHC class I polypeptide-related sequence A (MICA) have been related to disease severity and outcome, including the risk of amyloid A (AA) deposition [21–23]. A further complication in the understanding of FMF is represented by the combination of heterozygous *MEFV* mutations and mutations of other monogenic AIDs genes leading to clinical manifestations of auto-inflammation, as well as the rising role of environment that influences clinical phenotype [24–26].

Once activated, pyrin usually assembles the inflammasome through the ASC-dependent mechanism [27]. Negative control of this path is guaranteed by the GTPase RhoA that activates regulatory proteins 14-3-3 and PKN [28]. When mutated, pyrin escapes to its constitutive inhibition leading to inflammasome formation and uncontrolled production of IL-1 β through caspase 1 activation [29].

The disease typically appears within the second decade of life and the majority of patients presents the first clinical manifestation during the pediatric age [30–32]. However, delayed onset of FMF may occur and is characterized by an attenuated disease course, particularly in males, and a good response to colchicine [33,34].

Fever attacks usually are recurrent without a predictable periodicity and last between 12 and 72 h. FMF clinical manifestations are reported in Table 2.

The most concerning complication of FMF is the accumulation of AA. Amyloidosis accounts for the majority of morbidity and mortality related to FMF [35]. SAA is the circulating precursor of AA and reflects amyloidogenesis. Underlying inflammation is detectable in about 30% of FMF patients during free-intervals between the attacks; moreover, some asymptomatic carriers may have a constant elevation of SAA, with the risk of developing amyloidosis over time [36]. The persistent inflammation in children with FMF impacts growth and bone mineralization [37,38]. The risk of AA amyloidosis is higher in the presence of M694V mutations and SAA1a allele [35].

The diagnosis of FMF is principally clinical and genetic results should be carefully interpreted.

Colchicine is the milestone of the MF treatment since it inhibits the activation of pyrin inflammasome [39]. When colchicine fails, European League Against Rheumatism (EULAR) recommendations suggest starting an anti-IL-1 β medication along with the microtubule-depolymerizing drug [40]. This class of biological drugs has been proven to prevent attacks and reduce systemic inflammation [41,42].

2.1.1. Most recent developments in FMF

With the increasing availability of genetic tests, more patients with clinical FMF patterns are found to carry a heterozygous mutation of *MEFV*, and are successfully treated with colchicine. The paradigm of FMF as an autosomal recessive disease may be challenged since an autosomal dominant (AD) pattern of transmission has been reported [43]. More recently one British group has also described 21 patients out of 3500 tested harboring AD methionine deletion in a specific position (p.Met694) with classical manifestations of FMF and good response to colchicine [44]. Furthermore, in an Italian study including 107 FMF patients, the majority had heterozygous mutations (86%) (p.Met680Ile or p.Met694Val). Given this finding, authors speculated the presence of a “non classic” AR or an “atypical” AD transmission in FMF patients [45]. The presence of a positive genetic test may be crucial for the diagnosis although the exact value of each variant has been recognized as an important goal for future research [46].

The phase III CLUSTER study has recently assessed the efficacy of canakinumab in patients with FMF, mevalonate kinase deficiency (also known as hyperimmunoglobulinemia D syndrome; MKD or HIDS) and TRAPS. In this randomized trial, 63 FMF patients resistant to colchicine were randomized to receive canakinumab (150 mg every 4 weeks) or placebo. A significant portion of canakinumab treated patients achieved a complete response after 16 weeks, and this response was significantly higher when compared to those who received the placebo (61% vs. 6%). Furthermore, also subjects without complete response improved on anti-IL-1 β since they had both a reduction of flares and days of fevers [47].

2.2. Mevalonate kinase deficiency/hyper IgD syndrome (MKD/HIDS)

Mevalonate kinase deficiency (MKD) is an autosomal recessive autoinflammatory disease caused by mutation of the gene encoding for mevalonate kinase (MVK). MKD is also known as hyper IgD syndrome (HIDS) given the increase of immunoglobulins D during the attacks that later has been recognized absent in almost 20% of MKD cases [48,49]. The impairment of MVK enzyme leads to alteration into cholesterol and non-sterol isoprenoids pathway. According to the residual enzyme activity, the severity of the disease ranges from MKD/HIDS with a residual enzymatic activity ranging between 1.8% and 28% of normal and preponderant autoinflammatory features to mevalonic aciduria (MA) with almost no remaining enzymatic function, dysmorphic features and significant neurological involvement [50].

MKD is more common in the west area of Europe; indeed, several studies reported MKD patients with Dutch, French and Italian origin [49, 51,52].

MKD is due to loss of function mutation of *MVK* gene on chromosome 12; so far more than 210 sequence variants of this gene have been reported (<https://infervers.umai-montpellier.fr/web/search.php?n=3>). The most frequent mutation is V377I either in homozygous or as compound heterozygous with I268T mutation; patients carrying V377I/I268T genotype have the risk of amyloidosis despite the fact that this complication is very rare in MKD patients [52].

The loss of function of MVK reduces the prenylation of proteins such as geranylgeranyl pyrophosphate. This latter is necessary for RhoA activation and consequently the persistent inhibition of pyrin inflammasome. Low levels of geranylgeranyl pyrophosphate compromise this regulation and facilitate pyrin inflammasome assembly [53].

The disease usually appears during the first year of life with abrupt onset of fever lasting 3–7 days associated with several signs and/or symptoms and an increase of acute phase reactants (Table 2). Attacks recur with a monthly frequency and may be triggered by vaccination, stress and infections. The frequency of disease flares tends to decrease over time, although some of the patients continue to have more than 6 attacks per year during adulthood [49].

Clues for diagnosis are the very early onset along with classical clinical manifestations and the increase of urinary mevalonic acid during the attacks [54].

Table 2
Clinical features of Classical Inflammasomopathies Underlined features indicate clinical hallmarks of the disease.

	Fever Duration	Musculoskeletal involvement	Mucocutaneous	Ocular	Pleuritis/ Pericarditis	Abdominal	Spleen and Lymphatic system	Neurological	Other
FMF	Recurrent attacks lasting 12–72 h	<u>Non-deforming oligoarthritis of lower limbs</u> Protracted Febrile Myalgia (without muscle enzyme elevation) Less common chronic destructive arthritis	<u>Erysipela-like rash on lower limbs</u>	Uncommon	Pleuritic pain/effusion (often unilateral) Less commonly: Pericarditis	<u>Peritonitis</u>		Aseptic Meningitis	Orchitis
MVK/ HIDS	Recurrent attacks lasting 3–7 days, starting at age <1 year	Arthralgia Myalgia	<u>Aphthous stomatitis</u> Non migratory maculopapular or urticarial rash	Uncommon	Uncommon	Abdominal pain Diarrhea and vomiting	<u>Cervical Lymphadenopathy</u>	Severe neurological involvement (rare)	
TRAPS	Prolonged attacks lasting up to 3–4 weeks	<u>Myalgia associated with pseudo-cellulitic rash</u> Arthralgia	<u>Migratory pseudo-cellulitis rash</u>	<u>Periorbital edema</u>	Pleurisy	Peritonitis	Lymphadenopathy	Headache	
FCAS	<24 h	Arthralgia	<u>Cold induced urticarial – like rash</u>	Conjunctivitis	Rare	Rare	Rare	Uncommon	
MWS	2–3 days	Arthralgia	Urticarial - like rash (<i>no specific trigger</i>)	Conjunctivitis Episcleritis	Rare	Rare	Rare	<u>Sensoneurinal hearing loss</u>	
CINCA/ NOMID	Continuous	<u>Hypertrophic arthropathy of long bones extremities</u> Facial dysmorphism Chronic Arthritis	Intermittent urticarial rash presenting since the first weeks of life	Conjunctivitis Uveitis Papilledema	Rare	Rare	Rare	<u>Aseptic chronic meningitis</u> Sensorineural hearing loss	
PAPA		<u>Sterile pyogenic arthritis</u>	<u>Severe cystic acne</u> <u>Pyoderma gangrenosum</u> <u>Hydradenitis Suppurativa</u> ^a	Not seen	Not seen	Not seen	Hepatosplenomegaly ^b	Not seen	Pancytopenia ^b Growth failure ^b

^a Association with hydradenitis suppurativa is also known as PASH syndrome (pyoderma gangrenosum, acne, and hidradenitis suppurativa).

^b PAMI (PSTPIP1-Associated Myeloid-related-proteinemia Inflammatory syndrome) consists of the association of PAPA classical features plus hepatosplenomegaly, pancytopenia and growth failure.

Clinicians treat acute attacks of MKD with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids; colchicine and statins have shown poor efficacy in preventing disease flares [52]. Anakinra administered daily or “on-demand” during the attacks has been proven to be quite effective, comparable results have been achieved with canakinumab [52,55].

2.2.1. Most recent developments in MKD/HIDS

The exact mechanisms by which genetic mutations impact MKD/HIDS clinical phenotype are not completely known. So far researches have focused on the mutation of *MVK* gene, whereas looking for other genes influencing the disease expression through the combination of exome, transcriptome and proteome analyses (all together named multiomics) may be a new interesting approach. Recently, a gain of function mutation of signal transducer and activator of transcription signaling 1 (*STAT1*) gene (p.R241Q) discovered thanks to this multiomics approach has been found to play a critical role into disease phenotype expression. Indeed two sisters carrying the same homozygous V377I mutation showed asymptomatic and symptomatic clinical phenotype respectively due to the presence of *STAT1* mutation in the symptomatic patient [56]. This finding might have repercussions on the treatment since the janus kinase (*JAK*)/*STAT1* pathway can be targeted by several drugs.

Furthermore, new insight into immunity has led to the new concept of non-specific memory of innate immunity induced by several metabolic processes, called “trained immunity”, that may intensify or attenuate the innate immune response to a determinate stimulus. A Dutch group demonstrated that the trained immunity induction caused by mevalonate accumulation in MKD/HIDS monocytes leads to cytokine overproduction [57].

With regard to diagnosis, efforts towards the creation of a set of diagnostic criteria are ongoing. Besides genetic confirmation, the importance of direct or indirect *MVK* functional tests such as urinary mevalonic acid during the episodes and *MVK* enzymatic activity have been highlighted [46].

Two novel trials confirmed the efficacy of canakinumab for the treatment of MKD/HIDS patients [47,58]. However in MKD patients, inhibition of IL-1 β pathway, through canakinumab, seems not as effective as assessed in other monogenic AIDs and may need a higher dose to reach comparable results [47].

2.3. TNF receptor-associated periodic fever syndrome (TRAPS)

TNF receptor-associated periodic fever syndrome (TRAPS) is an autosomal dominant disease due to a mutation of the TNF receptor superfamily member 1 A. It has been initially described in a large Scottish/Irish family and named as familial Hibernian fever, however, all ethnicities can be affected [6]. This monogenic dominant disease is caused by a missense mutation of *TNFRSF1A* on chromosome 12 encoding for the 55-KF receptor of TNF- α ; 158 sequence variations, mainly on exon 2, 3 and 4, are known so far (<https://infevers.umai-montpellier.fr/web/search.php?n=2>). The majority of pathogenic mutations acts by altering cysteine–cysteine disulfide bonds in the extracellular domain (e.g. T50 M and C33Y). More than one-third of patients harbor R92Q and P46L mutations, although these low penetrance sequence variants have an unclear role and often result in milder disease [59].

Despite several speculations on defective receptor shedding and apoptosis [6,60], the most accredited effect of *TNFRSF1* mutation is the altered trafficking of TNF receptor type I (*TNFR1*) that accumulates into the endoplasmic reticulum. This results in impaired receptor clearance and an increase of reactive oxygen species (ROS) enhancing NF- κ B and mitogen-activated protein kinase (MAPK) pathway [61–63]. Autophagy is the process by which unfolded and accumulated proteins are removed by cells; the overload of *TNFR1* in TRAPS patients impairs this process fostering ROS production and may indirectly lead *NLRP3* inflammasome activation [62,64].

Typically TRAPS is characterized by prolonged attacks lasting up to

3–4 weeks, however, sometimes inflammatory episodes may be longer or may disappear in less than a week depending on the underline genotype. Peculiarities of TRAPS are the periorbital edema and pseudo-cellulitis rash. Mean age at onset is around 4 years with a mean diagnostic delay of one decade, however, one-fifth of patients have experienced first symptoms during the adulthood [59]. Recognizable triggers are found in a quarter of patients (emotional stress, menstrual cycle, exercise, infections and vaccination). AA is a possible complication, accounting for up to 18% of TRAPS adult patients [65].

Treatment of TRAPS is based on controlling clinical and subclinical inflammation in order to guarantee a good quality of life and to avoid AA. Corticosteroids decrease the severity of clinical manifestations but their long-term use is not advised. Despite promising results with etanercept [66], many patients discontinue the anti-TNF α treatment because of loss of efficacy and others do not respond [67,68]. As in other monogenic AIDs the blockage of IL-1 has been demonstrated to be efficacious in preventing attacks of TRAPS and AA. Both anakinra and canakinumab have shown good results [69,70].

2.3.1. Most recent developments in TRAPS

A new insight into the pathogenesis of TRAPS has been recently shown in a study reporting the gene expression profile of patients treated with canakinumab compared to healthy age-matched controls. *TNFRSF1* gene resulted upregulated in treatment naïve patients and canakinumab was able to reverse this process. This finding suggests that the accumulation of *TNFR1* protein is in part due to the increase of its gene transcription and not only to autophagy defection. Canakinumab downregulates IL-1 β gene expression as well as other proteins involved in crucial pathways in TRAPS (MAPK14 and NF- κ B); this may restore the normal process of neutrophils apoptosis reducing pro-inflammatory cytokines release [71].

The efficacy of canakinumab has been confirmed in the CLUSTER study: the rate of complete response at 16 weeks was 45% for those receiving the monoclonal antibody and 8% for placebo-treated patients ($P = 0.006$). Notably, patients who did not reach complete response showed a substantial reduction in the number of days of fever per year [47].

The study of signaling pathways and its regulation (signaloma) through the application of reverse-phase protein microarray (RPPA) technology has been recently adopted for TRAPS [72]. So far, the focus of the treatment of these patients has been the blockage of proinflammatory cytokines instead of targeting intracellular proinflammatory signaling pathways. RPPA technology was used to screen several drugs for their effects on signaling pathways known to be involved in TRAPS pathogenesis in order to find a repurposed medication that downregulates them. The most ranked drug was the antibiotic lomefloxacin that significantly reduced the expression of several molecules across the Jak/Stat, MAPK, NF- κ B and PI3K/AKT pathways. Although at a preliminary stage, this would be matter of future research for TRAPS and other AIDs [72].

2.4. Cryopyrin associated periodic syndrome (CAPS)

Cryopyrin associated periodic syndrome (CAPS) represents the prototype of inflammasomopathies in which a gain of function mutation of *NLRP3* gene is responsible for inflammasome overactivation and the consequence hyperinflammatory status. Under the term CAPS are included 3 clinical entities distinguishable for their increasing severity: family cold autoinflammatory syndrome (FCAS), Muckle Wells syndrome (MWS), and chronic infantile articular neurological periodic syndrome (CINCA) also known as neonatal onset multisystem inflammatory disease (NOMID) [73]. CAPS is a rare and world spread disease without any ethnicity preference.

NLRP3 gene formerly known as cold-induced autoinflammatory syndrome 1 (*CIAS1*) gene, is located on chromosome 1q44 and encodes for cryopyrin, a protein with a key role in *NLRP3* inflammasome

assembling. CAPS is caused by an AD inherited or *de novo* missense mutation in the NACHT domain of *NLRP3* gene [73]. So far more than 200 sequence variants of *NLRP3* gene are known (<https://infervers.umai-montpellier.fr/web/search.php?n=4>), mainly on exon 3. Furthermore, a not negligible portion of patients with CINCA clinical phenotype does not harbor any *NLRP3* mutation at conventional studies due to the presence of mosaicism or to unknown epigenetic factors [74,75].

The pathogenesis of CAPS has provided the model of caspase dependent IL-1 β production [76]. Indeed cryopyrin activates caspase 1 leading to the cleavage of pro-IL-1 to IL-1 β . *NLRP3* gain of function mutations foster this process resulting in overactivation of IL-1 β through *NLRP3* inflammasome [76].

CAPS displays a chronic or acute intermittent course according to disease severity; acute phase reactants are almost persistently elevated. Patients with FCAS have recurrent cold-triggered episodes of inflammation with fever, urticaria-like rash, arthralgia and conjunctivitis. MWS is more chronic rather than recurrent without recognizable triggers. Sensorineural hearing loss and eye involvement are common features of MWS and the risk of AA increases with the age.

CINCA patients manifest the classical triad of cutaneous, neurological and articular involvement with very early onset (Table 2). Long-term complications include failure to thrive and cognitive disability as well as AA [73].

Clinical manifestations of CAPS correlate with the underlying genotype; indeed, patients harboring the T348 M variant have a chronic course with an early-onset disease and hearing loss, whereas neurological involvement is rare in patients carrying V198 M, E311 K and A439 V mutations [73].

The inhibition of IL-1 in CAPS patients is extremely effective; this finding is not surprising considering its pathogenesis. The chronic blockage of IL-1 is recommended in CAPS patients with active disease, whereas NSAIDs and corticosteroids may be used as symptomatic therapy [77]. Both anakinra and canakinumab have been demonstrated efficacious in CAPS patients giving their capacity of abruptly systemic inflammation and arresting organ damage [78–80].

2.4.1. Most recent developments in CAPS

CAPS encompasses different clinical entities with unrelated and potentially confounding names. Furthermore, the term cryopyrin associated periodic syndrome may be misleading since disease course may be chronic rather than periodic in several patients. Recently, a group of experts has proposed a new name for CAPS, *NLRP3*-associated auto-inflammatory disease in which an adjective is added for each class of severity: mild for FCAS, moderate for MWS and severe for CINCA/NOMID [81]. The discovery of somatic mutations in previous labeled “mutation negative” patients with typical clinical manifestations of CAPS has pointed out the importance of highly sensitive genetic tests. A UK group reported 8 patients with somatic mutations found thanks to the amplicon-based deep sequencing (ADS), representing 8% of CAPS patients diagnosed in this centre. Four novel variants were detected and the mean allele frequency was higher in neutrophils and monocytes. Interestingly, 2 patients developed AA which has never been described for CAPS patients harboring somatic mutations [82]. The rate of *NLRP3* mosaicisms has been recently reported up to 19% in CAPS-like patients, thus a deep sequencing is advocated [83]. The importance of genetic confirmatory test is still considered very important for proper diagnosis [46], but the possibility of clinical diagnosis may help when mosaicisms is suspected and in case of unavailability of highly sensitive genetic tests. It has been suggested that CAPS clinical diagnosis may be made upon the presence of elevated acute phase reactants (C-reactive protein/SAA) along with at least 2 of the following clinical manifestations: urticaria-like rash, cold/stress-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis and skeletal abnormalities including frontal bossing and epiphyseal overgrowth. This set of criteria has shown high sensitivity and specificity (81% and 94%

respectively) [84]. Interestingly efforts are made in order to develop new agents capable to inhibit *NLRP3* function. In this regard, old drugs or medications coming from traditional Chinese medicine have been recently found to inhibit *NLRP3* inflammasome [85–88].

2.5. Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome is an autosomal dominant AIDs characterized by joint and severe skin involvement (Table 2). The mutated gene is located on chromosome 15 and codifies for proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1; also known as CD2-binding protein 1) [89]. PSTPIP1 plays a role in cytoskeletal scaffolding and cellular dynamics of innate immune cells. The underlying mechanism of PAPA is not completely clear, however, it seems related to pyrin inflammasome activation through direct interaction between PSTPIP1 and pyrin [89]. Sterile pyogenic arthritis that may be triggered by mild trauma and severe cystic acne represent the hallmarks of the disease. Joint involvement appears in early childhood and tends to regress over time; on the contrary skin lesions typically develop in puberty and persist. Furthermore, some patients present pyoderma gangrenosum with or without hidradenitis suppurativa; the latter clinical manifestation along with the other skin features has been named PASH syndrome (pyoderma gangrenosum, acne, and hidradenitis suppurativa) [90]. The clinical spectrum of *PSTPIP1* associated mutation is expanding, indeed PAMI (PSTPIP1-Associated Myeloid-related-proteinemia Inflammatory syndrome) is a newly recognized clinical entity characterized by severe systemic inflammation. PAMI is caused by p.E250K and p.E257K mutations resulting in charge reversal in the γ -domain of PSTPIP1 and increased interaction with pyrin. Besides PAPA-like manifestations, PAMI patients have hepatosplenomegaly, pancytopenia and growth failure [91].

PAPA patients present a variable response to steroids and cytokines targeting agents such as IL-1 β blocking agents and TNF α inhibitors [89, 92]. The variability in treatment response reflects the many different pathways in which PSTPIP1 is involved.

2.5.1. Most recent developments in PAPA

Several degrees of radiographic changes have been described in PAPA patients due to erosive arthritis: joint space narrowing, subchondral sclerosis, bone overgrowth and joint deformity. However, little is known on MRI findings in these patients. A recent paper described 2 PAPA patients with oligoarthritis: MRI findings were not specific and similar to those seen in other inflammatory diseases (multiloculated joint effusion, synovial thickening and hyperenhancement, bone marrow edema) [93]. The clinical spectrum of *PSTPIP1* mutations is constantly widening. A recent case report has illustrated a patient harboring the heterozygous E250K mutation resulting in a mild clinical phenotype consisting of recurrent knee monoarthritis and persistent bone marrow involvement, without typical skin lesions. Interestingly, the use of anakinra was effective in lowering systemic inflammation without controlling bone marrow involvement [94].

Giving the presence of different phenotypes coming from several *PSTPIP1* mutations, a broader term including all these clinical entities (PAPA/PASH and PAMI) has been proposed: *PSTPIP1*-associated AIDs. Furthermore, the term “pyogenic” of the acronym PAPA has been replaced by *PSTPIP1* in order to highlight the underlying mutation [81].

3. New inflammasomopathies

3.1. *NLR4*-inflammasomopathies

Since 2014 two clinical phenotypes have been related to mutations of *NLR*-family CARD domain-containing protein 4 (*NLR4*) gene: auto-inflammation and infantile enterocolitis (AIFEC) fever characterized by recurrent episodes of MAS and very early onset enterocolitis [95,96] and

Familial cold autoinflammatory syndrome 4 (FCAS4) with neonatal-onset, cold-induced urticarial rash and arthralgia resembling FCAS [97]. Both AIFEC and FCAS4 are caused by autosomal dominant NLRC4 gain-of-function mutations. So far, more than 10 sequence variants that exhibit complete penetrance have been related to AIFEC (<https://infevers.umai-montpellier.fr/web/search.php?n=25>). Two patients harboring somatic mutations have been identified, both with severe phenotypes: one with AIFEC and the other with CINCA-like clinical features and very high IL-18 serum levels [98,99]. It is unclear how gain-of-function mutations of *NLRC4* can produce such different clinical patterns, although a partial explanation might be the different protein domain interested by mutations [100]. Human NLRC4 inflammasome has been identified in myeloid cells and mucosal tissues; indeed, it has been detected in mouse intestinal epithelial cells playing a role in defense against gastrointestinal pathogens [101]. NLRC4 inflammasome fosters both IL-1 β and IL-18. Interestingly, AIFEC patients experienced the resolution of enterocolitis after the first year of age despite persistent elevated IL-18 serum levels; the reasons for this are unknown although they might be related to microbiota and mucosal immunity [102]. Elevated serum IL-18 concentration is a distinctive feature of MAS in AIFEC. FCAS4 patients have milder phenotypes dominated by skin manifestations (cold-induced urticarial rash). Skin biopsies revealed a lymphohistiocytic infiltrate [103]. Since there are no NLRC4 target drugs, the treatment of AIFEC patients is challenging and is based on anecdotal reports, whereas FCAS4 may benefit from NSAIDs during acute phases [96,99,103]. However, IL-18 recombinant binding protein has been successfully employed in an AIFEC patient with a refractory disease [104]. A phase III trial testing Tadekinig α , an IL-18 recombinant binding protein, is ongoing (NCT03113760).

3.2. *NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)*

A group recently described 3 subjects from 2 families with early onset of dyskeratosis, oligo/polyarthritis and recurrent fever episodes along with immunological dysfunction and vitamin A deficiency. All patients harbored a mutation of NLR family pyrin domain containing 1 (*NLRP1*) gene: 2 cousins of Algerian family born from related parents were homozygous for R726W and one Dutch patient was heterozygous for P1214R. The different inheritance patterns might be due to the different sites of mutations [105]. The authors named this disease *NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)*. Chronic or recurrent infections were reported in two patients. All patients showed high serum levels of caspase-1 and IL-18. These findings suggest that both keratinocyte differentiation and regulation of inflammation are influenced by *NLRP1* inflammasome. Furthermore, abnormal B-cell distribution was found in all patients in terms of either a high absolute number of circulating transitional B cells or a reduced number of circulating CD27⁺ B cells (marginal zone or memory B cells) when compared with unaffected subjects. Two patients had ocular involvement: uveitis and corneal dyskeratosis. Skin manifestations improved with acitretin treatment in all three patients, whereas one patient responded to IL-1 blockage with the resolution of arthritis and systemic inflammation [105].

3.3. *NALP12 periodic fever syndrome*

NLRP12 plays a role in the persistent inhibition of NF- κ B signaling and its mutation may alter this control. Indeed in 2008, 3 patients (2 monozygotic brothers and 1 girl) of two unrelated families, were found to harbor a heterozygous mutation of the *NLRP12* gene [106]. These patients had a very early onset disease with periodic fever lasting several days associated with arthralgia and headache and triggered by cold exposure. All three patients had a positive family history, although with a milder phenotype. Interestingly the two brothers developed urticaria and sensorineural hearing loss without acute phase reactant elevation,

Table 3
Overview on rheopatias.

NAME	CLINICAL FEATURES	THERAPEUTIC APPROACH DESCRIBED
NOD2 CARD 15-associated diseases		
Blau Syndrome	Granulomatous pan-uveitis; skin rash; symmetrical polyarthritis	Corticosteroids Immunosuppressants
NAID (Yao Syndrome)	Adult onset periodic fevre; arthralgias or non erosive arthritis; erythematous skin rash gastrointestinal symptoms; sicca-like symptoms	Corticosteroids; Sulfasalazine Tocilizumab or Canakinumab for refractory cases
CARD14-associated disease		
Familial pityriasis rubra pilaris	Erythematous plaques; keratotic follicular papule; palmoplantar keratoderma	Ustekinumab
Ubiquitinopathies		
LUBAC proteins associated disorders	HOLL-1 mutation: Susceptibility to invasive pyogenic bacteria; systemic autoinflammation; muscle amylopectinosis complicating with myopathy and cardiomyopathy HOIP mutation: similar to HOLL-1 symptoms, plus lymphagectasia	
A20 haploinsufficiency	Oral and genital ulcer; anterior uveitis; fever; skin rash; arthritis; bloody diarrhea	Immunomodulants Biologic agents
Otulin deficiency (ORAS)	Early onset recurrent fever; arthritis; diarrhea; skin lesions; failure to thrive; lypodystrophy	TNF- α blocking agents Anakinra

whereas aphthous ulcers and lymphadenopathy were observed in the other subject. The *NLRP12* mutations observed in these 2 families (p.Arg284X and p.Val635ThrfsX12 respectively) altered the constitutive inhibition of NF- κ B [106]. Later, the p.D294E missense mutation of *NLRP12* was identified in another Caucasian family with some affected family members presenting FCAS-like phenotype. Interestingly this mutation affects the ROS production rather than NF- κ B signaling leading to increase IL-1 β production [107]. Very few is known about the treatment of these patients. Anakinra led only to partial clinical improvement and no biological response in the two previously described brothers [108].

3.4. *Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)*

A mutation located in exon 2 of the *MEFV* gene (S242R) is associated with an autosomal dominant disease characterized by early onset of fever episodes associated with arthromyalgia and neutrophilic dermatosis named pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND). Severe acne, pyoderma grangenosum, sterile skin abscesses and neutrophilic small vessel vasculitis have been observed in PAAND patients [109]. S242R mutation interferes with 14-3-3 role of hindering pyrin causing induction of inflammasome assembly. The importance of 14-3-3 role was reinforced by the identification of another mutation, E244K, altering this function and resulting in a PAAND like clinical phenotype with pustular acne, suppurative hidradenitis and neutrophilic panniculitis [110]. PAAND patients have been treated with anakinra which resulted very effective, however, one patient who partially responded to IL-1 inhibition was also successfully treated with anti-TNF α therapy [109,110].

3.5. Autoinflammation and *PLCγ2*-associated antibody deficiency and immune dysregulation (APLAID)

An autosomal dominant inherited mutation of *PLCγ2*, named autoinflammation and *PLCγ2*-associated antibody deficiency and immune dysregulation (APLAID), is responsible for a syndrome with recurrent blistering skin lesions, cellulitis, interstitial pneumonitis, arthralgia, ocular ulceration and erosions, enterocolitis and mild immunodeficiency features such as recurrent sinopulmonary infections and low circulating antibodies (IgM and IgA) [111].

Skin manifestations range from epidermolysis-bullosa-like lesions to erythematous plaques and vesiculo-pustular eruptions; interestingly, high temperature and sun exposure make them worse. Biopsy reveals polymorphic dense infiltrate with neutrophils, eosinophils, histiocytes, and lymphocytes. *PLCγ2* encodes for a constitutively repressed phospholipase; its mutation (p.Ser707Tyr) removes this inhibition with the consequent increase of Ca^{2+} release by the endoplasmic reticulum and enhanced NLRP3 inflammasome activation [112]. So far, reported patients showed a good response to corticosteroids whereas IL-1 blockade did not lead to full disease activity control [111].

3.6. Periodic fever immunodeficiency and thrombocytopenia (PFIT)

This disease was first described in 2 sisters born from related parents of Pakistani origin, who presented with very early onset of recurrent fever episodes (lasting up to 7 days), mucosal ulcerations, thrombocytopenia and elevated acute phase reactants along with hyperferritinemia. Interestingly, both had recurrent invasive infections [113].

The underlying mutation was on WD40 repeat protein 1 (*WDR1*) gene encoding for a protein involved in actin depolymerization. This missense mutation leads to actin accumulation, resulting in pyrin activation and IL-18 release. Similar to what happens in Wiskott-Aldrich syndrome, the cytoskeleton alteration causes impairment of several cell lines including T cells and megakaryocytes [113,114]. Corticosteroids and colchicine were partial effective as well as anakinra, while hematopoietic stem cell transplantation (HSCT) was effective in one case [113].

4. Relopathies/nuclear factor Kappa-B (NFκB) related AIDs

4.1. *NOD2/CARD 15*-associated diseases

Nucleotide-binding oligomerization domain containing 2 (*NOD2*) or caspase recruitment domain-containing protein 15 is a cytosolic protein that binds several PAMPs such as muramyl dipeptide [115]. *NOD2/CARD15* sequence variants are associated with Blau syndrome (BS) and Crohn's disease (CD) (see Table 3) [116,117]. The gain of function mutations are associated with BS and lead to activation of NF-κB signaling even in the absence of any ligands, with activation of proinflammatory transcriptional genes [118]. Autosomal dominant (Blau Syndrome; BS) or *de novo* (early onset sarcoidosis) mutations result in a quite definite clinical phenotype with the classic triad of skin rash, granulomatous uveitis and symmetrical polyarthritis occurring in early childhood [116]. Almost all patients have tenosynovitis along with large joint arthritis, while the involvement of proximal interphalangeal joints leads to camptodactyly. The appearance of the rash in the first year of life may be misleading and often atopic dermatitis and ichthyosis are misdiagnosed. Maculo or micropapular lesions are typical, and sometimes the rash may resemble eczema; biopsy shows noncaseating granulomas. Uveitis is usually the last manifestation in order of appearance and is granulomatous, often involving all ocular cameras configuring a panuveitis framework [116]. According to the severity and type of organ involvement, several immunosuppressants and biologic agents have been used for BS and EOS, however, corticosteroids remain still frequently employed for the management of these patients [119,120].

CD is a fascinating condition on the verge between autoinflammation and autoimmunity [7]. Nowadays the definition of NF-κβ activation

disorder makes autoinflammation prevails [121]. Furthermore, sequence variants of LRRs domain of *NOD2/CARD15* (R702T, G908R and L1007fsinsC) have been identified as susceptible loci predisposing for CD, thus reinforcing its proximity to BS [117].

4.1.1. Most recent developments in *NOD2/CARD 15*-associated diseases

A new disorder associated with *NOD2/CARD15* variants has been recently recognized and named *NOD2*-associated autoinflammatory disease (NAID) also known as Yao syndrome [122]. Genotype study of these patients pointed out the presence of IVS8+158 alone or combined with R702W. NAID is a multisystemic disease presenting in adulthood (around 40 years of age). It is characterized by recurrent fever, constitutional symptoms (fatigue, malaise, weight loss), articular manifestation (arthralgia or non erosive arthritis), skin rash (erythematous patches and plaques) along with gastrointestinal and ocular involvement. More than half of patients have diarrhea and abdominal pain and few may present with noncaseating granulomatous colitis. Dry mouth or dry eyes occurred in more than half of patients and ocular myositis has been reported, as well as chest pain due to either pleuritis or pericarditis [123]. The majority of NAID patients receive corticosteroids or sulfasalazine with good response, however, refractory cases may benefit from biologic agents such as tocilizumab or canakinumab [124].

4.2. Familial pityriasis rubra pilaris/*CARD14*-associated psoriasis

Pityriasis rubra pilaris is characterized by the triad of erythematous plaques (mixed with normal skin), keratotic follicular papules and palmoplantar keratoderma (thick skin in palms and soles). Mutations of gene encoding caspase recruitment domain-containing protein 14 (*CARD14*) have been firstly reported in familial cases with a dominant inheritance pattern and variable penetrance. Later on, *de novo* mutations of *CARD14* with variable penetrance have been also identified [125]. *CARD14* is mainly expressed on keratinocytes and its gain of function mutations lead to activation of the NF-κB pathway fostering skin

Table 4
Overview on interferonopathies.

NAME	MAIN CLINICAL FEATURES	THERAPEUTIC APPROACHES DESCRIBED IN LITERATURE
Aicardi-Goutières Syndrome	Recurrent fever episodes starting in the first month of life; subacute leukoencephalopathy; basal ganglia calcification; Chilblains; livedo reticularis	Ongoing trial on reverse transcriptase inhibitors for AGS *Possible role for JAK/STAT inhibitors
SAVI	Systemic features including fever, anemia, failure to thrive; vasculopathy of the extremities resulting in ulceration and mutilation; livedo reticularis; raynaud phenomenon; lung interstitial disease	*Possible role for anti-IFN-α monoclonal antibodies * for all interferonopathies
PRAAS	JMP Syndrome: joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy Nakajo Nishimura Syndrome: pernio-like lesions, recurrent fever, nodular skin eruption, lipodystrophy of extremities and joint contractures. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE): recurrent fever, purpuric skin lesions, progressive lipodystrophy, atypical facies, failure to thrive	
Singleton-Merten Syndrome	Progressive calcifications of large blood vessels; dental dysplasia (absent in Atypical form); skeletal abnormalities; osteoporosis	

inflammation. Typically skin lesions appear before 3 years of age with a mild lymphocytic infiltrate [126]. Several immunomodulatory agents have been used for the treatment of this condition, recently a patient successfully treated with ustekinumab, an IL-12 and IL-23 blocking agent, has been reported [127].

4.3. Ubiquitinopathies

Ubiquitination defines the destiny of proteins through post-transduction changes starting with ubiquitin chains assembling after proper stimulation via innate immunity receptors. The linear ubiquitin chain assembly complex (LUBAC) assembles linear ubiquitin chains [128]. LUBAC is formed by heme-oxidized IRP2 ubiquitin ligase 1 L (HOIL-1), SHANK-associated RH domain-interacting protein (SHARPIN) and the catalytic subunit HOIL-1L-interacting protein (HOIP) [129,130]; this aggregate contributes to the steadiness of several receptors including TNFR1 and IL-1R [131,132]. According to the type and site of the bond between ubiquitin chains and the target protein, intracellular sensors ultimately determine the destiny of the protein [131,132]. The process by which ubiquitin chains are removed from proteins is named deubiquitination; several enzymes, including A20 and otulin, hydrolyze these bonds. Both ubiquitination and deubiquitination modulate the transcription of proinflammatory cytokines through the NF- κ B pathway, in particularly deubiquitination acts as negative regulator of this path [131, 132].

Defects in ubiquitination and deubiquitination are associated with NF- κ B pathway activation and consequent hyperproduction of proinflammatory cytokines. So far very few patients with these disorders have been identified, thus, available data are poor [131].

4.3.1. Autoinflammation/immunodeficiency associated with mutations in LUBAC proteins

Recently, loss of function mutations of LUBAC proteins have been associated with autoinflammation: homozygous mutation of *HOIP* was found in one patient and compound heterozygosis of *HOIL-1* in three patients, respectively [133,134]. Despite different involved genes, these patients shared several clinical features such as systemic autoinflammation, amylopectin deposition and susceptibility to infections. Patients with *HOIP* mutation present splenomegaly, lymphangiectasia, B and T cells defects [133]; *HOIL* patients have hepatosplenomegaly, enlarged lymph nodes and severe impairment of B cell function [134]. LUBAC complex function resulted defective in all patients regardless of the protein was altered. Interestingly, these mutations act on the NF- κ B pathway in different ways according to cell types. Indeed NF- κ B signaling is downregulated in fibroblasts in response to IL-1 β or TNF- α , while monocytes are hypersensitive to IL-1 β [133,134].

4.3.2. A20 protein haploinsufficiency (HA20)

A20 haploinsufficiency (HA20) results in a wide clinical phenotype with clinical overlapping with Behcet's disease. HA20 is due to heterozygous missense mutations or small frameshift deletions of tumor necrosis factor alpha-induced protein 3 gene (*TNFAIP3*) on chromosome 6 encoding for A20. Therefore, this protein is not sufficiently produced leading to defective deubiquitination and constitutive activation of the NF- κ B pathway as a result of genetic alteration [135].

HA20 shows a female predominance and more than half of reported cases are from Japan. Almost all patients present disease onset during early childhood with oral and genital ulcers, ocular inflammation (particularly anterior uveitis), along with fever spikes and elevated acute phase reactants during flares. Furthermore, polymorphic skin involvement (erythematous papules, folliculitis, skin abscesses), arthritis and bloody diarrhea reflecting underlying ulcerative colitis are common, as well as upper respiratory tract infections.

Autoimmunity features including the presence of antinuclear antibodies and antibodies against thyroid are frequently detected in HA20 patients. Although rarely, cerebral vasculitis and pulmonary embolism

related to vasculitis have been described. Several drugs (colchicine, methotrexate, azathioprine, thalidomide, cyclophosphamide) have been employed in these patients including biologic agents (TNF- α inhibitors, anakinra and tocilizumab) [135–137].

4.3.3. Otulin deficiency (ORAS)

Otulin is a deubiquitinase that hydrolyzes the bonding in position Met1 of ubiquitin chains, therefore it acts as a negative regulator of the NF- κ B pathway [138]. Homozygous loss of function mutations of the *FAM105B* gene on chromosome 5 encoding for otulin causes outline deficiency also known as otulipenia/otulin-related autoinflammatory syndrome (ORAS) [139]. Indeed affected patients overexpress Met1 ubiquitin chains due to otulin deficiency [138]. The disease starts very early, usually within 3 months of age, with prolonged fever episodes, arthritis and diarrhea precluding normal growth along with florid systemic inflammation. Lipodystrophy has been observed in these patients as well as other skin lesions such as pustules, nodules, panniculitis and nonspecific painful erythematous rash [138,139]. Skin biopsy reveals neutrophil infiltrate, small and medium size vasculitis and panniculitis. No clinical or laboratory features of immunodeficiency have been associated with ORAS. TNF- α blocking agents have been used for ORAS treatment with good results, whereas anakinra was partially effective [138,139].

5. Interferonopathies

Type I interferons (IFNs) are pleiotropic cytokines implicated in antiproliferative activities and host defense against viral agents and certain bacteria. Nucleic acid sensors in cytosol play a major role in type I interferonopathies. All nucleated cells express IFN receptors that when activated induce the signal transduction through the JAK/STAT pathway, resulting in the expression of IFN-stimulated genes (ISGs) [140]. Impaired regulation of this complex route is responsible for interferonopathies (see Table 4) [140].

5.1. Aicardi Goutieres Syndrome (AGS)

The neonatal onset of severe encephalopathy, basal ganglia calcifications, hepatic dysfunction, and skin involvement along with elevated acute phase reactants is characteristic of Aicardi Goutieres Syndrome (AGS). This disorder presents many clinical overlaps with transplacental congenital infections, named TORCH (Toxoplasma, Others, Rubella, Cytomegalovirus and Herpes simplex); indeed AGS results from the buildup of nucleic acids misinterpreted as viral/non-self by the innate immune system that leads to type I IFN driven inflammation [141].

AGS is due to defective function of enzymes involved in the regulation of acid nucleic metabolism; loss of function mutations, mainly autosomal recessive, of exonuclease (*TREX1*), ribonuclease (*RNASEH2*), phosphohydrolase (*SAMHD1*) and the dsRNA-specific adenosine deaminase (*ADAR1*), and autosomal dominant gain of function mutations of dsRNA sensor (*IFIH1*) have been identified in AGS patients [140]. Nevertheless, how these mutations lead to AGS is not completely known, although the accumulation of nucleic acids seems to play an important role in the pathogenesis of this condition. The CNS involvement in AGS is characterized by progressive leukoencephalopathy with loss of white matter leading to lifelong disabilities. Over time these patients develop fever episodes, chilblains, livedo reticularis, glaucoma and autoimmunity features with low autoantibodies titers [142].

5.2. STING-associated vasculopathy with onset in infancy (SAVI)

The autosomal dominant or sporadic gain of function mutation of *TMEM173* gene encoding for stimulator of interferon genes (STING) is accountable for a vasculopathy involving skin and lungs along with systemic inflammation known as STING-associated vasculopathy with onset in infancy (SAVI). STING is an adaptor molecule involved in signal

transduction through cGAS leading to hyperactivation of type I IFN pathways [143]. In addition to systemic features (fever, anemia, failure to thrive), SAVI presents painful and mutilating skin lesions of the extremities (loss of toes or fingers is not uncommon); Raynaud phenomenon may be present with nailfold capillary unspecific alteration. Skin biopsies show microthrombotic changes and neutrophilic infiltrate of capillaries.

Interstitial lung disease (ILD) can develop over time, and cough and tachypnea are common; computed tomography shows ground-glass opacities along with other typical features of ILD such as bronchiectasias and septal thickening. SAVI patients may have autoantibodies that may cause misdiagnosis and diagnostic delay; for instance, the detection of antineutrophil cytoplasmic antibodies (cANCA) along with pulmonary and skin involvement in these patients may be misdiagnosed as granulomatosis with polyangiitis [144].

5.3. Proteasome-associated autoinflammatory syndromes (PRAAS)

The defective function of the proteasome is associated with a range of diseases grouped under the term of proteasome-associated autoinflammatory syndromes (PRAAS). Several clinical conditions are included in PRAAS: joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy syndrome (JMP), Nakajo-Nishimura syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) [81].

The proteasome system is the effector of intracellular misfolded protein removal and generates many antigenic peptides recognized by the immune system [145].

It is formed by four rings (two α rings and two β rings) assembled together in a cylindrical shape. Each ring consists of 7 in different α or β protein subunits; β -subunits, once activated by IFN signaling, show active sites for degradation of proteins [146].

Loss of function mutations of immunoproteasome components causes upregulation of the type I IFN pathway. Indeed, mutations of proteasome ring proteins (PSMB8, PSMB4, PSMA3, PSMB9) or of proteins involved in proteasome assembly such as proteasome maturation protein (POMP) have been associated with PRAAS [147]. Despite the identification of causative mutations, the link to IFN stimulation is still a matter of research. Clinical phenotype of PRAAS consists in the early onset of lipodystrophy, joint contractures of extremities, abundant neutrophil infiltrates in perivascular derma resulting in chronic dermatitis ranging from nodular to pernio-like lesions. Periodic fever episodes, failure to thrive, hepatosplenomegaly, abdominal protrusion due to intra-abdominal fat deposition, panniculitis, basal ganglia calcifications, anemia, hypergammaglobulinemia are other common features of PRAAS [140].

5.4. Singleton-Merten Syndrome (SMS)

Singleton-Merten Syndrome (SMS) is due to autosomal dominant gain of function mutation of dsRNA sensors (IFIH1 and RIG-I). It results in hyperactivity of these PRRs that drives to constitutive activation of IFNs [148,149]. Typical SMS, due to mutation of *IFIH1*, consists of progressive calcifications of large blood vessels (i.e. aorta), dental and skeletal abnormalities, and osteoporosis. Less common features are psoriasis, glaucoma and systemic muscle weakness [148]. Atypical SMS was described in patients harboring mutation of *RIG-I* (also known as *DDX58* gene), these patients did not have dental alterations and showed variable expression of glaucoma, aortic calcification, and skeletal abnormalities [149]. Mutations of the gene encoding for the RNA sensor melanoma differentiation-associated protein 5 (MDA5) have been associated with both AGS and SMS phenotypes; interestingly, clinical overlaps of these two interferonopathies have been reported in patients harboring Arg822Gln and Ala489Thr mutations in *IFIH1* gene [150,151].

5.5. Treatment of interferonopathies

Since their discovery, a wide range of immunosuppressive agents has been employed in interferonopathies resulting in limited effects. The blockage of IL-1 and TNF- α is poorly effective, whereas some patients benefited from IL-6 inhibition [152,153].

Since the JAK/STAT pathway is involved in the IFNs signal transduction, JAK inhibitors (baricitinib and tofacitinib) have been tested in patient cells leading to the reduction of ISGs expression [152,154]. Recent researches have pointed out the effectiveness of baricitinib, a JAK1/JAK2 inhibitor, in CANDLE and SAVI patients; its clinical effects were associated with dose-dependent decreases of IFN biomarkers [155, 156]. A phase II study on reverse transcriptase inhibitors in AGS is ongoing (NCT02363452) although initial results seem encouraging [157]. Monoclonal anti IFN- α antibodies are promising drugs for these conditions; these drugs have shown good results in trials on SLE patients [158,159].

5.5.1. Most recent developments in interferonopathies

Recently, 3 patients from 2 unrelated families were reported sharing similar clinical phenotype: neonatal anemia along with several degree of pancytopenia, recurrent periodic fevers (starting between 5 and 7 years of age), membranoproliferative glomerulonephritis (mean age of proteinuria appearance at 8 years), mild neurological involvement (subcortical white matter hyperintensities on T2 weighted imaging of MRI), liver fibrosis, deforming arthropathy and presence of anti-DNA antibodies [160].

A homozygous loss of function mutation of *DNASE2* encoding for DNase II was found in all three patients. DNase II is a lysosomal endonuclease that degrades cytosolic DNA generated by apoptosis of erythroblast nuclei; its defective function leads to nucleic acid residues buildup in the lysosomes of macrophages, thus type I IFN signal is fostered through cytosolic PRRs persistent activation [160].

POMP is crucially involved in assembling of proteasome and its defective function has been related to PRAAS [161]. *De novo* heterozygous POMP truncating mutations have been recently identified in two unrelated patients. These mutations led to defective proteasome function and the POMP-related autoinflammation and immune dysregulation disease (PRAID). PRAID is associated with an early-onset of both immunodeficiency and autoimmunity along with inflammatory neutrophilic dermatosis. Both T and B cells are negatively influenced by this mutation: T cells present altered production of Th1 cytokines (IFN- γ , TNF- α and IL-2) leading to increase susceptibility to infections; B cell maturation is altered towards plasma cell transformation with increased antibody formation, thus explaining the autoimmunity phenotype of PRAID. The presence of combined immunodeficiency limits the JAK inhibitors use in these patients [162].

6. Other monogenic AIDs

6.1. Adenosine deaminase 2 (ADA2) deficiency

Adenosine deaminase 2 (ADA2) deficiency is a monogenic autoinflammatory disease characterized by vasculopathy and hematologic alterations along with mild immunodeficiency features [163]. It is due to homozygous or compound heterozygous loss of function mutations of the *ADA2* gene (formerly known as Cat Eye Syndrome Chromosome Region candidate 1; CERC1) located on chromosome 22 [163]. ADA2 is an enzyme involved in purine catabolism and is expressed in myeloid cells. The pathogenesis of ADA2 deficiency is not completely clear; ADA2 mutations skew macrophage differentiation towards pro-inflammatory activity (M1 subsets) rather than an anti-inflammatory one (M2 subsets) with the result of alteration in vascular integrity [163]. ADA2 acts as a growth factor involved in the proliferation and differentiation of macrophages and promotes proliferation of monocyte-activated CD4⁺ T cells [164]. Furthermore, a prominent interferon signature has been

identified in ADA2 deficient patients [165]. Typically the disease onset is in early childhood with the clinical phenotype of medium and small size vasculitis that often overlaps with polyarteritis nodosa (PAN). Vasculopathy represents the main feature with skin and CNS as the major sites of involvement although gastrointestinal tract, liver and kidney may also be affected. As in other autoinflammatory diseases, recurrent episodes of fever with elevated inflammatory markers are common.

More than half of patients shown neurological involvement, mostly due to lacunar ischemic strokes with MRI showing involvement of deep brain nuclei, brainstem and typical white matter sparing. Immune dysregulation affects principally the humoral arm of the immune system with hypogammaglobulinemia (especially low IgM) as major manifestation, and some patients displaying a complete framework of common variable immunodeficiency (CVID) [166,167]. The hematological involvement varies widely from mild anemia to pancytopenia [168].

Treatment is based on anti-TNF therapies capable both to control inflammatory vasculopathy and to prevent strokes. The use of anti-platelet drugs is still matter of debate, because of the risk of hemorrhagic events [163]. Immune defects benefit of substitutive immunoglobulins therapy, whereas for severe hematological involvement hematopoietic stem cell transplantation (HSCT) can be an option [169].

6.1.1. Most recent developments in ADA2 deficiency

The clinical spectrum of ADA2 deficiency is constantly expanding. A child with a clinical phenotype of splenomegaly, generalized lymphadenopathy along with high levels of inflammatory markers, anemia and hypergammaglobulinemia, resembling a multicentric Castleman disease, was found harboring homozygous mutation of ADA2. Interestingly, tocilizumab leads to prolonged remission also in Castleman disease [170]. Autoimmune lymphoproliferative syndrome (ALPS)-like features have been recently reported in a young girl who successfully responded to anti-TNF α therapies [171]. Two brothers were diagnosed with JIA in childhood, but later on, both developed vasculopathy features and the diagnosis of ADA2 deficiency was made around the age of 40 [172].

Screening for ADA2 deficiency was performed in a cohort of patients with antibody deficiency regardless of the presence of vasculopathy. Eleven patients carrying homozygous or compound heterozygous ADA2 mutations were identified, with a median age at onset of 8 years; some of these patients had just isolated antibody deficiency, whereas almost all patients had low numbers of memory B cells. Interestingly, a significant inverse correlation between CRP and IgG levels was found; thus, the authors of this study postulated that ongoing inflammation leads to worsening of B cell function; furthermore, one patient achieved normalization of IgM levels with anti-TNF α therapy [166]. The identification of ADA2 mutations, either homozygous or compound heterozygous, is the milestone for the diagnosis. Giving the ADA2 deficiency wide clinical spectrum, a rational algorithm driving the decision whether and how to screen for ADA2 mutation has been recently proposed [173]. Very recently two studies have highlighted the role of neutrophils in the pathogenesis of ADA2 deficiency and efficacy of anti-TNF α treatment [174,175].

6.2. Sideroblastic anemia, immunodeficiency, fevers and developmental delay (SIFD)

Sideroblastic anemia, immunodeficiency, fevers and developmental delay (SIFD) is a disorder due to an autosomal recessive loss of function mutation of the *TRNT1* gene. This gene encodes for a polymerase involved in the maturation of cytosolic and mitochondrial transfer RNAs. The disease onset is in early childhood with severe microcytic anemia, fragile hair, fever episodes, neurological involvement ranging from epilepsy to sensorineural hearing loss and development delay and multi-organ failure [176,177]. Increased number of immature B cells causing hypogammaglobulinemia and B cell lymphopenia are characteristics of SIFD [178].

6.3. Deficiency of IL-36 receptor antagonist (DITRA)

Episodes of generalized pustular psoriasis and fever along with systemic inflammation are characteristic of another monogenic AID named deficiency of IL-36 receptor antagonist (DITRA) [179]. Autosomal recessive loss of function mutations of IL-36 receptor antagonist gene results in the decrease of NF- κ B pathway inhibition, leading to inflammation particularly in keratinocytes.

Typically palmoplantar sterile pustular rash and fever episodes develop during infancy and may be accompanied by arthritis and nail dystrophies. Treatment is not codified, and both anakinra and infliximab have been successfully used; moreover promising results have been achieved with ustekinumab and secukinumab [180–183].

7. Autoinflammatory diseases without an identified monogenic etiology

7.1. Systemic-onset juvenile idiopathic arthritis (SoJIA)

Systemic-onset juvenile idiopathic arthritis (SoJIA) is well separated from the other forms of JIA on both clinical and pathogenic basis with several consequences in terms of treatment and outcomes [184]. SoJIA is characterized by the presence of systemic features (high spiking fever, skin rash, lymphadenopathy and serositis) while arthritis may manifest later [184].

Laboratory and clinical features of SoJIA have pointed out the pivotal role of innate immunity, expressed through the aberrant activation of phagocytes leading to overproduction of certain cytokines (IL-1, IL-6, and IL-18) and other inflammatory proteins (e.g. S100A8, S100A9, and S100A12) [184]. Among other severe complications (osteopenia, growth retardation, erosive arthritis, and amyloidosis), a major burden is represented by macrophage activation syndrome [184,185]. The therapy of SoJIA is based upon IL-1 blocking agents similar to several AIDs [186]. IL-6 inhibition is also effective and approved for this indication [187]. Although SoJIA is considered the result of the interaction between polygenic susceptibility and environmental factors, monogenic forms have been described [188]. Indeed an autosomal recessive mutation of the *LACC1/FAMIN* gene has been associated to SoJIA; *LACC1* encodes the enzyme laccase (multicopper oxidoreductase) domain-containing 1 that catalyzes the oxidation of several molecules (polyphenols, aromatic amines and inorganic ions), even if its exact activity is not yet well understood. All patients harboring this particular genotype experienced an early onset (from 1 to 3 years of age) of systemic features along with polyarthritis [189]. Adult onset Still's disease (AOSD) represents the adult counterpart of SoJIA, sharing comparable clinical and pathogenic features; thus, AOSD and SoJIA are more likely the same auto-inflammatory disease with a clinical phenotype that develops at different ages [190].

7.2. Idiopathic pericarditis

Pericarditis may be due to several causes, even though, in developed countries, it is frequently labeled as idiopathic. The underlying mechanism is not completely known although viral agents may act as triggers resulting in activation of the IL-1 pathway [191]. Pericarditis shares several similarities with AIDs. The intermittent pattern of AIDs retraces the spontaneous onset of pericarditis along with their recurrences, moreover many AIDs may present pericarditis as one of their manifestations and others may have pericarditis as only clinical manifestation [192]. The other major similarity regards treatment. NSAIDs represent first line therapy for idiopathic pericarditis, with indomethacin (2 mg/kg daily, divided every 6–12 h) and ibuprofen (30–50 mg/kg daily, divided every 6–8 h) as drugs of choice; on the contrary, steroids should be avoided and, when necessary, employed at the lowest effective dose [193]. Furthermore, colchicine, drug extensively used in FMF patients, has shown to decrease recurrences in patients with idiopathic pericarditis

and it is frequently administered in combination with NSAIDs [193]. The AIRTRIP randomized trial demonstrated the efficacy of anakinra in difficult to treat patients with recurrent pericarditis [194]. More recently canakinumab has been also used in pericarditis [195]. For all these reasons, the role of innate immune in the pathogenesis of idiopathic pericarditis is becoming prominent. Indeed, identified autoantibodies in pericarditis show low titers and low specificity [196,197].

8. Autoinflammatory bone disorders

8.1. Chronic Recurrent Multifocal Osteomyelitis (CRMO)

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare disease occurring in childhood. The onset of clinical manifestations is subtle and variable, mimicking infections or neoplasms; laboratory and radiological features are non-specific. CRMO is progressively being grouped under the term chronic non-bacterial osteomyelitis (CNO) in which sterile osteomyelitis is the shared feature [81]. The adult counterpart of CRMO is the synovitis, acne, pustulosis, hyperostosis and osteitis syndrome (SAPHO) [198]. The majority of CRMO patients do not show a clear genetic background although, susceptible loci have been identified [199]. Furthermore, both CRMO familial cases and other inflammatory diseases (psoriasis, inflammatory bowel disease) amongst relatives have been documented [200]. Even if CRMO pathogenesis is mostly unknown, an aberrant regulation of the innate immune system seems to promote the recurrence of bone inflammation [201]. Indeed, CRMO patients present cytokine disproportion toward a proinflammatory state (high levels of IL-1, IL-6 and TNF- α and low level of IL-10) leading to an alteration in bone metabolism. Mononuclear cells from CRMO patients express an overproduction of proteins such as IL-1 β , ASC and caspase 1 [202]. On the contrary, IL-10 levels are downregulated in these patients; this may lead to inflammatory bone loss through NLRP3 inflammasome [203].

CRMO onset is often insidious, with nonspecific systemic symptoms such as low-grade fever, pain, malaise and fatigue. The disease course is characterized by recurrent episodic attacks that may last few weeks to months, with a self-limited trend [204]. Bone lesions are often multifocal, most frequently located within the long bones (typically femur and tibia) with symmetrical distribution; however, the whole skeleton can be affected. Spinal involvement can lead to debilitating consequences. Laboratory investigations may result negative; a mild elevation of white blood cell count and inflammatory markers can also occur [205]. Imaging is very useful to detect bone lesions. Conventional radiography is not able to identify initial lesions, while it can show the presence of osteolytic lesions with sclerosis (typical of an advanced stage of disease). On the other hand, whole-body MRI (with STIR sequences) is a more sensitive technique that can detect early bone lesions and unrecognized vertebral compressions [206]. Bone biopsy is the most useful technique in order to exclude the presence of neoplastic disease and to document the presence of bone marrow infiltrate. Indeed CRMO is a diagnosis of exclusion established by clinical presentation, imaging studies, and culture-negative bone biopsy [207]. In order to not miss any possible alternative diagnosis, several approaches depending on clinical, radiological and laboratory features have been proposed [205,208]. NSAIDs are recognized as first line therapy for CRMO, with good efficacy on pain relief and bone damage prevention [209]. Bisphosphonates are used in case of spinal involvement as first line therapy or after the failure of NSAIDs when no systemic features are present. A trial on pamidronate in CRMO patients is now in the recruiting phase (NCT02594878). Since TNF- α is involved in bone resorption and osteoclastogenesis, anti-TNF α agents are also not surprisingly very effective in CRMO patients [210]. IL-1 blocking agents are not usually employed.

8.1.1. Most recent developments in CRMO

The etiology of CRMO is still a matter of research; recently an autosomal recessive mutation of the *FBLIM1* gene has been found in a South Asian child with CRMO and psoriasis. *FBLIM1* gene encodes for Filamin-

binding LIM protein 1 (FBLP1) or migfilin that is crucial for bone remodeling; indeed its mutation skewed bone metabolism towards osteoclastogenesis rather than osteoblastogenesis, leading to an increase of bone resorption. After this proband, 96 CRMO patients were screened for *FBLIM1* mutations and another subject was found harboring a compound heterozygosis for this gene [211]. The wide clinical spectrum of CRMO has been highlighted by data coming from the Eurofever registry. The Eurofever cohort consisted of 486 patients (310 female and 176 male), almost all of Caucasian origin, with a mean age at onset of 10 years (range 1–18 years). Interestingly more than one third of patients presented persistent disease activity. Mucocutaneous manifestations were more frequent among adult patients rather than children (41 vs 19% respectively). About half of the cohort showed raised inflammatory markers. Bone biopsy was performed in 60% of the cases showing un-specific inflammatory infiltrate. The majority of the cohort received NSAIDs, of that 9% resulted unresponsive to this treatment. Of note, 4 patients were treated with anakinra, 2 achieved total remission, 1 partial remission and 1 did not respond [212].

As already discussed, CRMO is an exclusion diagnosis, thus having diagnostic biomarkers would be a significant breakthrough. In a recent study, blood samples from 71 patients with CRMO were analyzed and compared with healthy controls and subjects with other diagnoses (leukemia and lymphoma, osteoarticular infections, para-infectious arthritis, and JIA). IL-6 was found particularly elevated in CRMO patients (≥ 17 ng/ml), whereas low levels of the eosinophil attracting chemokine (CCL11/eotaxin) (< 110 ng/ml) were useful to discriminate patients with non allergic inflammatory conditions from healthy controls [213].

Recently the Childhood Arthritis and Rheumatology Research Alliance (CARRA) proposed a consensus for CRMO treatment [214]. After NSAIDs failure following at least 4 weeks of continuous treatment, 3 different treatment plans have been proposed: methotrexate or sulfasalazine, anti-TNF- α agents with or without methotrexate, and bisphosphonates [214].

8.2. Majeed syndrome

Majeed syndrome, also known as LPIN2-CNO, is a monogenic bone autoinflammatory disease characterized by dyserythropoietic anemia with or without a neutrophilic dermatosis (Sweet syndrome or pustulosis) along with sterile osteomyelitis. It is caused by autosomal recessive loss of function mutation of *LPIN2* gene encoding for a phosphatidic acid phosphatase named LIPIN2 and involved in lipid metabolism [215]. Recently, LIPIN2 deficiency in mouse has been related to P2X7R activation leading to alteration of cytosolic K $^{+}$ with the final result of NLRP3 inflammasome hyperactivity [216]. The classic triad (sterile osteomyelitis, anemia and dermatosis) is not always present; indeed several Majeed patients do not develop skin involvement. The onset is very early in life, typically before 2 years of age, and it is often accompanied by fever episodes, failure to thrive and joint contractures [217]. The efficacy of IL-1 blocking agents has indirectly confirmed the autoinflammatory pathogenesis of Majeed syndrome [218].

8.3. Deficiency of IL-1 receptor antagonist (DIRA)

The deficiency of IL-1 receptor antagonist (DIRA) leads to systemic inflammation along with skin and bone involvement, usually without fever. DIRA is caused by recessive mutation of the *IL1RN* gene that codifies for IL-1 receptor antagonist (IL-1RA). Thus, IL-1 β and IL-1 α lack their physiological inhibition resulting in pro-inflammatory imbalance [219].

The onset is usually within the first months of life with pustular lesions along with the increase of inflammatory markers followed by osteitis and periostitis; these patients rarely develop mild fever [219]. Bone involvement is severe with multiple osteolytic lesions and periostitis, prevalently over long bones (proximal femur) and vertebral bodies [220]; biopsy shows sterile neutrophilic osteomyelitis, fibrosis and

sclerosis [219]. Classically imaging pattern of DIRA includes diffuse osteolytic lesions, widening of anterior rib ends and periostitis of long bones [219,220]. Moreover, osteolytic lesions of the scalp, widening of the clavicles and heterotopic ossification of the proximal femurs have been described [219]. DIRA patients respond very well to exogenous IL-1RA, anakinra [219].

8.4. Cherubism

The development of osteolytic lesions of mandibles and the following fibrotic dysplastic soft tissues overgrowth within these lesions confer typical puffy cheeks face to patients with cherubism. This disease is due to heterozygous missense mutations of the SH3 binding protein 2 (SH3BP2) gene with variable penetrance and expressivity amongst members of the same families; moreover, sporadic mutations are not uncommon [221]. Interestingly, similar lesions of jaws can be detected in patients with other genetic diseases such as Noonan syndrome and neurofibromatosis [222,223]. Recently, the name “SH3BP2 deficiency with multilocular cystic disease of the mandibles (SDCM)” has been proposed instead of the biblical “cherubism” in order to reinforce both genetic and clinical disease features [81]. SH3BP2 is a protein that binds several other proteins with different functions in both innate and adaptive immunity cells [224]; furthermore, SH3BP2 plays a crucial role in bone remodeling and its mutations are related to hyperfunction of osteoclast resulting in an increase of bone resorption [225]. The course of the disease is characterized by the early development of osteolytic lesion (around 2–5 years of age) of mandibles followed by reparative mechanisms with activation of fibroblasts and osteoblasts [226]. Although facial involvement is the predominant feature, lesions of ribs may be detected [226]. Cherubism treatment is driven by anecdotal reports in which adalimumab and bisphosphonates have been used, but not always with satisfactory effects [227,228].

9. Conclusions

The autoinflammatory field is exponentially expanding, and a better knowledge of the pathogenesis of such diseases will lead to the identification of new therapeutic targets. The advances in AIDs have led to new insights into immune system understanding; indeed the boundaries between autoimmunity and autoinflammation are fading and both may be simultaneously present [7]. Advances in technology will certainly lead to the identification of new genes and new syndromes, with important consequences both in terms of patient care and of knowledge of immunological mechanisms.

Conflict of interest

None.

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