Lung involvement in monogenic interferonopathies

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Progressive severe lung impairment may occur clinically hidden during monogenic interferonopathies. Pulmonologists should be aware of the main patterns of presentation in order to allow prompt diagnosis and initiate targeted therapeutic strategy. https://bit.ly/2UeAeLn

ABSTRACT Monogenic type I interferonopathies are inherited heterogeneous disorders characterised by early onset of systemic and organ specific inflammation, associated with constitutive activation of type I interferons (IFNs). In the last few years, several clinical reports identified the lung as one of the key target organs of IFN-mediated inflammation. The major pulmonary patterns described comprise children's interstitial lung diseases (including diffuse alveolar haemorrhages) and pulmonary arterial hypertension but diagnosis may be challenging. Respiratory symptoms may be either mild or absent at disease onset and variably associated with systemic or organ specific inflammation. In addition, associated extrapulmonary clinical features may precede lung function impairment by years, and patients may display severe/endstage lung involvement, although this may be clinically hidden during the long-term disease course. Conversely, a few cases of atypical severe lung involvement at onset have been reported without clinically manifested extrapulmonary signs. Hence, a multidisciplinary approach involving pulmonologists, paediatricians and rheumatologists should always be considered when a monogenic interferonopathy is suspected. Pulmonologists should also be aware of the main pattern of presentation to allow prompt diagnosis and a targeted therapeutic strategy. In this regard, promising therapeutic strategies rely on Janus kinase-1/2 (JAK-1/2) inhibitors blocking the type I IFN-mediated intracellular cascade.

Introduction

Monogenic type I interferonopathies comprise a group of inherited heterogeneous disorders characterised by early onset of systemic and organ specific inflammation associated with constitutive activation of type I

interferons (IFNs) [1–8]. Since their initial description in 2011 [1], type I interferonopathies have drawn the attention of many parts of the scientific community, and involved expanding medical fields as the understanding of these entities has grown. The concept of the potentially harmful effects of an unrestrained IFN pathway was first outlined by GRESSER *et al.* [9] in rodents. Subsequently, LEBON *et al.* [10] reported increased synthesis of IFN-α in children with Aicardi–Goutières syndrome (AGS), and defined the first Mendelian disease associated with enhanced type I IFN activation. In 2003, CROW *et al.* [11] assumed the existence of IFN-α hyperactivity as a common pathological keystone accounting for the overlapping features observed among apparently disparate human diseases, *i.e.* congenital HIV-1 infection, Mendelian encephalopathy AGS and autoimmune systemic lupus erythematosus (SLE). Growing insights were also derived from investigating the AGS molecular foundation [12], dissecting the type I IFN upregulation in monogenic forms of SLE and exploiting nucleic acid metabolism-driven IFN induction. In 2011, CROW *et al.* [1] described this new group of Mendelian disorders, termed interferonopathies, and defined them as novel inborn errors of immunity characterised by enhanced type I IFN signalling as a pathogenic keyplayer rather than a simple biomarker. Since then, the knowledge of the molecular mechanisms underlying these entities has widened exponentially leading to a "position framework" for type I IFN-mediated monogenic inflammation [2], representing the counterpart of other genetically determined immune signalling disorders, such as primary immunodeficiency [13] and monogenic auto-inflammation [14].

In the past few years, the list of putative monogenic interferonopathies has broadened as new molecular mechanisms and associated clinical phenotypes have been described [8, 15]. Type I IFN-driven inflammation may target a wide range of tissues and organs, including the lungs. A predominant auto-inflammatory or auto-immune phenotype may occur, respectively, according to the underlying signalling mainly employed (*i.e.* IFN-driven engagement of innate rather than adaptive immune responses) [15]. In the light of this concept, type I interferonopathies have been proposed to be part of the continuum model of self-directed immune disorders in which diseases rely on an auto-inflammatory-auto-immune spectrum. Nevertheless, despite growing evidence pointing to unleashed type I IFN signalling as the core of the so-called interferonopathies, a causal relationship to disease pathogenesis is still largely under debate [8].

Disease mechanisms of type I interferonopathies

The type I IFNs were originally described in 1957 as soluble molecules produced by cells in response to inactivated influenza virus exposure [16]. Once released, those cytokines were demonstrated to be capable of interfering with viral replication and infection onset. Since then, type I IFNs have been widely recognised as the first line of defence, empowering the host to counteract pathogen invasion by inducing a sustained antiviral inflammatory state and antiproliferative activity [5]. In order to achieve efficient immune defence that avoids exaggerated inflammation once the pathogen has been cleared, cells are equipped with timely switch-on/off intracellular machinery (figures 1 and 2). In the past few years, the identification of monogenic conditions displaying type I IFN upregulation and presenting with overlapping clinical pictures has provided invaluable insights on the multifaceted mechanisms that tightly regulate type I IFN production [3, 6, 8].

Although a prompt stimulation of type I IFN is crucial to overcome viral infection, either inappropriate activation (*e.g.* triggered by self-nucleic acids) or impaired negative regulation of the type I IFN system may give rise to interferonopathies (figure 2). The current putative disease model of such entities is based on type I IFN pathway aberrant activation in response to either: 1) an excessive burden of nucleic acids derived from endogenous retro-elements; or 2) constitutive induction of nucleic acid sensors/mediators, leading to a nucleic acid-drive inflammation. Of note, the burden of nucleic acids may originate from either disruption in the sensing machinery or pattern recognition receptor (PRR) downstream mediators, as well as impairment of their processing, metabolism (including autophagy) and repair. Furthermore, aberrancies in the proteasome components have been proposed to induce type I IFN signalling through an indirect effect upon nucleic acid species processing (figure 2).

It is conceivable that for disruption in any driving step of the type I IFN system, homeostasis may account for type I IFN overproduction (figure 2). Whether or not the observed type I IFN enhanced signalling is actually the driving player or is an epiphenomenon is still highly debated [8]. In the past few years, several inborn monogenic errors affecting key components of the type I IFN machinery have been reported [17–92]. These clinical entities relate to a breakdown of self/nonself discrimination, involving mutant genotypes targeting molecules playing direct or indirect roles in nucleic acid signalling and IFN-driven inflammation. However, despite compelling data linking enhanced type I IFN signalling to clinical phenotypes, definitive evidence supporting the causal relationships to pathogenesis is still lacking [8]. Nevertheless, any diseases consistently associated with increased type I IFN activity underline the biological link between the observed disorder and type I IFN homeostasis disruption. The clinical
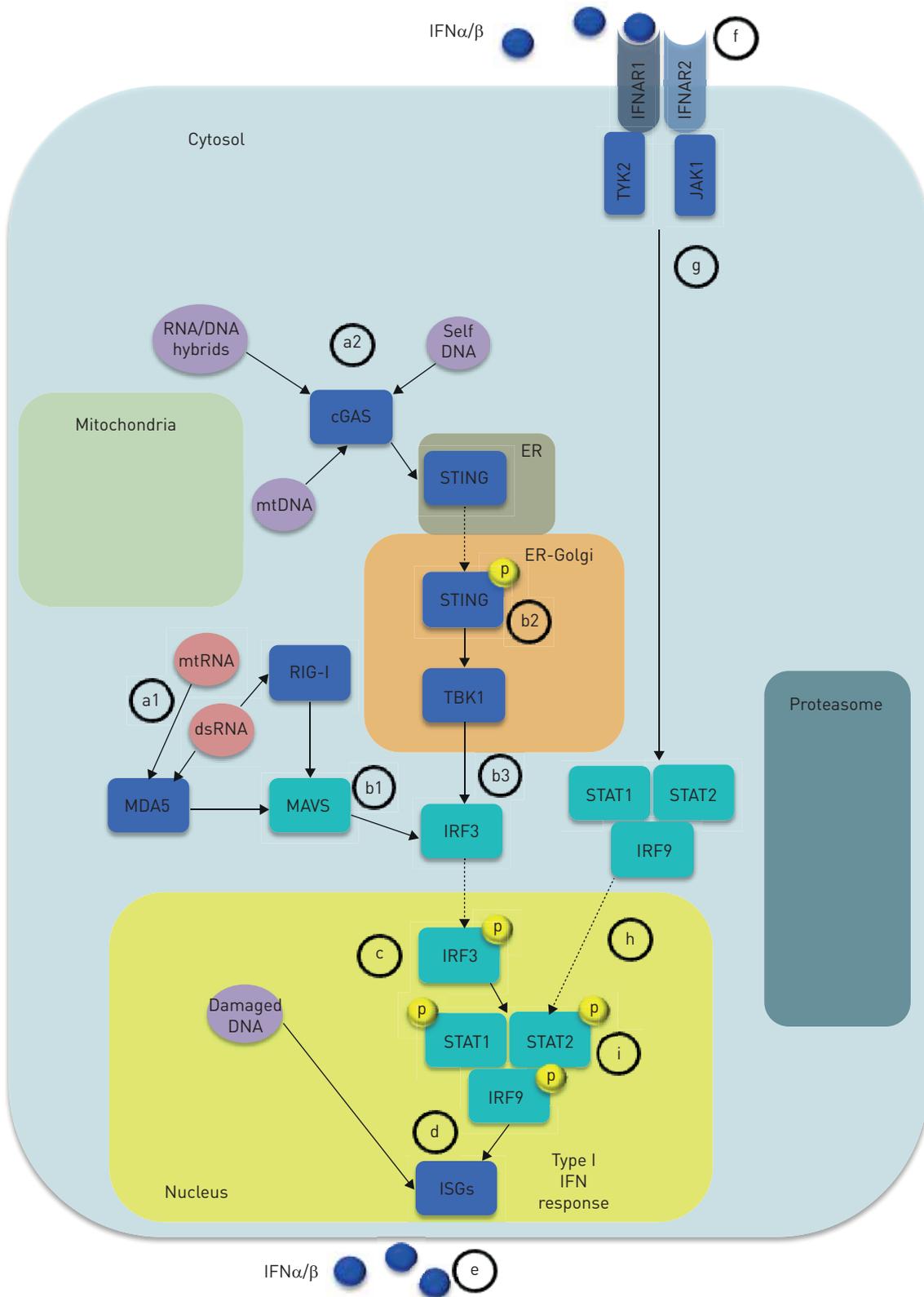
FIGURE 1 Type I interferon (IFN) response. Any nuclear cell is capable of producing type I IFNs in response to viral-derived or endogenous nucleic acids, sensed by distinct cytosolic PPRs, that signal through cytosolic adapters and downstream signals causing activation of IRFs. IRFs translocate to the nucleus and induce ISG expression resulting in type I IFN response and IFN production. a1) Detection of cytosolic dsRNA and mtRNA largely relies on members of the RLR family including MDA5 (also known as IFN-induced helicase C domain containing protein 1, IFIH1) and RIG-I. b1) MDA5 and RIG-I mediate RNA sensing through the cytosolic adapter MAVS/IPS1. Thus, upon engaging nucleic acids, RLRs undergo conformational changes thereby allowing interaction with their adaptor proteins leading to activation of IRFs that c) translocate to the nucleus thus inducing d) IFNαβ

transcription. Less defined is the DNA sensing machinery. a2) Cytoplasmic dsDNA seems to interact with cGAS, leading to the production of cGAMP, which eventually engages the adapter molecule STING (also known as TMEM173) STING, located in the ER. b2) Once activated, STING translocates to the ER–Golgi compartment, where the signal is propagated through the phosphorylation of the TBK1. b3) Finally, TBK1 leads to c) IRF-3 activation that d) induces type I IFN response following IRF-3 nuclear translocation. Once released, e) type I IFNs (blue circles) may act *via* autocrine/paracrine manner f) by binding a single heterodimeric type I IFN transmembrane receptor composed of the subunits IFNAR1 and IFNAR2. Upon engaging one of the IFNR subunits, type I IFNs cause dimerisation of IFNAR1 and IFNAR2, leading to g) activation of the JAKs: TYK2 and JAK-1. Activated TYK2 and JAK1 h) drive the phosphorylation and subsequent translocation to the cell nucleus of the STAT family members (*i.e.* STAT1 and STAT2) and IRF9, resulting in formation of STAT1-STAT2-IRF9 ternary complex ISGF3. The final outcome is type I IFN response refuelling, consisting of ISG expression and IFN production. cGAS: cyclic GMP-AMP synthase; dsDNA: double-stranded DNA; ER: endothelial reticulum; IFNAR1: IFNα receptor-1; IFNAR2: IFNα receptor-2; ISG: IFN stimulated gene; IPS1: interferon-β promoter stimulator 1; IRF: IFN regulatory factor; JAK-1: Janus kinase-1; JAK: Janus kinase; MAVS: mitochondrial antiviral signalling; MDA5: melanoma differentiation-associated protein 5; mtDNA: mitochondrial DNA; mtRNA: mitochondrial RNA; PPR: pattern recognition receptor; RIG-I: retinoic acid-inducible gene I; RLR: RIG-I-like receptors; STAT: signal trasducer activator of transcription; STING: stimulator of interferon genes; TBK1, TANK-binding kinase 1; TYK2: tyrosine-protein kinase 2.

spectrum of these entities is extremely heterogeneous. Furthermore, the number of clinical pictures is increasing within the context of known genotypes. Here, we provide an overview of the currently known main patterns of presentation featuring monogenic interferonopathies (supplementary table 1).

Lung involvement in monogenic interferonopathies: patterns of presentation

In the last few years, several clinical reports have identified the lung as one of the key target organs of IFN-mediated inflammation. Pulmonary involvement may occur as a major clinical feature overlapping different genotypes associated with type I IFN-signalling disruption. Respiratory symptoms may be either mild or absent at disease onset and variably associated with systemic or organ specific inflammation (*e.g.* skin, central nervous system, vascular and gastrointestinal systems). While signs of ongoing systemic inflammation are usually present, associated extrapulmonary clinical features may precede lung function impairment by years. Thus, patients may display functional, radiological or histological signs of severe/ endstage lung involvement, although these may be clinically hidden during long-term disease course. Conversely, a few cases of monogenic interferonopathies with atypical onset characterised by major lung involvement have been reported without clinically manifested extrapulmonary signs. To date, two major clinical patterns of lung involvement have been described during monogenic interferonopathies: 1) interstitial lung disease (ILD), including diffuse alveolar haemorrhage (DAH); and 2) pulmonary arterial hypertension (PAH) (table 1 and figure 3). However, advances in type I IFN signalling and its impact on targeted organs indicate other potentially related clinical pictures (*e.g.* bronchiectasis in STAT1), but further investigation is needed to confirm the actual clinical significance.

ILD

ILD is recognised as the major pulmonary phenotype occurring during monogenic interferonopathy. To date, the ILD spectrum has been variably reported in STING (stimulator of interferon genes)-associated vasculopathy with onset in infancy (SAVI), chronic atypical dermatosis with lipodystrophy and elevated temperatures (CANDLE) and coatomer protein complex, subunit-α (COPA) syndrome (table 1).

ILD in SAVI

SAVI is an auto-inflammatory disease caused by a mutation in *TMEM173* (encoding STING protein) and clinically characterised by systemic and peripheral vessel inflammation leading to distal tissue damage and cutaneous vasculopathy [15, 32, 93–101, 118–120] (table 1). In addition to persistent elevation of inflammatory markers, laboratory findings often include antinuclear antibodies (ANA) positivity and raised IgG and IgA. Since its initial description, pulmonary involvement has been a major clinical feature of SAVI [32]. All six patients described presented in early infancy with systemic inflammation and violaceous lesions of fingers, toes, cheeks and ears, eventually leading to acral necrosis and telangiectasia in most of the patients. Two patients presented with isolated tachypnea in the first weeks of life, and later developed typical cutaneous and systemic inflammation. Lung biopsies unveiled scattered mixed lymphocytic inflammatory infiltrate, interstitial fibrosis and emphysematous changes. Overall, five out of six SAVI patients displayed evidence of ILD, but two of them had no history of respiratory symptoms. Death from pulmonary complications and secondary infection occurred in other two patients. Autopsy performed in one of them demonstrated widespread vasculopathy of systemic and pulmonary vasculature [32].

There is variable clinical expression even in the presence of the same genotype [15, 62, 93–101, 118–120]. To date, total 30 patients with inherited *TMEM173* gain-of-function mutations in variable ethnic backgrounds (*e.g.* mixed European, Japanese/northern European, Algerian, Caribbean, Hazaras, Turkish) have been described in 12 published works consisting of single case reports or small cohort studies [15, 93–101, 118–120].
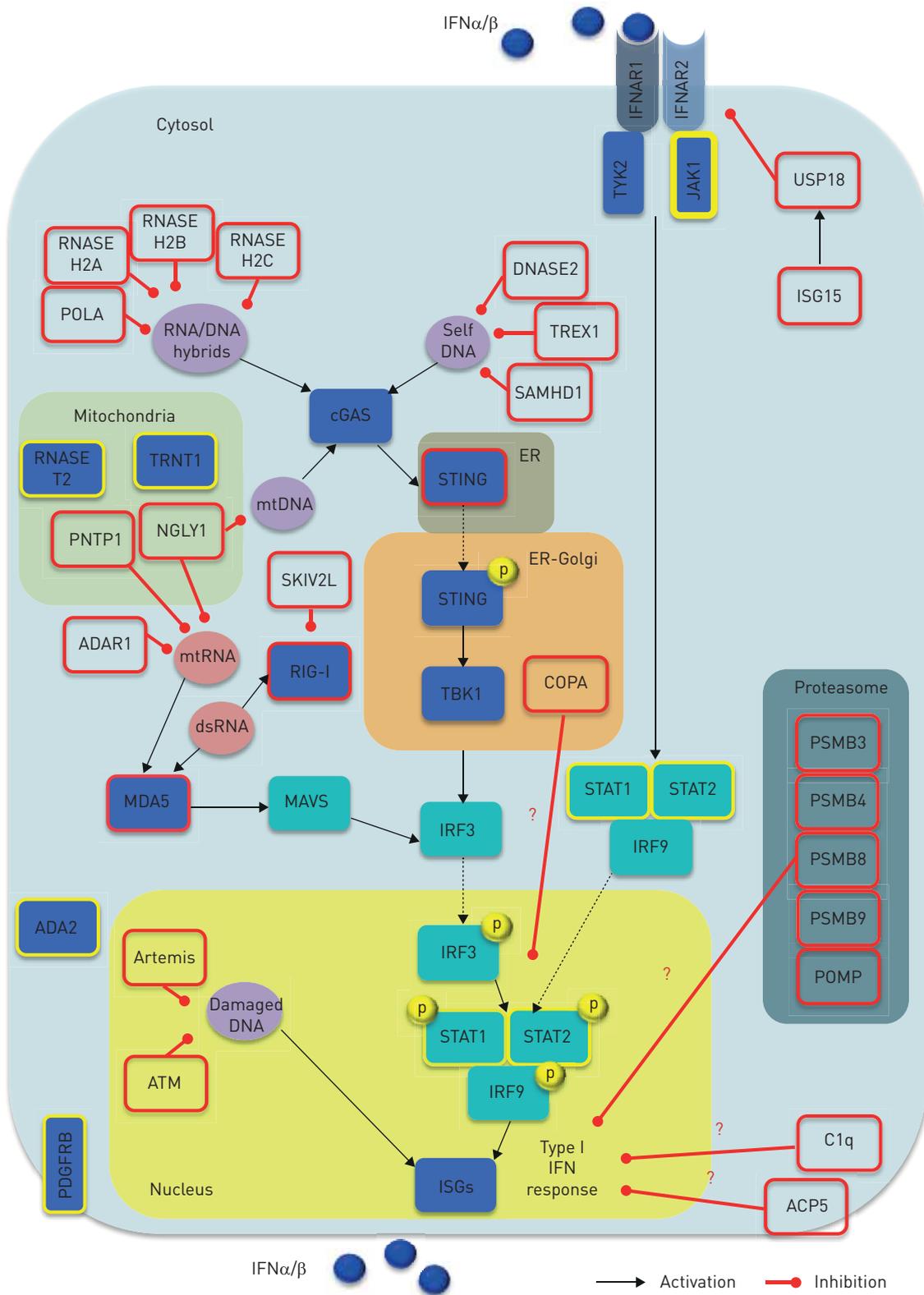
FIGURE 2 Type I interferon (IFN) activity regulation and monogenic interferonopathies. Both inappropriate activation (*e.g.* triggered by self-nucleic acids) and impaired negative regulation of the type I IFN system can give rise to interferonopathies (red border boxes). Nucleic acid-driven inflammation may originate either from disruption in the sensing machinery or PPR downstream mediators, as well as impairment of their processing, metabolism (including autophagy) and repair. In turn, aberrant activity of deoxyribonuclease, ribonuclease, DNA polymerase, RNA helicase, RNA editing machinery, polynucleotide phosphorylase, N-deglycosylation, dsDNA break repairs and ER-localised UPR may account for overproduction of type I IFNs. Furthermore, aberrancies in the proteasome component have been proposed to induce type I IFN signalling through indirect effects upon nucleic acid species processing. Overall, aberrant type I IFN enhancement may be due to either: 1) abnormal stimulation

(*e.g.* increased accumulation or change in composition of endogenous nucleic acids); 2) aberrant sensing (*e.g.* constitutive activation or enhanced sensitivity of PPRs, leading to a change in threshold at which endogenous nucleic acids are sensed); 3) perpetuated activation (*e.g.* increased sensitivity or constitutive activation of IFN-inducing mediators other than PPRs); or 4) impaired negative regulation (*e.g.* unrestrained signalling due to defective negative feedback). A key negative regulator of this loop is represented by the ISG15, which causes induction of USP18 that, in turn, inhibits IFNAR2 activity, thus providing negative feedback to restrain an appropriate type I IFN pathway activity. Genes causing monogenic interferonopathies are depicted by red border boxes. Red question marks indicate unknown mechanisms. Yellow border boxes indicate genes suggested to cause type I IFN signalling aberrancies, but putative mechanisms are provisional. Black arrows indicate activation; red lines address inhibitory activity. ACP5: acid phosphatase 5; ADA2: adenosine deaminase 2; ADAR1: adenosine deaminase, RNA-specific, 1; ATM: ataxia-telangiectasia mutated gene; C1q: complement component C1Q; cGAS: cyclic GMP-AMP synthase; COPA: coatomer protein complex, subunit-α; dsRNA: double-stranded RNA; ER: endothelial reticulum; IFNAR1: IFNα receptor-1; IFNAR2: IFNα receptor-2; ISG: IFN stimulated gene; IRF: IFN regulatory factor; JAK-1: Janus kinase-1; JAKs: Janus kinases; MAVS: mitochondrial antiviral signalling; MDA5: melanoma differentiation-associated protein 5; mtRNA: mitochondrial RNA; NGLY1: N-glycanase 1; PDGFRB: platelet-derived growth factor receptor β; PNTP1: polyribonucleotide nucleotidyltransferase 1; POLA: POLA DNA polymerase-α; POMP: proteasome maturation protein; PSMB: proteasome subunit β; RIG-I: retinoic acid-inducible gene I; SKIV2L: superkiller viralicidic activity 2-like alias SK12 like RNA helicase; STAT: signal trasducer activator of transcription; STING: stimulator of interferon genes; TBK1, TANK-binding kinase 1; TRNT1: tRNA nucleotidyl transferase 1; TYK2: tyrosine-protein kinase 2; UPR: unfolded protein response; USP18: ubiquitin-specific peptidase 18.

Age of disease onset varies from neonatal to infancy. However, some patients with onset in adulthood have been reported. Despite signs of systemic inflammation and failure to thrive being essentially constant, associated clinical symptoms at onset ranged from typical cutaneous vasculopathy to less common clinical pictures such as lupus-like features with arthritis [93], symptoms mimicking childhood granulomatosis with polyangiitis [93], erythematosus-infiltrated skin lesions with pustular evolution followed by scarring, chilblains, and severe nail dystrophy [105] or isolated tachypnea [32, 95]. Mild respiratory symptoms (*e.g.* tachypnea, chronic cough, moderate distress associated with intermittent fever, recurrent bronchospasm, digital clubbing) often arose in the first months of life or preschool age, but were underestimated for a long time. Conversely, a few cases (two familial and one sporadic) of atypical onset characterised by severe pulmonary fibrosis as the first major manifestation have been reported without clinically manifested extrapulmonary signs [96].

Additional rare associated manifestations occurring during disease history included granulomatous hepatitis [98] and mild renal involvement (*i.e.* microscopic haematuria and mild proteinuria) with hypertension [101] reported in two patients. In two cases, given the history of intrauterine growth retardation, failure to thrive, early onset of recurrent bacterial respiratory infections, and severe septicaemia [98] or early-onset recurrent low-grade fever, dermatitis and diarrhoea [101], immunodeficiency was initially suspected and ruled out. Given the rarity of the disorder and the extreme variability of its onset and disease history, diagnosis was always reached after years/decades since the clinical onset, often facilitated by the occurrence of typical onset and definitive diagnosis in a family member or, sometime, *post mortem* pathology findings. When assessed (nine out of 28), the blood IFN signature (*i.e.* evaluation of increased expression of IFN stimulated genes (ISGs whose transcription is induced by IFN) was consistently positive, suggesting type I IFN pathway activation [93, 96, 100, 101]. Variants in pulmonary fibrosis causing genes (*i.e.* SFTPC, SFTPB, ABCA3, TERT, TERC and NKX-2) were analysed in two familial cases [96] and turned out negative.

Because of the variable presentation, pulmonary function tests (PFTs) were not routinely performed. However, data available from seven patients demonstrated a predominant restrictive or mixed pattern with reduced diffusing capacity for carbon monoxide (D_{LCO}) [96, 100, 101]. When obtained, bronchoalveolar lavage fluid demonstrated inflammatory infiltrate with large amount of lymphocytes or pattern consistent with neutrophilic alveolitis [93]. Given the occurrence of pulmonary manifestations during the disease course, most of the patients eventually underwent chest computed tomography (CT). Data available from eight patients [93, 96–98] variably demonstrated diffuse ground glass and reticular opacity [93, 98], honeycombing/cysts with ground glass areas [96], hilar and paratracheal lymphadenopathy, lung fibrosis and emphysema [96], ground glass with lung fibrosis [97], focal thickening of the interlobular septa with areas of ground-glass opacities with predominant subpleural distribution [101].

Overall, 24 out of 30 SAVI patients had disease courses characterised by ILD, in one case associated with secondary PAH [94]. Thus, lung biopsy was eventually performed in the majority of the patients, and variably showed: macrophage alveolitis, follicular hyperplasia and interstitial fibrosis [118]; neutrophils and macrophages within chronic alveolar and interstitial inflammation with following progressive fibrosis and associated PAH [94]; active inflammation with type 2 pneumocyte hyperplasia and lymphocyte infiltrate [95]; multiple pulmonary nodules in central alveolar peribronchiolar area, including lymphocytic inflammatory infiltrate forming aggregates with associated fibrosis without vasculitis [96]; bronchiectasis associated with lymphoid infiltrate and interstitial fibrosis [96], additional examination with electron microscopy performed in one case [95] unveiled endothelial tubureticular inclusions, which were suggestive for type 1 IFN excess. Sudden worsening of pulmonary functions with manifested evidence of ILD and endstage pulmonary fibrosis was frequently described while ILD-associated PAH was reported in one case [66]. All the patients had disease activity poorly controlled by ongoing immunosuppressant therapies, and in a few cases, lung disease required

TABLE 1 Known pulmonary features of recognised monogenic interferonopathies

Pulmonary features	IFNopathy (OMIM#)	Inheritance	Gene (location)	Protein function	Putative disease mechanism	Mutation effect	Clinical picture	[Reference]
ILD/PAH	SAVI (615934)	AD	*TMEM173* (5q31.2)	Cytosolic DNA signal transduction	DNA sensing	GOF leading to constitutive activation of sensitivity to cytosolic nucleic acids	Systemic and peripheral vessel inflammation, cutaneous vasculopathy (fingers, toes, cheeks and ears), distal tissue damage, nasal septum perforation, telangiectasia, ILD, DAH	[15, 32, 61, 63, 66, 93–103]
ILD/PAH	CANDLE/PRASS (256040, 177045, 602177 176843 613386)	AR	*PSMB8* (6p21.32), *PSMB9* (6p21.32), *PSMB4* (1q21.3), *PSMA3* (14q23.1), *POMP* (13q12.3	Proteasome	Proteasome	LOF causing proteasomal dysfunction leading to increased IFN signalling through an unknown mechanism	Recurrent fever, severe growth retardation, violaceous periorbital changes, JMP, mild lymphocytic meningitis, headache, basal ganglia calcifications, ILD, non-erosive synovitis, arthralgia, myositis, recurrent infections, cytopenias, systemic hypertension, dyslipidaemia, elevated acute phase reactants and hypergammaglobulinaemia, joint contractures, muscular atrophy, microcytic anaemia and JMP, Japanese auto-inflammatory syndrome with lipodystrophy, Nakajo–Nishimura syndrome with nodular erythema, elongated and thickened fingers and emaciation, orofacial and dental abnormalities	[65–82, 104]
ILD/DAH	COPA (601924)	DN (dominant)	*COPA* (1q23.2)	Vesicle transport	ER–Golgi	Unclear	Inflammatory arthritis, ILD with alveolar haemorrhages, PAH, glomerulonefritis	[65, 105–115]
PAH	AGS1 (225750)	AR or DN (AD?)	*TREX1* (3p21.31)	Deoxyribonuclease	DNA sensing	LOF leading to increased DNA sensing	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[10, 17–19, 116]
PAH	AGS7 (615846)	AD	*MDA5/ IFIH1* (2q24.2)	dsRNA sensing	RNA sensing	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[37, 116]
PAH	DNaseII deficiency (126350)	AR	*DNASE2* (19p13.13)	Deoxyribonuclease	DNA sensing	LOF leading to constitutive activation of sensitivity to cytosolic nucleic acids	Severe neonatal anaemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy and increased anti-DNA antibodies	[34, 117]
ARDS	USP18 deficiency 617397	AR	*USP18* (22q11.21)	ISG transcription inhibition	ISG transcription inhibition	LOF in molecules responsible for limiting IFNAR1/2 signalling, leading to uncontrolled ISG production	Pseudo-TORCH syndrome two with hydrocephalus, necrotising cellulitis, systemic inflammation and respiratory failure	[56]

ILD, DAH and PAH as major patterns of lung manifestations variably observed the following monogenic interferonopathies: SAVI, CANDLE/ PRAAS syndrome, COPA syndrome, AGS-1, AGS7 and DNAse II deficiency. Acute respiratory distress syndrome (ARDS) was recently reported in inherited USP18 deficiency. IFN: interferonopathy; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SAVI: STING-associated vasculopathy with onset in infancy; STING: stimulator of interferon genes; AD: autosomal dominant; GOF: gain-of-function; DAH: diffuse alveolar haemorrhage; CANDLE: chronic atypical dermatosis with lipodystrophy and elevated temperatures; PRASS: proteasome-associated auto-inflammatory syndrome; AR: autosomal recessive; LOF: loss-of-function; JMP: panniculitis-induced lipodystrophy; DN: dominant; COPA: coatomer protein complex, subunit-α; ER: endothelial reticulum; AGS: Aicardi–Goutières syndrome; dsRNA: double-stranded RNA; USP: ubiquitin-specific peptidase; ISG: IFN stimulated gene.
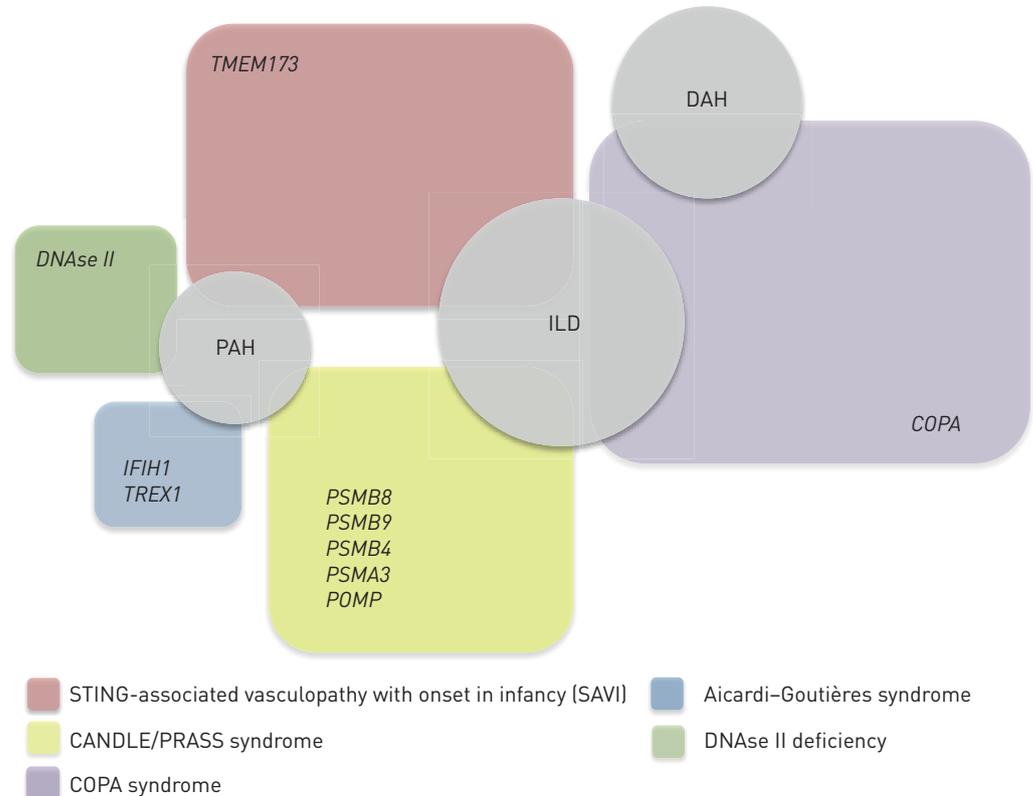
FIGURE 3 Patterns of lung involvement in monogenic interferonopathies. interstitial lung disease (ILD), diffuse alveolar haemorrhage (DAH) and pulmonary arterial hypertension (PAH) as major patterns of lung manifestation in monogenic interferonopathies. SAVI, COPA, Aicardi–Goutières syndrome, DNAse II deficiency and CANDLE/PRASS are depicted by specific coloured boxes, listing putative genes so far identified in patients displaying severe pulmonary manifestation during monogenic interferonopathies. CANDLE: chronic atypical dermatosis with lipodystrophy and elevated temperatures; COPA: coatomer protein complex, subunit-α; PRASS: proteasome-associated auto-inflammatory syndrome; SAVI: STING-associated vasculopathy with onset in infancy; STING: stimulator of interferon genes.

patients to be listed for early lung transplant [32, 96]. Regardless the ongoing therapeutic strategies, death for pulmonary complications with secondary infection or respiratory insufficiency, and multi-organ failure following lung transplant have been described [32, 96, 99].

ILD in CANDLE syndrome
CANDLE syndrome is an auto-inflammatory disorder caused by autosomal recessive loss-of-function mutations in the proteasome subunit beta type 8 (*PSMB8*) [15, 66–68]. Following its initial description, it has become evident that loss-of-function *PSMB8* variants may account for several distinct conditions (table 1), and similar clinical disorders have been related to mutation of other components of the proteasome (*i.e. PSMB9, PSMB4, PSMA3, POMP*) [15, 69–74]. Hence, CANDLE syndrome is now considered to be part of the wider spectrum defined proteasome-associated auto-inflammatory syndrome (PRASS) [65, 79]. Usually, CANDLE/PRASS syndrome clinical features variably include recurrent fever, severe growth retardation, violaceous periorbital changes, panniculitis-induced lipodystrophy, mild lymphocytic meningitis, headache, basal ganglia calcifications, ILD, nonerosive synovitis, arthralgia, myositis, recurrent infections, cytopenias, systemic hypertension, dyslipidaemia, elevated acute phase reactants and hypergammaglobulinaemia (table 1). CANDLE syndrome was first described in four Spanish/Hispanic patients [66]. One of the four subjects displayed ILD but further clinical information on pulmonary pattern is lacking. This patient was treated with a variety of anti-inflammatory and immunosuppressive therapies but the disease progressed with sudden death at 14 years of age. Cause of death was unclear. The patient's family history was unremarkable until the age of 12 years, when her newborn sister manifested similar cutaneous manifestation without lung involvement. Subsequently, the five CANDLE syndrome patients clinically reported [66, 67] were genetically screened [68]. *PSMB8* pathogenic variants were then identified in seven out of eight subjects with clinical presentations consistent with CANDLE syndrome and disease onset by 6 months of age. Beside the patient already

described, a 5 year-old American/Caucasian with CANDLE syndrome also displayed lung involvement, consisting of an organising pneumonia (OP)-like pattern. In a review paper [15], an additional CANDLE syndrome patient previously unpublished and affected by interstitial pneumonitis was also reported. Overall, ILD may rarely occur in CANDLE/PRASS [15, 79]. However, subclinical pulmonary involvement was not routinely investigated, and thus cannot be definitely excluded [15, 65–82].

ILD and alveolar haemorrhages in COPA syndrome

ILD represents a major clinical manifestation in COPA syndrome. COPA syndrome is due to mutations in the *COPA* gene, which encodes the α-subunit of the coatomer protein complex (COPI), involved in transiting molecular cargo from the Golgi to the endoplasmic reticulum [61, 105]. Despite the fact that the encoded protein is ubiquitously expressed, this syndrome typically targets joints, lungs and, to a lesser extent, the kidneys [61, 105–115, 121]. All patients present with early onset of inflammatory arthritis of small and large joints, variably associated with ILD and pulmonary haemorrhages. A subset of patients have been reported to have immune-mediated kidney disease (table 1). High-titre autoantibodies (*i.e.* antimyeloperoxidase and ANA) are usually present as well as increased Th17 cells and interleukin (IL)-1β/IL-6 expression. Originally reported in 21 genetically confirmed patients [61], average age of presentation was 3.5 years (6 months–22 years) and 16 subjects had disease onset before the age of 5 years. All patients had lung disease diagnosed as pulmonary haemorrhage, ILD or both, and lung pathology findings consistent with pattern observed in systemic autoimmune syndromes. The potential role of IFN in COPA syndrome pathogenesis was first highlighted by Volpi *et al.* [107] who demonstrated a positive IFN signature in five genetically confirmed patients, opening novel therapeutic opportunities. As in other interferonopathies, the diagnosis is often challenging. As described in the following reports, clinical picture mimicking juvenile idiopathic arthritis (JIA) may occur as isolated early manifestations [108, 109]. Onset of pulmonary symptoms and progressive lung damage may appear only years [108, 109] or decades [109] after disease presentation, often facilitated by familial cases with similar symptoms [109]. The clinical picture is poorly responsive to standard immunosuppressive therapies, leaving lung transplant often as the only therapeutic option. Conversely, initial presentation may resemble idiopathic pulmonary hemosiderosis with delayed definitive diagnosis only at the late appearance of morning stiffness and nonerosive arthritis [110].

Although recognised as a main clinical feature of the syndrome, the pulmonary features of COPA syndrome patients have not been comprehensively described until lately, when Tsui *et al.* [111] systematically analysed a cohort of 14 subjects, with onset within 12 years of age, *i.e.* <1 year (7%), 2–9 years (71%), 10–12 years (21%). Initial presentation ranges from isolated joint pain (three out of 14), pulmonary symptoms (six out of 14) or a combination of the two (five out of 14). Four out of 14 had haemoptysis as initial lung manifestation while two patients presented with anaemia and fatigue, due to DAH. Those without haemoptysis presented with chronic cough, shortness of breath and dyspnoea on effort. Eventually, all subjects developed ILD and arthritis without uveitis. Among those who had isolated articular onset, all developed lung symptoms within 10–20 years. Thus, subjects were given several clinical diagnoses prior to discovery of COPA syndrome including JIA, rheumatoid arthritis and idiopathic pulmonary haemosiderosis. Seven out of 14 patients developed DAH. Notably, a biopsy confirmed immune-mediated kidney disease and renal failure was present in three out of seven subjects with DAH. PFTs performed in all the patients unveiled a prevalent restrictive pattern (eight out of 14) but obstructive (one out of 14) and mixed (two out of 14) profiles were found in a minority, with normal lung function in one patient. Initial D_{LCO} % predicted was abnormal for all subjects tested (eight out of eight). Longitudinal PTF surveillance was available for 10 subjects, and showed decline in predicted FEV_1 and forced vital capacity (FVC) over time for nearly all subjects (nine out of 10), with average of 2.6% and 1.8% per year for FEV_1 and FVC, respectively. Only one of the 14 patients did not undergo CT imaging since this patient had early onset suggestive of ILD diagnosed *via* lung biopsy. Overall, CT findings included cysts (described as thin-walled and scattered throughout the parenchyma in a variable distribution) (nine out of 11), ground-glass opacities (six out of 11), nodules (five out of 11) and fibrosis (one out of 11). CT scans showed stabilisation or amelioration while on various immunosuppressive regimens but radiological improvement did not correlate with lung function recovery. Histopathological features on lung biopsy were follicular bronchiolitis (seven out of 10), DAH (four out of 10), acute interstitial fibrosis in a non-usual interstitial pneumonitis pattern (two out of 10) and airspace enlargement/cystic changes (two out of 10). All seven with follicular bronchiolitis had ground glass opacities and/or nodules on CT scan. Three subjects did not receive any lung biopsy while three were biopsied at the time they developed haemoptysis and diagnosed with DAH *via* bronchoscopy. Two of these subjects had evidence of acute lung injury with capillaritis. Interestingly, earlier age of onset was observed in successive generations in a three-generation kindred later described [98]. Presenting symptoms were cough and dyspnoea in four out of four, and histopathological findings included small lung cysts, follicular bronchiolitis, ILD and neuroendocrine cell hyperplasia. Neither alveolar haemorrhage nor glomerular disease were present. Features not previously

associated with COPA syndrome included neuromyelitis optica, pulmonary carcinoid tumour, clear cell renal carcinoma, renal cysts, hepatic cysts, nephrolithiasis, pyelonephritis and meningitis. Kidney involvement may not be present [121]. Conversely, lupus nephritis was the clinical manifestation at onset in a 10-year-old girl with unremarkable medical history [113]. Her disease course included transient arthralgia without joint/synovial lesions, and no signs of early lung involvement. COPA syndrome was suspected based on positive history of glomerulonephritis, arthritis and lung haemorrhages variably occurring in her family members, eventually leading to genetically confirmed COPA syndrome diagnosis. She developed endstage renal failure while on immunosuppressive therapies.

PAH

PAH occurrence has been described in both *ab estrinseco* and constitutive exposure to type I IFNs, highlighting the potential role of IFNα/β in PAH pathogenesis. PAH has been associated with increased IFN signature in its early phases of development, and it can be induced by therapeutic use of type I IFNs in several disorders [122]. In addition, PAH has been described in monogenic interferonopathies including SAVI, CANDLE syndrome, AGS and DNaseII deficiency (figure 3), as well as in multifactorial diseases associated with increased IFN signalling, such as SLE. Although the disease model and causal link of IFN-induced PAH is still to be defined, *ex vivo* treatment with a selective JAK2 inhibitor reduces proliferation of human arterial endothelial cells in idiopathic PAH [122]. Furthermore, potential efficacy of the JAK1/2 inhibitor ruxolitinib has been recently described in IFN-associated PAH in children with SAVI or DNaseII deficiency. Even if the underlying mechanism is still largely undefined, PAH represents one of the major pulmonary complications (although rare) observed in some monogenic interferonopathies.

PAH in SAVI

PAH was firstly reported in a male patient of Japanese/northern European ancestry with SAVI [94]. Following severe systemic inflammatory onset during the first weeks of life, the child developed the typical vasculitic rash associated with persistent elevation of inflammatory markers. Lung biopsy performed at age of 2 years displayed neutrophils and macrophages within chronic alveolar and interstitial inflammation. The child lately developed progressive pulmonary fibrosis and associated PAH. High-dose corticosteroid treatment provided partial beneficial effect, mainly on respiratory symptoms. Disease-modifying and immunosuppressive agents as well as biologic drugs were tried but failed to provide clinical improvement, and the child died of respiratory failure at the age of 16 years. PAH was later described in another two SAVI patients who were of Chinese/Malasyan ancestry. Disease onset and course were variable. While one patient history was characterised by early-onset growth retardation, chilblain lesions on the ear, skin telangiectasia and long, clubbed fingers, associated with chronic dry cough along with progressive decreased activity tolerance leading to ILD and associated PAH in adolescence [102], the other patient displayed a more abrupt onset with life-threatening PAH at 3 years of age [103]. The child had previously suffered of acute respiratory distress at the age of 2 months during interstitial pneumonitis due to *Pneumocystis jirovecii*, followed by full recovery. He later presented failure to thrive, developmental delay, livedo reticularis and vesicular rash without cutaneous vasculitis nor increased inflammatory markers. Echocardiogram performed during follow-up at 21 months of age was normal. At 33 months, the child developed a PAH and was started on a pulmonary vasodilator (*i.e.* sildenafil). Given the unusual presentation, the IFN gene signature was assessed and found positive, and genetic testing identified a *de novo* missense *TMEM173* variant. Interestingly, in this case the presence of a concomitant ILD could not be assessed, and whether or not the observed PAH was isolated or secondary to IFN-related lung fibrosis is still an open question.

PAH in CANDLE syndrome

The first case of non-ILD-related PAH in these disorders was described in a 2-year-old Guatemalan female from a consanguineous union, who was eventually diagnosed with CANDLE syndrome [104]. The child presented with failure to thrive, facial lipodystrophy, recurrent fevers associated with steroid-dependent neutrophilic dermatosis lesions. A chest radiograph highlighted cardiomegaly and an echocardiogram demonstrated PAH. Chest CT scan ruled out a concomitant ILD but unveiled dilated pulmonary arteries consistent with the presence of PAH. In addition, acute thrombosis of the superior vena cava and left brachiocephalic vein was reported in the CT scan, although antiphospholipid antibodies were present at low titres. Given the lack of evidence of thromboembolic disease or the presence of autoantibodies, the degree to which the acute thrombosis contributed to the development of PAH remains undefined. Targeted sequencing of *PSMB8* identified homozygous missense variant, which is a founder mutation in Hispanic patients.

PAH in Aicardi–Goutières syndrome

Although previously unrecognised, a recent retrospective analysis of an AGS cohort unveiled that PAH may occur also in this set of monogenic diseases [116]. AGS is an early onset, progressive encephalopathy

characterised by basal ganglial calcifications, white matter abnormalities and chronic cerebrospinal fluid lymphocytosis (table 1). Interestingly, four out of 22 individuals with complete medical information were shown to have developed PAH. Three carried *IFIH1* gain-of-function mutations while one had a heterozygous *TREX1* mutation. Typical symptom onset was between birth and 10 months of age at the latest, and PAH presentation variably occurred between the first month and 16 years. All the patients displayed concomitant elevated IFN signature scores, with the highest levels in those carrying *IFIH1* variants. Thus, genetic variants of *IFIH1* and *TREX1* have been suggested to be putative causes of congenital PAH.

PAH in DNaseII deficiency

Recently, onset of PAH at 17 years of age was described in a patient affected by DNaseII deficiency, and this occurrence appeared to be IFN-mediated [123]. DNaseII deficiency is characterised by a spectrum of clinical features including neonatal anaemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy and increased anti-DNA antibodies [34] (table 1). The patient had a history of neonatal hepatopathy, cytopenia, lupus pernio, growth retardation, recurrent fever, polyarticular arthritis, chronic glomerulonephritis and lipodystrophy. At 14-years-old, the patient's IFN signature was suggestive of an underlying interferonopathy, and a pathogenic DNaseII mutation identified by whole exome sequencing (WES). The patient's clinical picture progressively declined in spite of several therapeutic strategies. The introduction of off-label treatment with ruxolitinib allowed a dramatic clinical improvement and steroid tapering. However, after 5 months of treatment, and about 1 month following a likely viral illness, the patient was diagnosed with PAH, raising the question of whether this was drug-related or due to IFN-related inflammation during an uncontrolled disease activity. In fact, at the time of PAH diagnosis, a dramatic increased of IFN-score had been observed. Furthermore, a combination therapy with steroid pulses, epoprostenol, sildenafil and furosemide failed to ameliorate the clinical picture. Conversely, once ruxolitinib was reintroduced at higher doses a dramatic improvement of pulmonary pressure was achieved and the patient's cardiologic follow-up showed slow, progressive further recovery.

Diagnostic approach

As evident by the clinical overview on monogenic interferonopathies described here, diagnosis can be extremely challenging due to the high variability in disease onset and course. In addition, diagnostic tools for definitive diagnoses are not available worldwide, and validation of most of them is still ongoing, mainly in research hospitals. Since severe lung impairment may occur clinically hidden during monogenic interferonopathies, useful hints may be derived from a detailed medical history, focusing on the occurrence of early-onset systemic inflammation variably associated to a wide spectrum (supplementary table 1) of extrapulmonary manifestations (*e.g.* suggestive cutaneous manifestations, peripheral vasculitis, panniculitis, nasal septum perforation, failure to thrive, recurrent fevers, suggestive neurological involvement, arthritis, contractures, autoimmune kidney disease, cytopenias, recurrent infections). In addition, family history of ILD, autoimmune kidney disease or arthritis as well as suggestive cutaneous manifestations in a young patient with early-onset systemic inflammation, should drive attention to potential underlying inborn errors of the IFN pathway. Conversely, early onset of either respiratory symptoms with suggestive family history or suggestive *tout court* lung involvement (*i.e.* ILD, alveolar haemorrhages, PAH or bronchiectasis) should prompt a hypothesis-driven work-up aimed at assessing the presence of monogenic interferonopathy (supplementary figure 1). Once clinically suspected, enhanced type I IFN signalling should be tested for. However, the development of diagnostic tools to reach a definitive diagnosis of type I IFN-related disease has been hampered by the current inability to directly detect and quantify type I IFN protein in biological samples using the available ELISA assays. Recently, an ultrasensitive single molecule array for detecting human IFNα in biological fluids has been developed and validated [117]. However, to date, the most employed available tool is the so-called IFN signature [124, 125], which assesses the increased expression of ISGs whose transcription is induced by IFN. It consists of a 6- or 28-IFN response gene scoring, based on QRT-PCR or NanoString technology. Of note, the IFN signature is not specific to type I IFN. The possibility that enhanced IFN signalling induced by types II and III IFNs might also have detrimental effects deserves further investigation. Despite its limitations, including interlaboratory variability, the IFN signature may help to screen patients for IFN-aberrancies, thus identifying those worth of genetic testing [124–126]. Recently, a clinical score correlating with the ISG score has been developed, providing a potential additional tool to guide in decision making for diagnostic work-up in monogenic interferonopathies [127]. In the presence of suggestive clinical picture, disease course and family history, especially if an IFN-positive signature has been identified, panel next-generation sequencing or targeted Sanger sequencing should be performed to make a definitive diagnosis, based on the known potential genes involved (table 1, figures 2 and 3). Furthermore, given the fact that some intereferonopathies may have severe lung impairment as the presenting clinical picture, a young patient presenting with early-onset lung involvement such as ILD, alveolar haemorrhages or PAH, should be investigated for IFN-related genes

TABLE 2 Effects of interferonopathy (IFN)-signalling blockade on lung involvement in monogenic interferonopathies

First author [ref.]	Treatment	Disease	Lung involvement	Effect on IFN signature	Clinical response/outcome	Side-effects
FRÉMOND [97]	Ruxolitinib	SAVI (n=3)	ILD (n=2)	Partial inhibition	Improvement	None
CHIA [119]	Baricitinib	SAVI (n=1)	ILD (n=1)	ND	Improvement	NA
SANCHEZ [100]	Baricitinib	SAVI (n=4) CANDLE (n=10)	ILD (n=4) PAH (n=1)	Inhibition	Improvement	ND
BUCHBINDER [104]	Tofacitinib	CANDLE (n=1)	PAH (n=1)	ND	Initial improvement	None
SALDANHA [103]	Ruxolitinib	SAVI (n=1)	PAH (n=1)	Inhibition	Improvement	None
YU [102]	Tofacitinib	SAVI (n=1)	PAH (n=1)	ND	Partial improvement/sudden death (unknown cause)	NA
BOYADZHIEV [133]	Baricitinib	CANDLE (n=1)	ND (n=1)	ND	Improvement	None
TROMBETTA [123]	Ruxolitinib	DNAse II deficiency (n=1)	PAH (n=1)	Inhibition	Improvement	None
VOLPI [101]	Ruxolitinib	SAVI (n=3)	ILD (n=3) PAH (n=1)	Partial inhibition	Improvement (transitory: n=2; persistent: n=1)	Severe viral infection (n=1)
FRÉMOND [134]	Ruxolitinib	COPA (n=1)	DAH (n=1)	Inhibition	Partial improvement	None

SAVI: STING-associated vasculopathy with onset in infancy; STING: stimulator of interferon genes; ND: not determined; ILD: interstitial lung disease; NA: not available; CANDLE: chronic atypical dermatosis with lipodystrophy and elevated temperatures; PAH: pulmonary arterial hypertension; COPA: coatomer protein complex, subunit-α; DAH: diffuse alveolar haemorrhage.

as well as those already known for congenital lung diseases (figure 3), even in the absence of suggestive extrapulmonary manifestations (supplementary figure 1).

Therapeutic options

Given the recognised key role of nucleid acid-induced type I IFN response and inflammation, current therapeutic approaches mostly rely on strategies aiming at: 1) restraining the production of endogenous nucleic acids (*i.e.* reverse-transcriptase inhibitors (RTIs)); 2) limiting their sensing (*i.e.* cGAS inhibition by hydroxychloroquine [128]); 3) promoting their clearance (mTOR inhibitors [129]); or 4) inhibiting downstream signalling (*i.e.* TBK1 inhibition [130, 131] anti-type I IFN antibodies [132], JAK inhibitors [55, 97, 100, 101, 102–104, 119, 123, 133, 134]).

A recent clinical trial of RTIs in AGS patients provided promising results, indicating an effect of restraining IFN signalling [135]. To date, the most clinically explored approach in a wide spectrum of interferonopathies is that described with JAK1/2 inhibition (*i.e.* tofacitinib, ruxolitinib, baricitinib), which displayed promising beneficial effects on lung manifestation in patients with SAVI, COPA syndrome, CANDLE syndrome and DNaseII deficiency [55, 97, 100, 101, 102–104, 119, 123, 133, 134, 136, 138]) (table 2).

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References

1   Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. *Ann N Y Acad Sci* 2011; 1238: 91–98.
2   Crow YJ. Type I interferonopathies: Mendelian type I interferon up-regulation. *Curr Opin Immunol* 2015; 32: 7–12.
3   Rodero MP, Crow YJ. Type I interferon-mediated monogenic autoinflammation: the type I interferonopathies, a conceptual overview. *J Exp Med* 2016; 213: 2527–2538.
4   Eleftheriou D, Brogan PA. Genetic interferonopathies: an overview. *Best Pract Res Clin Rheumatol* 2017; 31: 441–459.
5   Crow YJ, Lebon P, Casanova JL, *et al.* A brief historical perspective on the pathological consequences of excessive type I interferon exposure *in vivo*. *J Clin Immunol* 2018; 38: 694–698.
6   Davidson S, Steiner A, Harapas CR, *et al.* An update on autoinflammatory diseases: interferonopathies. *Curr Rheumatol Rep* 2018; 20: 38.
7   Volpi S, Picco P, Caorsi R, *et al.* Type I interferonopathies in pediatric rheumatology. *Pediatr Rheumatol Online J* 2016; 14: 35.
8   Uggenti C, Lepelley A, Crow YJ. Self-awareness: nucleic acid-driven inflammation and the type I interferonopathies. *Annu Rev Immunol* 2019; 37: 247–267.
9   Gresser I, Morel-Maroger L, Rivière Y, *et al.* Interferon-induced disease in mice and rats. *Ann N Y Acad Sci* 1980; 350: 12–20.
10   Lebon P, Badoual J, Ponsot G, *et al.* Intrathecal synthesis of interferon-alpha in infants with progressive familial encephalopathy. *J Neurol Sci* 1988; 84: 201–208.

11   Crow YJ, Black DN, Ali M, et al. Cree encephalitis is allelic with Aicardi–Goutières syndrome: implications for the pathogenesis of disorders of interferon alpha metabolism. J Med Genet 2003; 40: 183–187.

12   Crow YJ, Manel N. Aicardi–Goutières syndrome and the type I interferonopathies. Nat Rev Immunol 2015; 15: 429–440.

13   Casanova JL, Fieschi C, Bustamante J, et al. From idiopathic infectious diseases to novel primary immunodeficiencies. J Allergy Clin Immunol 2005; 116: 426–430.

14   Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. Cell 2010; 140: 784–790.

15   Kim H, Sanchez GA, Goldbach-Mansky R. Insights from Mendelian interferonopathies: comparison of CANDLE, SAVI with AGS. Monogenic Lupus J Mol Med (Berl) 2016; 94: 1111–1127.

16   Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 1957; 147: 258–267.

17   Aicardi J, Goutières F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 1984; 15: 49–54.

18   Rice G, Patrick T, Parmar R, et al. Clinical and molecular phenotype of Aicardi–Goutieres syndrome. Am J Hum Genet 2007; 81: 713–725.

19   Stetson DB, Ko JS, Heidmann T, et al. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell 2008; 134: 587–598.

20   Hiller B, Achleitner M, Glage S, et al. Mammalian RNase H2 removes ribonucleotides from DNA to maintain genome integrity. J Exp Med 2012; 209: 1419–1426.

21   Mackenzie KJ, Carroll P, Lettice L, et al. Ribonuclease H2 mutations induce a cGAS/STING-dependent innate immune response. EMBO J 2016; 35: 831–844.

22   Rice GI, Bond J, Asipu A, et al. Mutations involved in Aicardi–Goutières syndrome implicate SAMHD1 as regulator of the innate immune response. Nat Genet 2009; 41: 829–832.

23   Behrendt R, Schumann T, Gerbaulet A, et al. Mouse SAMHD1 has antiretroviral activity and suppresses a spontaneous cell-intrinsic antiviral response. Cell Rep 2013; 4: 689–696.

24   Rehwinkel J, Maelfait J, Bridgeman A, et al. SAMHD1-dependent retroviral control and escape in mice. EMBO J 2013; 32: 2454–2462.

25   Xin B, Jones S, Puffenberger EG, et al. Homozygous mutation in SAMHD1 gene causes cerebral vasculopathy and early onset stroke. Proc Natl Acad Sci USA 2011; 108: 5372–5377.

26   Rice G, Newman WG, Dean J, et al. Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi–Goutieres syndrome. Am J Hum Genet 2007; 80: 811–815.

27   Lee-Kirsch MA, Gong M, Schulz H, et al. Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. Am J Hum Genet 2006; 79: 731–737.

28   Günther C, Hillebrand M, Brunk J, et al. Systemic involvement in TREX1-associated familial chilblain lupus. J Am Acad Dermatol 2013; 69: e179-81.

29   Günther C, Berndt N, Wolf C, et al. Familial chilblain lupus due to a novel mutation in the exonuclease III domain of 3′ repair exonuclease 1 (TREX1). JAMA Dermatol 2015; 151: 426–431.

30   Ravenscroft JC, Suri M, Rice GI, et al. Autosomal dominant inheritance of a heterozygous mutation in SAMHD1 causing familial chilblain lupus. Am J Med Genet A 2011; 155A: 235–237.

31   König N, Fiehn C, Wolf C, et al. Lee-Kirsch MA Familial chilblain lupus due to a gain-of-function mutation in STING. Ann Rheum Dis 2017; 76: 468–472.

32   Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014; 371: 507–518.

33   Starokadomskyy P, Gemelli T, Rios JJ, et al. DNA polymerase-α regulates the activation of type I interferons through cytosolic RNA:DNA synthesis. Nat Immunol 2016; 17: 495–504.

34   Rodero MP, Tesser A, Bartok E, et al. Type I interferon-mediated autoinflammation due to DNase II deficiency. Nat Commun 2017; 8: 2176.

35   Liddicoat BJ, Piskol R, Chalk AM, et al. RNA editing by ADAR1 prevents MDA5 sensing of endogenous dsRNA as nonself. Science 2015; 349: 1115–1120.

36   Rice GI, Kasher PR, Forte GM, et al. Mutations in ADAR1 cause Aicardi–Goutières syndrome associated with a type I interferon signature. Nat Genet 2012; 44: 1243–1248.

37   Rice GI, Del Toro Duany Y, Jenkinson EM, et al. Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. Nat Genet 2014; 46: 503–509.

38   Rice GI, Kitabayashi N, Barth M, et al. Genetic, phenotypic, and interferon biomarker status in ADAR1-related neurological disease. Neuropediatrics 2017; 48: 166–184.

39   Livingston JH, Lin JP, Dale RC, et al. A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1. J Med Genet 2014; 51: 76–82.

40   Rutsch F, MacDougall M, Lu C, et al. A specific IFIH1 gain-of-function mutation causes Singleton–Merten syndrome. Am J Hum Genet 2015; 96: 275–282.

41   Buers I, Rice GI, Crow YJ, et al. MDA5-associated neuroinflammation and the Singleton–Merten syndrome: two faces of the same type I interferonopathy spectrum. J Interferon Cytokine Res 2017; 37: 214–219.

42   Jang MA, Kim EK, Now H, et al. Mutations in DDX58, which encodes RIG-I, cause atypical Singleton–Merten syndrome. Am J Hum Genet 2015; 96: 266–274.

43   de Carvalho LM, Ngoumou G, Park JW, et al. Crow musculoskeletal disease in MDA5-related type I interferonopathy: a mendelian mimic of Jaccoud's arthropathy. Arthritis Rheumatol 2017; 69: 2081–2091.

44   Liu Q, Jiang L, Liu WL, et al. Two novel mutations and evidence for haploinsufficiency of the ADAR gene in dyschromatosis symmetrica hereditaria. Br J Dermatol 2006; 154: 636–642.

45   Wang P, Yu S, Liu J, et al. Seven novel mutations of ADAR in multi-ethnic pedigrees with dyschromatosis symmetrica hereditaria in China. Mol Genet Genomic Med 2019; 7: e00905.

46   Gul E, Sayar EH, Gungor B, et al. Type I IFN-related NETosis in ataxia telangiectasia and Artemis deficiency. J Allergy Clin Immunol 2018; 142: 246–257.

47   Volk T, Pannicke U, Reisli I, et al. DCLRE1C (ARTEMIS) mutations causing phenotypes ranging from atypical severe combined immunodeficiency to mere antibody deficiency. Hum Mol Genet 2015; 24: 7361–7372.

48   Dhir A, Dhir S, Borowski LS, *et al.* Mitochondrial double-stranded RNA triggers antiviral signalling in humans. *Nature* 2018; 560: 238–242.

49   Tonduti D, Orcesi S, Jenkinson EM, *et al.* Clinical, radiological and possible pathological overlap of cystic leukoencephalopathy without megalencephaly and Aicardi–Goutières syndrome. *Eur J Paediatr Neurol* 2016; 20: 604–610.

50   Kameli R, Amanat M, Rezaei Z, *et al.* RNASET2-deficient leukoencephalopathy mimicking congenital CMV infection and Aicardi–Goutieres syndrome: a case report with a novel pathogenic variant. *Orphanet J Rare Dis* 2019; 14: 184.

51   Sasarman F, Thiffault I, Weraarpachai W, *et al.* The 3′ addition of CCA to mitochondrial tRNASer(AGY) is specifically impaired in patients with mutations in the tRNA nucleotidyl transferase *TRNT1. Hum Mol Genet* 2015; 24: 2841–2847.

52   Giannelou A, Wang H, Zhou Q, *et al.* Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors. *Ann Rheum Dis* 2018; 77: 612–619.

53   Zhang X, Bogunovic D, Payelle-Brogard B, *et al.* Human intracellular ISG15 prevents interferon-α/β over-amplification and auto-inflammation. *Nature* 2015; 517: 89–93.

54   Meuwissen ME, Schot R, Buta S, *et al.* Human USP18 deficiency underlies type 1 interferonopathy leading to severe pseudo-TORCH syndrome. *J Exp Med* 2016; 213: 1163–1174.

55   Alsohime F, Martin Fernandez M, Temsah M, *et al.* JAK inhibitor therapy in a child with inherited USP18 deficiency. *N Engl J Med* 2020; 382: 256–265.

56   Eren Akarcan S, Ulusoy Severcan E, Edeer Karaca N, *et al.* Gain-of-function mutations in *STAT1*: a recently defined cause for chronic mucocutaneous Candidiasis disease mimicking combined immunodeficiencies. *Case Reports Immunol* 2017; 2017: 2846928.

57   Stellacci E, Moneta GM, Bruselles A, *et al.* The activating p.Ser466Arg change in *STAT1* causes a peculiar phenotype with features of interferonopathies. *Clin Genet* 2019; 96: 585–589.

58   Duncan CJA, Thompson BJ, Chen R, *et al.* Severe type I interferonopathy and unrestrained interferon signaling due to a homozygous germline mutation in *STAT2. Sci Immunol* 2019; 4: eaav7501.

59   Del Bel KL, Ragotte RJ, Saferali A, *et al.* JAK1 gain-of-function causes an autosomal dominant immune dysregulatory and hypereosinophilic syndrome. *J Allergy Clin Immunol* 2017; 139: 2016–2020.e5. Epub 2017 Jan 19.

60   Johnston JJ, Sanchez-Contreras MY, Keppler-Noreuil KM, *et al.* A point mutation in *PDGFRB* causes autosomal-dominant Penttinen syndrome. *Am J Hum Genet* 2015; 97: 465–474.

61   Watkin LB, Jessen B, Wiszniewski W, *et al.* COPA mutations impair ER–Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. *Nat Genet* 2015; 47: 654–660.

62   Lood C, Gullstrand B, Truedsson L, *et al.* C1q inhibits immune complex-induced interferon-alpha production in plasmacytoid dendritic cells: a novel link between C1q deficiency and systemic lupus erythematosus pathogenesis. *Arthritis Rheum* 2009; 60: 3081–3090.

63   Santer DM, Hall BE, George TC, *et al.* C1q deficiency leads to the defective suppression of IFN-alpha in response to nucleoprotein containing immune complexes. *J Immunol* 2010; 185: 4738–4749.

64   Eckard SC, Rice GI, Fabre A, *et al.* The SKIV2L RNA exosome limits activation of the RIG-I-like receptors. *Nat Immunol* 2014; 15: 839–845.

65   Brehm A, Liu Y, Sheikh A, *et al.* Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J Clin Invest* 2016; 126: 795.

66   Torrelo A, Patel S, Colmenero I, *et al.* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol* 2010; 62: 489–495.

67   Ramot Y, Czarnowicki T, Maly A, *et al.* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome: a case report. *Pediatr Dermatol* 2011; 28: 538–541.

68   Liu Y, Ramot Y, Torrelo A, *et al.* Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum* 2012; 64: 895–907.

69   Tanaka M, Miyatani N, Yamada S, *et al.* Hereditary lipo-muscular atrophy with joint contracture, skin eruptions and hyper-gamma-globulinemia: a new syndrome. *Intern Med* 1993; 32: 42–45.

70   Agarwal AK, Xing C, DeMartino GN, *et al.* PSMB8 encoding the β5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *Am J Hum Genet* 2010; 87: 866–872.

71   Garg A, Hernandez MD, Sousa AB, *et al.* An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy. *J Clin Endocrinol Metab* 2010; 95: E58–E63.

72   Arima K, Kinoshita A, Mishima H, *et al.* Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo–Nishimura syndrome. *Proc Natl Acad Sci USA* 2011; 108: 14914–14919.

73   Kitamura A, Maekawa Y, Uehara H, *et al.* A mutation in the immunoproteasome subunit *PSMB8* causes autoinflammation and lipodystrophy in humans. *J Clin Invest* 2011; 121: 4150–4160.

74   Kunimoto K, Kimura A, Uede K, *et al.* A new infant case of Nakajo–Nishimura syndrome with a genetic mutation in the immunoproteasome subunit: an overlapping entity with JMP and CANDLE syndrome related to *PSMB8* mutations. *Dermatology* 2013; 227: 26–30.

75   McDermott A, Jesus AA, Liu Y, *et al.* A case of proteasome-associated auto-inflammatory syndrome with compound heterozygous mutations. *J Am Acad Dermatol* 2013; 69: e29–e32.

76   Wang H, Das L, Tan Hung Tiong J, *et al.* CANDLE syndrome: an extended clinical spectrum. *Rheumatology (Oxford)* 2014; 53: 2119–2120.

77   Roberts T, Stephen L, Scott C, *et al.* CANDLE Syndrome: orofacial manifestations and dental implications. *Head Face Med* 2015; 11: 38.

78   Cavalcante MP, Brunelli JB, Miranda CC, *et al.* CANDLE syndrome: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature-a rare case with a novel mutation. *Eur J Pediatr* 2016; 175: 735–740.

79   Torrelo A. CANDLE syndrome as a paradigm of proteasome-related autoinflammation. *Front Immunol* 2017; 8: 927.

80   Prencipe G, Bracaglia C, Caiello I, *et al.* The interferon-gamma pathway is selectively up-regulated in the liver of patients with secondary hemophagocytic lymphohistiocytosis. *PLoS One* 2019; 14: e0226043.

81   Yamazaki-Nakashimada MA, Santos-Chávez EE, de Jesus AA, *et al.* Systemic autoimmunity in a patient with CANDLE syndrome. *J Investig Allergol Clin Immunol* 2019; 29: 75–76.

82   Ebstein F, Poli Harlowe MC, Studencka-Turski M, *et al.* Contribution of the unfolded protein response (UPR) to the pathogenesis of proteasome-associated autoinflammatory syndromes (PRAAS). *Front Immunol* 2019; 10: 2756.

83   Briggs TA, Rice GI, Daly S, *et al.* Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat Genet* 2011; 43: 127–131.

84   Lausch E, Janecke A, Bros M, *et al.* Genetic deficiency of tartrate-resistant acid phosphatase associated with skeletal dysplasia, cerebral calcifications and autoimmunity. *Nat Genet* 2011; 43: 132–137.

85   Briggs TA, Rice GI, Adib N, *et al.* Spondyloenchondrodysplasia due to mutations in ACP5: a comprehensive survey. *J Clin Immunol* 2016; 36: 220–234.

86   Sacri AS, Bruwier A, Baujat G, *et al.* Childhood-onset autoimmune cytopenia as the presenting feature of biallelic ACP5 mutations. *Pediatr Blood Cancer* 2017; 64: 306–310.

87   Yang K, Huang R, Fujihira H, *et al.* N-glycanase NGLY1 regulates mitochondrial homeostasis and inflammation through NRF1. *J Exp Med* 2018; 215: 2600–2616.

88   Enns GM, Shashi V, Bainbridge M, *et al.* Mutations in *NGLY1* cause an inherited disorder of the endoplasmic reticulum-associated degradation pathway. *Genet Med* 2014; 16: 751–758.

89   Lam C, Ferreira C, Krasnewich D, *et al.* Prospective phenotyping of NGLY1-CDDG, the first congenital disorder of deglycosylation. *Genet Med* 2017; 19: 160–168.

90   Zhou Q, Yang D, Ombrello AK, *et al.* Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med* 2014; 370: 911–920.

91   Skrabl-Baumgartner A, Plecko B, Schmidt WM, *et al.* Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel *CECR1* mutation. *Pediatr Rheumatol Online J* 2017; 15: 6.

92   Insalaco A, Moneta GM, Pardeo M, *et al.* Variable clinical phenotypes and relation of interferon signature with disease activity in ADA2 deficiency. *J Rheumatol* 2019; 46: 523–526.

93   Munoz J, Rodière M, Jeremiah N, *et al.* Stimulator of interferon genes-associated vasculopathy with onset in infancy: a mimic of childhood granulomatosis with polyangiitis. *JAMA Dermatol* 2015; 151: 872–877.

94   Omoyinmi E, Melo Gomes S, Nanthapisal S, *et al.* Stimulator of interferon genes-associated vasculitis of infancy. *Arthritis Rheumatol* 2015; 67: 808.

95   Clarke SL, Pellowe EJ, de Jesus AA, *et al.* Interstitial lung disease caused by STING-associated vasculopathy with onset in infancy. *Am J Respir Crit Care Med* 2016; 194: 639–642.

96   Picard C, Thouvenin G, Kannengiesser C, *et al.* Severe pulmonary fibrosis as the first manifestation of interferonopathy (*TMEM173* mutation). *Chest* 2016; 150: e65–e71.

97   Frémond ML, Rodero MP, Jeremiah N, *et al.* Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immunol* 2016; 138: 1752–1755.

98   Melki I, Rose Y, Uggenti C, *et al.* Disease-associated mutations identify a novel region in human STING necessary for the control of type I interferon signaling. *J Allergy Clin Immunol* 2017; 140: 543–552.e5.

99   Konno H, Chinn IK, Hong D, *et al.* Pro-inflammation associated with a gain-of-function mutation (R284S) in the innate immune sensor STING. *Cell Rep* 2018; 23: 1112–1123.

100   Sanchez GAM, Reinhardt A, Ramsey S, *et al.* JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest* 2018; 128: 3041–3052.

101   Volpi S, Insalaco A, Caorsi R, *et al.* Efficacy and adverse events during Janus kinase inhibitor treatment of SAVI syndrome. *J Clin Immunol* 2019; 39: 476–485.

102   Yu ZX, Zhong LQ, Song HM, *et al.* Stimulator of interferon genes-associated vasculopathy with onset in infancy: first case report in China. *Zhonghua Er Ke Za Zhi* 2018; 56: 179–185.

103   Saldanha RG, Balka KR, Davidson S, *et al.* A mutation outside the dimerization domain causing atypical STING-associated vasculopathy with onset in infancy. *Front Immunol* 2018; 9: 1535.

104   Buchbinder D, Montealegre Sanchez GA, Goldbach-Mansky R, *et al.* Rash, fever, and pulmonary hypertension in a 6-year-old female. *Arthritis Care Res (Hoboken)* 2018; 70: 785–790.

105   Kumrah R, Mathew B, Vignesh P, *et al.* Genetics of COPA syndrome. *Appl Clin Genet* 2019; 12: 11–18.

106   Vece TJ, Watkin LB, Nicholas S, *et al.* COPA syndrome: a novel autosomal dominant immune dysregulatory disease. *J Clin Immunol* 2016; 36: 377–387.

107   Volpi S, Tsui J, Mariani M, *et al.* Type I interferon pathway activation in COPA syndrome. *Clin Immunol* 2018; 187: 33–36.

108   Brennan M, McDougall C, Walsh J, *et al.* 013. COPA syndrome – a new condition to consider when features of polyarthritis and interstitial lung disease are present. *Rheumatology* 2017; 56: Suppl. 6, kex356.059.

109   Jensson BO, Hansdottir S, Arnadottir GA, *et al.* COPA syndrome in an Icelandic family caused by a recurrent missense mutation in COPA. *BMC Med Genet* 2017; 18: 129.

110   Noorelahi R, Perez G, Otero HJ. Imaging findings of COPA syndrome in a 12-year-old boy. *Pediatr Radiol* 2018; 48: 279–282.

111   Tsui JL, Estrada OA, Deng Z, *et al.* Analysis of pulmonary features and treatment approaches in the COPA syndrome. *ERJ Open Res* 2018; 4: 00017-2018.

112   Taveira-DaSilva AM, Markello TC, Kleiner DE, *et al.* Expanding the phenotype of COPA syndrome: a kindred with typical and atypical features. *J Med Genet* 2019; 56: 778–782.

113   Boulisfane-El Khalifi S, Viel S, Lahoche A, *et al.* COPA syndrome as a cause of lupus nephritis. *Kidney Int Rep* 2019; 4: 1187–1189.

114   Krutzke S, Rietschel C, Horneff G. Baricitinib in therapy of COPA syndrome in a 15-year-old girl. *Eur J Rheumatol* 2019; 7: Suppl 1., 1–4.

115   Frémond ML, Legendre M, Fayon M, *et al.* Use of ruxolitinib in COPA syndrome manifesting as life-threatening alveolar haemorrhage. *Thorax* 2019; 75: 92–95.

116   Adang LA, Frank DB, Gilani A, *et al.* Aicardi–Goutières syndrome is associated with pulmonary hypertension. *Mol Genet Metab* 2018; 125: 351–358.

117   Melki I, Devilliers H, Gitiaux C, *et al.* Circulating interferon-α measured with a highly sensitive assay as a biomarker for juvenile inflammatory myositis activity: comment on the article by Mathian *et al. Arthritis Rheumatol* 2019; 72: 195–197.

118   Jeremiah N, Neven B, Gentili M, *et al.* Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *J Clin Invest* 2014; 124: 5516–5520.

119   Chia J, Eroglu FK, Özen S, *et al.* Failure to thrive, interstitial lung disease, and progressive digital necrosis with onset in infancy. *J Am Acad Dermatol* 2016; 74: 186–189.

120   Kim H, Brooks KM, Tang CC, *et al.* Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI Patients. *Clin Pharmacol Ther* 2018; 104: 364–373.

121   Patwardhan A, Spencer CH. An unprecedented COPA gene mutation in two patients in the same family: comparative clinical analysis of newly reported patients with other known COPA gene mutations. *Pediatr Rheumatol Online J* 2019; 17: 59.

122   George PM, Oliver E, Dorfmuller P, *et al.* Evidence for the involvement of type I interferon in pulmonary arterial hypertension. *Circ Res* 2014; 114: 677–688.

123   Trombetta A, Ghirardo S, Pastore S, *et al.* Pulmonary arterial hypertension in interferonopathies: a case report and a review of the literature. *Pulm Circ* 2019; 9: 2045894019869837.

124   Rice GI, Melki I, Frémond ML, *et al.* Assessment of type I interferon signaling in pediatric inflammatory disease. *J Clin Immunol* 2017; 37: 123–132.

125   Kim H, de Jesus AA, Brooks SR, *et al.* Development of a validated interferon score using NanoString technology. *J Interferon Cytokine Res* 2018; 38: 171–185.

126   Pin A, Monasta L, Taddio A, *et al.* An easy and reliable strategy for making type I interferon signature analysis comparable among research centers. *Diagnostics (Basel)* 2019; 9.

127   Sönmez HE, Karaaslan C, de Jesus AA, *et al.* A clinical score to guide in decision making for monogenic type I IFNopathies. *Pediatr Res* 2019; 87(4): 745–752.

128   An J, Woodward JJ, Lai W, *et al.* Inhibition of cyclic GMP-AMP synthase using a novel antimalarial drug derivative in Trex1-deficient mice. *Arthritis Rheumatol* 2018; 70: 1807–1819.

129   Bartsch K, Knittler K, Borowski C, *et al.* Absence of RNase H2 triggers generation of immunogenic micronuclei removed by autophagy. *Hum Mol Genet* 2017; 26: 3960–3972.

130   Hasan M, Dobbs N, Khan S, *et al.* Cutting edge: inhibiting TBK1 by compound II ameliorates autoimmune disease in mice. *J Immunol* 2015; 195: 4573–4577.

131   Gitiaux C, Bondet V, Bekaddour N, *et al.* Inhibition of IFNα secretion in cells from patients with juvenile dermatomyositis under TBK1 inhibitor treatment revealed by single-molecular assay technology. *Rheumatology (Oxford)* 2019; 59: 1171–1174.

132   Chasset F, Arnaud L. Targeting interferons and their pathways in systemic lupus erythematosus. *Autoimmun Rev* 2018; 17: 44–52.

133   Boyadzhiev M, Marinov L, Boyadzhiev V, *et al.* Disease course and treatment effects of a JAK inhibitor in a patient with CANDLE syndrome. *Pediatr Rheumatol Online J* 2019; 17(1): 19.

134   Frémond ML, Legendre M, Fayon M, *et al.* Use of ruxolitinib in COPA syndrome manifesting as life-threatening alveolar haemorrhage. *Thorax* 2020; 75: 92–95.

135   Rice GI, Meyzer C, Bouazza N, *et al.* Reverse-transcriptase inhibitors in the Aicardi–Goutières Syndrome. *N Engl J Med* 2018; 379: 2275–2277.

136   Briand C, Frémond ML, Bessis D, *et al.* Efficacy of JAK1/2 inhibition in the treatment of chilblain lupus due to TREX1 deficiency. *Ann Rheum Dis* 2019; 78: 431–433.

137   Kothur K, Bandodkar S, Chu S, *et al.* An open-label trial of JAK 1/2 blockade in progressive IFIH1-associated neuroinflammation. *Neurology* 2018; 90: 289–291.

138   Sabbagh S, Almeida de Jesus A, Hwang S, *et al.* Treatment of anti-MDA5 autoantibody-positive juvenile dermatomyositis using tofacitinib. *Brain* 2019; 142: e59.