



The type I interferonopathies: 10 years on

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Abstract | As brutally demonstrated by the COVID-19 pandemic, an effective immune system is essential for survival. Developed over evolutionary time, viral nucleic acid detection is a central pillar in the defensive armamentarium used to combat foreign microbial invasion. To ensure cellular homeostasis, such a strategy necessitates the efficient discrimination of pathogen-derived DNA and RNA from that of the host. In 2011, it was suggested that an upregulation of type I interferon signalling might serve as a defining feature of a novel set of Mendelian inborn errors of immunity, where antiviral sensors are triggered by host nucleic acids due to a failure of self versus non-self discrimination. These rare disorders have played a surprisingly significant role in informing our understanding of innate immunity and the relevance of type I interferon signalling for human health and disease. Here we consider what we have learned in this time, and how the field may develop in the future.

Although the term ‘type I interferonopathy’ entered the medical lexicon only in 2011 (REF.¹), the idea that interferon might be harmful in humans was first posed almost 30 years earlier. On the basis of a series of experiments in rodents, in 1982, Ion Gresser suggested the possibility that interferon might “either cause or contribute to human pathology”^{2–4}. Six years later, Pierre Lebon, a virologist, together with his paediatric neurology colleagues Jean Aicardi and Françoise Goutières, described increased levels of interferon- α (IFN α) activity in the serum and cerebrospinal fluid (CSF) of children affected by a genetic disorder that resembled in utero-acquired viral infection⁵. In so doing, they defined the first Mendelian disease associated with enhanced type I interferon signalling, now referred to as Aicardi–Goutières syndrome (AGS)⁶.

The aforementioned observations overlapped with the advent of recombinant leukocyte interferon as a therapy, and the first reports of neurological disease^{7,8} and autoimmune disease — particularly, systemic lupus erythematosus (SLE)^{9,10} — apparently triggered by iatrogenic exposure. The neurotoxic potential of type I interferon was further highlighted by the group of Iain Campbell, who described a recapitulation of the neuropathological features of AGS in transgenic mice chronically producing IFN α from astrocytes^{11,12}. In 2003, specific attention was drawn to the phenotypic overlap of AGS with SLE and in utero HIV-1 infection, and the possibility that such overlap might result from the common pathological feature of type I interferon upregulation¹³. Subsequent partial dissection of the genetic^{14–16} and molecular¹⁷ basis of AGS, the identification of mutations

in *ACP5* as the cause of a Mendelian form of SLE^{18,19} and the definition of a link between C1q deficiency and IFN α production^{20,21} eventually led to the suggestion that an upregulation of type I interferon signalling might serve as a defining feature of a novel set of Mendelian inborn errors of immunity¹.

The 10 years since the coining of the term ‘type I interferonopathy’ have seen a widespread adoption of the concept within the broader classification of auto-inflammatory disorders^{22,23}. Expert clinical phenotyping, the use of screening assays and the advent of next-generation sequencing have resulted in an increase in the number of type I interferonopathies from seven to close to 40 discrete genotypes, and the recognition of a remarkably broad associated phenotypic spectrum. This rapid increase in knowledge has both informed and been informed by fundamental discoveries in innate immunity, leading to a better understanding of the role of type I interferons in health and disease, and the possibility of therapeutic initiatives aimed at limiting type I interferon signalling. In this Review, we consider what the type I interferonopathies have taught us, and look forward to how this exciting field might develop in the future.

Definitions

Simply put, the ability to fight infection is necessary for survival²⁴, and landmark studies have led to an appreciation of the centrality of foreign nucleic acid detection in the mortal battle waged with viruses^{25,26}. We argue that the single most important lesson deriving from the study of the type I interferonopathies is that these essential antiviral systems can also be triggered by host

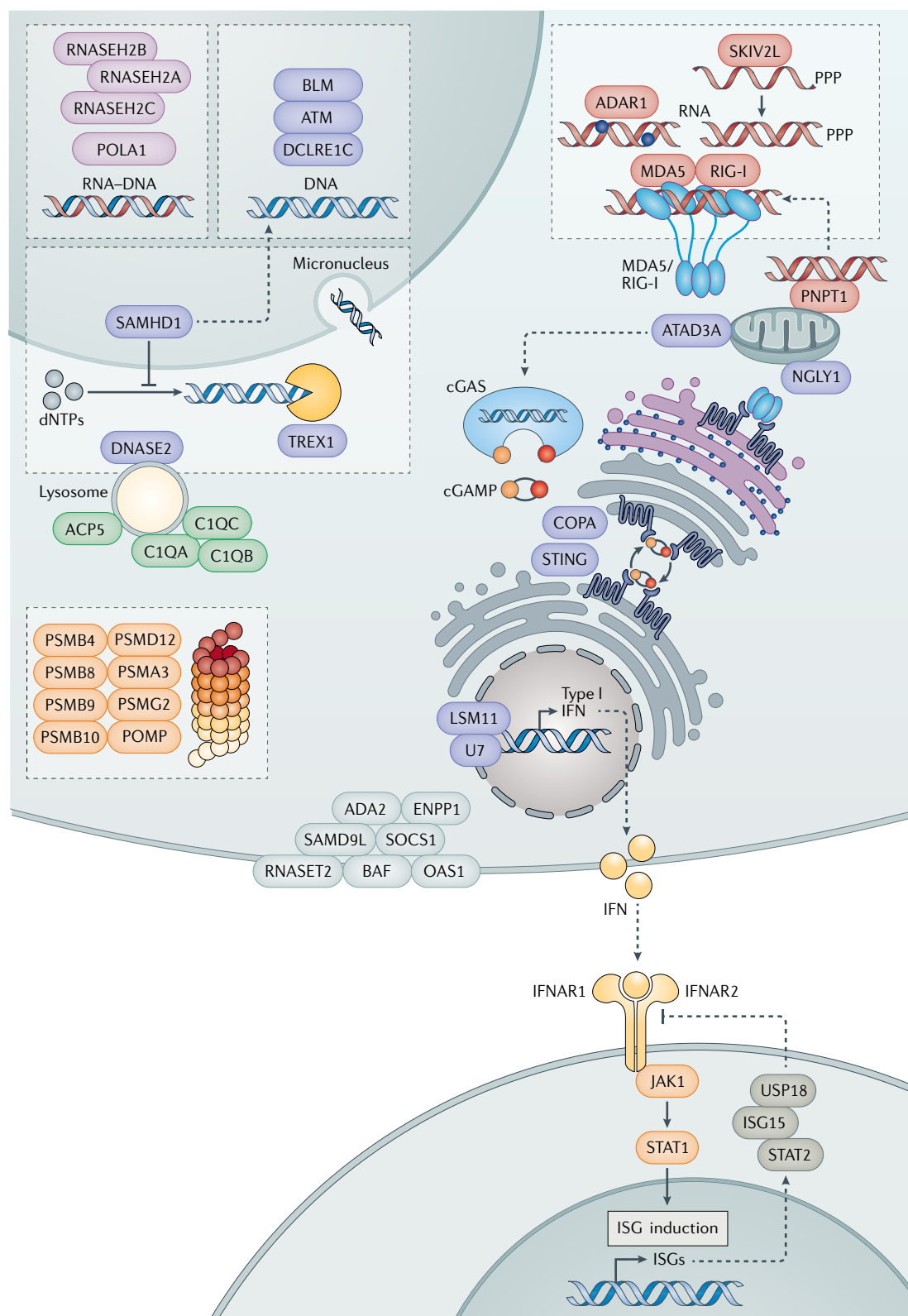
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DNA and RNA. That is to say, at the most basic level, the monogenic type I interferonopathies represent a failure of self versus non-self discrimination. If we take a pragmatic approach to their definition²⁷, and put aside for the moment the question of the causal relationship to pathogenesis (considered further later), the consistent ex vivo

and in vitro observation of enhanced type I interferon signalling in a specific disease setting indicates a biological link between that mutant genotype and interferon homeostasis. On the basis of this simple criterion, we suggest that, currently, at least 38 Mendelian genotypes can be considered as type I interferonopathies (FIG. 1).

◀ **Fig. 1 | Putative type I interferonopathy genotypes.** Mutations affecting ribonuclease H2 (RNase H2), a trimeric protein (encoded by *RNASEH2A*, *RNASEH2B* and *RNASEH2C*), and POLA1, the catalytic subunit of DNA polymerase- α , an essential component of the DNA-replication machinery, are suggested to result in an alteration in cytosolic levels of RNA–DNA hybrids. Mutations in *BLM*, *ATM* and *DCLRE1C*, encoding the RecQ-like helicase BLM, the DNA repair protein ataxia telangiectasia mutated (ATM) and the DNA double-strand break repair protein Artemis, respectively, lead to the accumulation of products of DNA damage. SAMHD1 hydrolyses deoxynucleoside triphosphates (dNTPs) and may also play a role in DNA repair, while TREX1 degrades single-stranded and double-stranded DNA molecules. DNASE2, encoding the lysosomal endonuclease DNase II (DNASE2), promotes clearance of nucleic acids generated through apoptosis and the phagocytosis of maturing erythroblast nuclei. Mutations in *LSM11* and *RNU7-1* result in a disturbance of histone stoichiometry, leading to sensing of nuclear DNA. *ATAD3A* mutations result in a leakage of mitochondrial DNA into the cytosol. All of the aforementioned mutant genotypes signal to interferon induction through cyclic GMP–AMP (cGAMP) synthase (cGAS)–STING signalling, which leads to the production of type I interferon (via activation of TANK-binding kinase 1 (TBK1)–interferon regulatory factor 3 (IRF3) and possibly NF- κ B (not shown)). Gain-of-function mutations in STING lead to constitutive translocation of the protein from the endoplasmic reticulum to the Golgi apparatus, and dominant negative mutations in coatamer subunit- α (COPA), involved in retrograde Golgi apparatus to endoplasmic reticulum vesicular transport, also result in abnormal STING trafficking. MDA5 (encoded by *IFIH1*) and RIG-I (encoded by *DDX58*) normally sense exogenous viral double-stranded RNA (dsRNA); Aicardi–Goutières syndrome-related gain-of-function mutations in MDA5 lower its activation threshold to enable sensing of endogenous dsRNA species. dsRNA-specific adenosine deaminase 1 (ADAR1) deaminates adenosine to inosine, and loss-of-function mutations are proposed to result in the generation of abnormally immunogenic dsRNA species derived from Alu inverted repeats. Mutations in any of these proteins activate interferon signalling via an RNA-sensing pathway involving MAVS. The same is true of mutations in the mitochondrial ribonuclease polynucleotide phosphorylase (PNPT1) and in the RNA helicase SKIV2L, which plays a role in limiting the activation of the cytosolic dsRNA receptor machinery in response to IRE1-mediated RNA degradation. The predominant signalling pathway induced by mutations in N-glycanase (NGLY1), a conserved deglycosylation enzyme, remains unclear. The signalling pathways involved in inducing an interferon signature due to mutations in C1q, the first protein of the classical complement pathway, encoded by *C1QA*, *C1QB* and *C1QC*, and *ACP5*, which encodes the lysosomal phosphatase tartrate-resistant acid phosphatase (TRAP), and in the multiple genes encoding distinct proteasomal components, are also currently undefined. After induction, interferon (IFN) binds to heterodimeric interferon- α/β receptor 1 (IFNAR1), leading to phosphorylation of JAK1 and TYK2 and subsequent activation of the transcription factor complex ISGF3. ISGF3 binds to interferon-stimulated response elements in gene promoters and induces the expression of interferon-stimulated genes (ISGs). USP18 is a negative regulator of signalling downstream of IFNAR1. Ubiquitin-like protein ISG15 stabilizes the level of intracellular USP18. Mutations in *ISG15* cause a reduction of the level of USP18, resulting in enhanced interferon production. While STAT2 plays a role in positive interferon signal induction, homozygous separation-of-function mutations at p.Arg148 lead to disruption of a role in limiting IFNAR2 signalling. Gain-of-function mutations in JAK1 and STAT2 lead to enhanced type I interferon and other cytokine signalling pathways. We are uncertain of the interferon status of disease related to mutations in adenosine deaminase 2 (ADA2), sterile α -motif domain-containing protein 9-like (SAMD9L), suppressor of cytokine signalling 1 (SOCS1), barrier-to-autointegration factor 1 (BAF), ENPP1 ectonucleotide pyrophosphatase/phosphodiesterase (ENPP1), ribonuclease T2 (RNASET2) and oligoadenylate synthetase 1 (OAS1), encoded by *CECR1*, *SAMD9L*, *SOCS1*, *BAF1*, *ENPP1*, *RNASET2* and *OAS1* respectively, either because of a current lack of or because of the presence of conflicting clinical, in vitro, ex vivo or in vivo evidence. PPP, triphosphate.

Notably, 17 of these 38 mutated gene products act directly on nucleic acid substrates, referred to here as nucleic acid ‘metabolism’, or mediate their sensing (FIG. 2). Of the remaining 21 genotypes, two encode genes that have a primary role in transducing a DNA signal to an innate immune response, five are involved in type I interferon receptor signalling — leading to a gain of function or affecting negative feedback — and two gene products contribute to the maintenance of mitochondrial integrity. Eight further genes relate to the

proteasome, where the precise link to type I interferon induction remains enigmatic. Finally, the relationship of mutations in *ACP5* (which encodes tartrate-resistant acid phosphatase type 5) and in *C1QA*, *C1QB* or *C1QC* (which encode the complement component C1q) to disease remains unclear to our mind. What these observations additionally highlight is the importance of ‘sterile’ self nucleic acid disposal (for example, by TREX1 or DNase II (DNASE2)), ‘compartmentalisation’ of self nucleic acids from nucleic acid sensors (disrupted by, for example, dysfunction of N-glycanase 1 (NGLY1), ATPase family AAA domain-containing protein 3A (ATAD3A) and the U7 small nuclear RNP complex) and modification of endogenous nucleic acids (for example, by double-stranded RNA-specific adenosine deaminase 1 (ADAR1)) in avoiding an autoinflammatory state.

A second interesting lesson arising from the definition of the type I interferonopathies is that mutations in the DNA-sensing pathway and the RNA-sensing pathway can have ‘equivalent’ effects in terms of disease outcome. This is best exemplified by AGS, where a disturbance of either DNA-mediated signalling (due to mutations affecting TREX1, the RNase H2 complex, the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 and the U7 small nuclear RNP complex) or RNA-mediated signalling (due to mutations affecting ADAR1 or MDA5) can result in indistinguishable phenotypes. This is notable, given that these systems are presumed to have evolved to detect distinct classes of pathogen.

Diagnosis

Testing for type I interferonopathies. The first description of enhanced interferon signalling in a monogenic type I interferonopathy involved an assessment of the ability of serum and CSF from patients with AGS to protect Madin–Darby bovine kidney cells from death following exposure to vesicular stomatitis virus⁵ (BOX 1). An antibody neutralization assay showed that the protective antiviral activity was dependent on IFN α but not IFN β , and an absence of IFN γ was recorded by radioimmunoassay. Subsequently, it was shown that evaluating the expression of interferon-stimulated genes (ISGs) — a so-called interferon signature — was more sensitive in defining AGS mutant status²⁸. More recently, digital enzyme-linked immunosorbent assay technology has allowed the direct measurement of IFN α ^{29,30}. These tests have proven highly useful in directing genetic analysis, the interpretation of sequence variants³¹ and the identification of novel type I interferonopathy genotypes³², including where a link to interferon signalling had not been previously recognized. Important examples of the latter situation include the demonstration of type I interferon induction due to dysfunction of PSMB8 (REFS^{33,34}), coatamer subunit- α (COPA)^{35,36} and ATAD3A^{37,38} 2, 3 and 5 years, respectively, after the initial description of disease-associated mutations in the genes encoding these proteins. Tests of type I interferon signalling status are still not included in mainstream clinical medicine assessment, although the use of digital enzyme-linked immunosorbent assay, Nanostring³⁹ and other⁴⁰ technologies may change this situation, particularly as the (early)

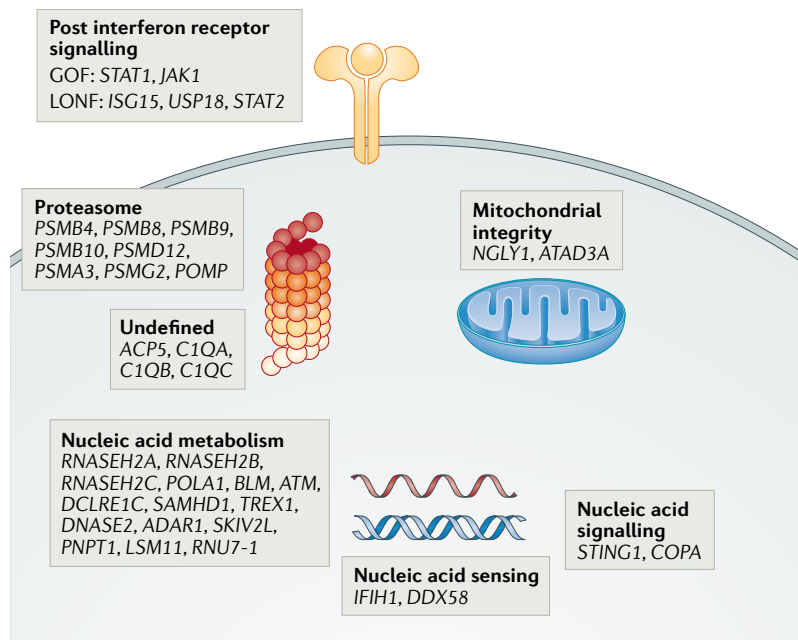


Fig. 2 | Categorization of putative type I interferonopathy genotypes according to the function of the encoded gene product. Seventeen of the 38 putative type I interferonopathy mutated gene products act directly on nucleic acid substrates (nucleic acid ‘metabolism’) or are involved in nucleic acid sensing, two have a primary role in transducing a DNA signal to an innate immune response, five are involved in downstream regulation of type I interferon receptor signalling and two contribute to the maintenance of mitochondrial integrity. Eight further genes relate to the proteasome, where the precise link to type I interferon induction remains unclear. The relationship of mutations in *ACP5* and *C1QA*, *C1QB*, and *C1QC* mutations to disease remains unproven to our mind. GOF, gain of function; LONF, loss of negative feedback.

recognition of phenotypes associated with enhanced type I interferon signalling becomes more important with the introduction of anti-interferon treatments. In this regard, intriguing recent data have suggested that AGS might be associated with a disturbance of very long chain fatty acid metabolism. Specifically, Armangue et al.⁴¹ and Tise et al.⁴² described cases of AGS identified through newborn screening programmes for X-linked adrenoleukodystrophy, raising the possibility that AGS might be ascertained presymptomatically. The mechanism here remains unknown, perhaps relating to a disturbance of central nervous system (CNS) myelination or of a link between antiviral signalling and peroxisome integrity worthy of further investigation^{43,44}. Alternative biomarkers will be desirable to assess new therapies, and might include indicators of end organ damage not specifically related to underlying pathogenesis (for example, neurofilament light and glial fibrillary acidic protein in the case of the CNS).

Mechanisms of interferon induction

We can reasonably consider endogenous nucleic acid species driving type I interferon to be of either nuclear or mitochondrial origin. Here we highlight recent insights derived from the study of the type I interferonopathies relating to this point, as well as genotypes associated with a disturbance of DNA stimulus signal transduction, downstream interferon receptor signalling and proteasomal function.

The nucleus. As previously discussed²⁷, immunostimulatory nucleic acids originating in the nucleus most likely arise from either chronic DNA damage or the misprocessing of retroelements. While not formally addressed here, the observation of enhanced type I interferon signalling in the context of Bloom syndrome⁴⁵, Artemis deficiency⁴⁶ and ataxia telangiectasia^{46,47} highlights the immunostimulatory potential of products of DNA damage in triggering innate immune signalling. In regard to AGS, the precise nature of the putative stimulating nucleic acid ligands remains uncertain, with the case perhaps most convincingly made for a role of Alu elements related to mutations in *ADAR*, which encodes *ADAR1* (REF.⁴⁸).

Cyclic GMP–AMP (cGAMP) synthase (cGAS) is the principal intracellular DNA sensor, catalysing the synthesis of the 2',3'-linked dinucleotide cGAMP upon DNA binding^{49,50}. cGAMP subsequently activates the transmembrane adaptor protein STING (stimulator of interferon genes) on the endoplasmic reticulum (ER), thereby linking DNA detection to TANK-binding kinase 1 (TBK1)–interferon regulatory factor 3 (IRF3) activation. It was previously proposed that the sensing of foreign DNA occurs in the cytosol⁵¹. However, recent data have placed cGAS in the nucleus⁵², begging the question as to how activation of cGAS in response to host genomic DNA is avoided. Related to this point, in 2020, biallelic mutations in *LSM11* and *RNU7-1*, which are genes encoding components of the replication-dependent histone pre-mRNA processing complex, were described as two additional AGS-associated genotypes⁵³. These mutations result in the misprocessing of core and linker histone mRNA transcripts and a disturbance of linker histone protein stoichiometry, leading to an altered distribution of nuclear cGAS, and enhanced interferon signalling mediated by the cGAS–STING pathway. It has been shown that cGAS can bind to, and be activated by, chromatin⁵⁴, and that nucleosomes limit the activation of cGAS by naked DNA⁵⁵. Furthermore, recent cryo-electron microscopy structures have demonstrated that cGAS is physically sequestered away from nuclear DNA through its binding to the acidic patch of the core histones H2A and H2B^{56–60}. While a disturbance of core histones cannot be ruled out, mutations in *LSM11* and *RNU7-1* were shown to particularly affect the level of the linker histone H1.4, and the in vitro production of cGAMP by recombinant cGAS was increased following exposure to chromatin lacking linker histone compared with chromatin incorporating it. These data raise the possibility that other histone-related proteins might also play essential physiological roles in limiting cGAS activation within the nuclear compartment.

The mitochondria. Each cell can contain thousands of mitochondria, and nucleic acids with immunostimulatory potential are generated during the transcription and replication of mitochondrial DNA. Mutations in *PNPT1* represent the first described Mendelian mitochondrial disease associated with enhanced type I interferon signalling⁶¹. Bidirectional transcription of the mitochondrial circular genome necessitates the decay of one strand so as to prevent the formation of double-stranded RNA,

Alu elements

Part of a family of short interspersed nuclear elements that replicate via long interspersed nuclear element-mediated reverse transcription of an RNA polymerase III transcript. Each Alu element is roughly 280 bp long, followed by a poly(A) tail of variable length. Alu elements are the most abundant sequence repeats in the human genome, making up 5–10% of the total.

with this function mediated by the mitochondrial degradosome, a complex including the ribonuclease polynucleotide phosphorylase, encoded by *PNPT1*. Notably, loss of polynucleotide phosphorylase activity resulted in the escape of mitochondrial double-stranded RNA into the cytoplasm and enhanced expression of ISGs through MDA5 in the blood of patients with biallelic *PNPT1* mutations. Loss of function of NGLY1, a conserved deglycosylation enzyme, has also been reported to result in chronic activation of cytosolic nucleic acid sensing, this time as a result of mitochondrial fragmentation and the release of immunostimulatory nucleic acid into the cytoplasm⁶², with increased ISG expression observed in patient-derived lymphoblastoid cell lines. More recently, pathogenic mutations in *ATAD3A*, which encodes the ubiquitously expressed ATPase *ATAD3A*, have been shown to cause mitochondrial DNA-dependent upregulation of type I interferon signalling in the context of autoimmunity (specifically, features of systemic sclerosis) and neurological disease³⁸. Ex vivo, there was a marked and persistent elevation of the expression of ISGs and IFN α in the blood, CSF and primary fibroblasts of patients with mutations in *ATAD3A*. Although the precise mechanism remains unclear, as in the case of NGLY1, these findings possibly result from a leakage

of mitochondrial DNA into the cytoplasm, and beg questions as to the ways in which nucleic acids are retained in, and might escape from, mitochondria⁶³. The observation that both mitochondrial RNA and mitochondrial DNA can induce interferon signalling raises the possibility that innate immune system engagement may contribute to the phenotype of monogenic mitochondrion-related disorders more generally. Of note, type I interferon induction by mitochondrion-derived nucleic acid has also been implicated in a number of common phenotypes, including Parkinson disease⁶⁴, motor neuron disease⁶⁵ and SLE⁶⁶.

The ER–Golgi apparatus axis. Heterozygous dominant-negative mutations in *COPA* cause inflammatory arthritis and severe interstitial pulmonary disease³⁵. This phenotype overlaps with that seen in patients with STING-associated vasculopathy with onset in infancy (SAVI)^{67,68}, where gain-of-function heterozygous *STING1* mutations cause constitutive translocation of STING from the ER to the ER–Golgi intermediate compartment^{69,70}, a process central to the activation and subsequent termination of type I interferon production in response to cytoplasmic DNA signalling⁷¹. *COPA* is a subunit of the coatomer COPI, a complex involved in the retrograde transport of vesicles from the Golgi apparatus to the ER, and recently published results implicate this function as essential in maintaining immunological homeostasis^{72–74}. Specifically, these new data suggest that basal cGAS–cGAMP-mediated STING stimulation triggers STING trafficking towards the Golgi apparatus, but that type I interferon pathway activation is limited by the active reverse shuttling of STING back to the ER⁷⁵. Such retrograde trafficking is mediated by the COPI machinery and involves the sorting protein *COPA*, which, through the adaptor molecule SURF4, tethers STING as cargo in COPI vesicles. Disruption of Golgi apparatus to ER trafficking, due to dominant-negative mutations in *COPA*, results in the trapping of STING in the Golgi apparatus and an immune response equivalent to that observed in SAVI. All told, these data highlight the importance of the ER–Golgi apparatus axis in the regulation of STING activation, the potential for manipulating this axis both to dampen and to enhance interferon signalling, and the possibility that other mutant genotypes involved in this pathway might be novel type I interferonopathies.

Interferon receptor signalling. The binding of type I interferons to the receptor subunits interferon- α/β receptor 1 (IFNAR1) and IFNAR2 induces the activation of the Janus family tyrosine kinases TYK2 and JAK1. Activated TYK2 and JAK1 in turn phosphorylate STAT1 and STAT2, resulting in formation of the DNA-binding STAT1–STAT2–IRF9 ternary complex ISGF3, which then activates the transcription of genes with an interferon-stimulated response element in their promoters. USP18 exerts a negative regulatory effect on type I interferon signalling by competing with JAK1 for IFNAR2 binding, and mutations in *USP18* and *ISG15*, which directly regulates USP18 stability, result in aberrant type I interferon induction in humans^{76,77}.

Box 1 | Interferon signalling assays

Cytopathic protection assay

Assessment of the ability of patient serum or cerebrospinal fluid (CSF) to protect cells against virus-induced death. The direct link to antiviral activity reflects physiological relevance, but the test is less sensitive in defining mutant status than interferon-stimulated gene (ISG) expression.

Interferon signature

Quantification of the expression of (a variable number of) ISGs initially chosen on the basis of genome-wide microarray and RNA sequencing. The PAXgene system, with samples travelling stably at room temperature for at least 72 hours, is highly practicable. ISG expression is not specific to any interferon subtype. ISGs cannot normally be assessed in CSF because of low cell numbers.

Single-molecule array

Measurement of interferon- α (IFN α) by digital enzyme-linked immunosorbent assay in multiple tissues, including CSF. Costs of the platform/reagents, antibody specificity and the need to transfer material on dry ice are important considerations.

Comments

- Depending on the clinical context, serial testing may be necessary to minimize the risk of misinterpretation of a 'false positive' result (for example, due to infection).
- The ability to record a disease signal in blood and CSF has proven highly useful, even if neither necessarily represents the relevant tissue in terms of underlying disease (so a negative result does not preclude a role for interferon in pathogenesis).
- Although reliable in many genotypes (for example, the interferon signature is positive in close to 100% of patients with *STING1* mutations), there are exceptions; most particularly, around 25% of patients with *RNASEH2B* mutations did not show ISG upregulation when tested after the age of 4 years.
- These tests are not disease specific, being common to a number of apparently distinct phenotypes, such as Aicardi–Goutières syndrome, systemic lupus erythematosus and dermatomyositis.
- There is poor correlation between the interferon score and clinical status, exemplified by individuals with a completely normal phenotype demonstrating marked, and apparently lifelong, upregulation of interferon signalling.
- While the interferon score is an excellent disease biomarker, our experience is it has not behaved as a (highly) reactive biomarker relating to JAK1 inhibition in patients with Aicardi–Goutières syndrome and *STING1* mutations, at least at the doses used.

More recently, a third autosomal recessive genotype associated with defective negative regulation of IFNAR signalling was reported^{78,79}. Here, a homozygous p.Arg148Trp or p.Arg148Gln separation-of-function mutation in STAT2 results in a failure of the protein to interact with USP18, which is apparently essential for the recruitment of USP18 to IFNAR2 (REF.⁸⁰). These three disorders are of particular significance as they implicate a 'pure' defect of unrestrained interferon signalling alone as the cause of disease rather than a specific nucleic acid-sensing pathway. The phenotypic overlap with other type I interferonopathies is notable, particularly with regard to neurological involvement — so much so that we suggest that mutations in *USP18* and *STAT2* might reasonably be considered as 'severe AGS'. These mutant genotypes provide compelling support for the type I interferonopathy hypothesis, strengthening the clinical rationale for the therapeutic blockade of interferon signalling. Indeed, a child with a homozygous donor splice-site mutation in *USP18* demonstrated an apparently favourable response to JAK1 inhibition⁸¹.

Contrasting mechanistically with loss of post-interferon receptor negative feedback, increased ISG expression in whole blood⁸² and hyperphosphorylation of STAT1 in response to type I interferon in peripheral blood mononuclear cells⁸³ is seen with *STAT1* gain-of-function mutations. While intracranial calcification⁸⁴ and aortic calcification⁸⁵ have been reported in this context, the core phenotype includes chronic mucocutaneous candidiasis and autoimmune

hypothyroidism. Gain of function downstream of IFNAR has also been recorded due to *JAK1* mutations, which are associated with a complex multisystem inflammatory phenotype^{86,87}. It is important to note that both of these disorders involve the triggering of multiple cytokine pathways in addition to type I interferon signalling, likely explaining aspects of their phenotypes not observed in other type I interferonopathies.

Proteasome. Loss of function of proteasome-related proteins appears to be consistently associated with enhanced type I interferon signalling, with the number of genes so far identified — eight in total — outnumbered only by the bewildering array of alternative names and acronyms coined. Here, as first suggested by Sanchez et al.⁸⁸, we refer to this group of disorders as 'proteasome-associated autoinflammatory syndromes' (PRAAS), variably encompassing early-onset neutrophilic infiltrative skin disease, panniculitis and lipodystrophy, blood dyscrasias (anaemia and thrombocytopenia), immunological dysfunction (for example, lymphopenia, dysgammaglobulinaemia and immunodeficiency), muscle atrophy, joint contractures and intracranial calcification. Proteasomes are heteromultimeric protein complexes found in all eukaryotic cells that catalyse the non-lysosomal proteolytic degradation of ubiquitinated proteins⁸⁹. Known PRAAS-associated mutations occur in genes encoding constitutive proteasome subunits (PSMB4 and PSMA3), immunoproteasome subunits (PSMB8, PSMB9 and PSMB10), the 19S regulatory particle (PSMD12) and proteasome assembly factors (POMP and PSMG2). Brehm et al.⁹⁰ made the notable observation of 'additive' loss-of-function mutations in proteasome components conforming to a pattern of digenic inheritance. Mutations in these genes result in decreased proteasome activity, an aberrant accumulation of cytosolic ubiquitinated protein conjugates and activation of an unfolded protein response. Importantly, these mutant genotypes are also associated with a marked induction of ISG expression. While several groups are known to be working in this area, the mechanism by which decreased proteasome activity causes innate immune activation awaits elucidation (with Brehm et al.⁹⁰ indicating that the pathway involved was not dependent on STING).

Phenotypes, expression and penetrance

Given the hypothesized fundamental role of type I interferon in the pathogenesis of type I interferonopathies, we hold that the type I interferonopathies should be considered as autoinflammatory in basis, with 'spillover' into autoimmunity in some cases. Discrete phenotypic labels can be important for affected families and individuals when thinking about prognosis (BOX 2; TABLE 1). At the same, the premise of the type I interferonopathy categorization is that these disorders have a common pathology (and, possibly, route to therapy), so we think that there is value in the use of the umbrella term type I interferonopathies. There is a striking overlap of clinical features, particularly the involvement of the brain and skin, across several type I interferonopathies. However, clear phenotypic differences also exist between

Box 2 | Phenotypes

The range of phenotypes encompassed by the type I interferonopathies is remarkably broad. However, a number of clinical entities are easily recognizable, including 'classical' Aicardi–Goutières syndrome (AGS), STING-associated vasculopathy of infancy (SAVI), COPA syndrome and spondyloenchondrodysplasia.

Shared clinical features are seen across the type I interferonopathies, most particularly intracranial calcification and vasculitic skin lesions. Neurological disease with lupus-like stigmata should act as a diagnostic prompt. Interstitial lung (fibrosis/haemorrhage) plus joint disease is characteristic of SAVI and COPA syndrome.

Overviews of clinical phenotype based on important cohorts are available for a number of genotypes, including AGS overall¹³⁷, specific AGS-related genotypes due to mutations in double-stranded RNA-specific adenosine deaminase 1 (ADAR1)¹³⁸ and MDA5 (REF.³¹), spondyloenchondrodysplasia¹³⁹, SAVI⁹¹ and COPA syndrome^{72,140}.

Marked phenotypic differences can occur within the same genotype (and the same family). For example, gain-of-function MDA5 mutations can be associated with AGS, non-syndromic spastic paraparesis, Singleton–Merten syndrome and complete clinical non-penetrance into old age. Of passing note, patient 2 in the original description by Singleton and Merten developed a fever and lost the ability to walk aged 14 months — in keeping with an AGS-like phenotype.

Clinical non-penetrance is common in interferonopathies inherited as autosomal dominant traits (13.5% for MDA5; perhaps 30% for COPA syndrome). The rate of non-penetrance in the autosomal recessive disorders is unknown, as clinically asymptomatic siblings are not normally genotyped. While clinically non-penetrant individuals with *IFIH1* mutations usually demonstrate robust interferon signalling upregulation, tests of interferon signalling status are close to normal in asymptomatic individuals heterozygous for *COPA* mutations.

Environmental triggers (infections and vaccination) and additive/protective genetic factors might influence disease onset, expression and flares/progression.

'Outlier' disorders — that is, those showing little clinical overlap with other type I interferonopathies (for example, Bloom syndrome) — likely reflect the importance of distinct functions of the relevant protein and a lesser, if any, contribution of enhanced interferon signalling to the phenotype.

Table 1 | Genotypes linked to putative type I interferonopathies

Gene	Protein function	Proposed link to type I interferon signalling	Mutation effect	Phenotypic label/features
<i>TREX1</i>	Deoxyribonuclease	Cytosolic DNA	LOF (autosomal recessive or dominant negative)	AGS, FCL, SLE
<i>DNASE2</i>	Deoxyribonuclease	Cytosolic DNA	LOF (autosomal recessive)	Neonatal anaemia, glomerulonephritis, liver fibrosis, deforming arthropathy
<i>SAMHD1</i>	Control of dNTP pool	Cytosolic DNA	LOF (autosomal recessive)	AGS, FCL, cerebrovascular disease
<i>STING1</i>	Cytosolic DNA signal transduction	Cytosolic DNA	GOF (autosomal dominant)	STING-associated vasculopathy with onset in infancy, FCL
<i>RNASEH2A</i>	Ribonuclease	Cytosolic RNA–DNA hybrids	LOF (autosomal recessive)	AGS
<i>RNASEH2B</i>	Ribonuclease	Cytosolic RNA–DNA hybrids	LOF (autosomal recessive)	AGS, spastic paraparesis
<i>RNASEH2C</i>	Ribonuclease	Cytosolic RNA–DNA hybrids	LOF (autosomal recessive)	AGS
<i>POLA1</i>	DNA polymerase	Cytosolic RNA–DNA hybrids	LOF (X-linked recessive)	X-linked reticulate pigmentary disorder
<i>ADAR1</i>	RNA editing	Cytosolic dsRNA	LOF (autosomal recessive or dominant negative)	AGS, dyschromatosis symmetrica hereditaria, bilateral striatal necrosis, spastic paraparesis
<i>IFIH1</i>	dsRNA sensor	Cytosolic dsRNA	GOF (autosomal dominant)	AGS, spastic paraparesis, Singleton–Merten syndrome
<i>DDX58</i>	dsRNA sensor	Cytosolic dsRNA	GOF (autosomal dominant)	Singleton–Merten syndrome, juvenile open-angle glaucoma
<i>SKIV2L</i>	RNA helicase	Cytosolic RNA (UPR)	LOF (autosomal recessive)	Trichohepatoenteric syndrome
<i>LSM11</i>	RDH pre-mRNA processing	Histone stoichiometry/genomic DNA	LOF (autosomal recessive)	AGS
<i>RNU7-1</i>	RDH pre-mRNA processing	Histone stoichiometry/genomic DNA	LOF (autosomal recessive)	AGS
<i>PNPT1</i>	Polynucleotide phosphorylase	Mitochondrial RNA	LOF (autosomal recessive)	Infantile encephalopathy, bilateral striatal necrosis
<i>NGLY1</i>	N-deglycosylation	Mitochondrial DNA and RNA (indirect)	LOF (autosomal recessive)	Infantile encephalopathy, movement disorder
<i>ATAD3A</i>	Multiple	Mitochondrial DNA	Dominant negative (autosomal dominant)	Global developmental delay, systemic sclerosis, spastic paraparesis
<i>ATM</i>	dsDNA break repair	dsDNA breaks	LOF (autosomal recessive)	Ataxia telangiectasia
<i>DCLRE1C</i>	dsDNA break repair	dsDNA breaks	LOF (autosomal recessive)	Immunodeficiency
<i>BLM</i>	Genome stability	DNA damage	LOF (autosomal recessive)	Bloom syndrome
<i>COPA</i>	Vesicle transport (ER to Golgi apparatus)	STING trafficking	Dominant negative (autosomal dominant)	Interstitial lung disease, pulmonary haemorrhage, arthropathy, glomerulonephritis
<i>ISG15</i>	Inhibition of ISG transcription	IFNAR2 signalling	LOF (autosomal recessive)	Intracranial calcification, Mendelian susceptibility to mycobacterial disease
<i>UPS18</i>	Inhibition of ISG transcription	IFNAR2 signalling	LOF (autosomal recessive)	AGS-like
<i>STAT2</i>	Inhibition of ISG transcription	IFNAR2 signalling	LOF (autosomal recessive; separation-of-function)	AGS-like
<i>STAT1</i>	Cytokine signalling	ISG signalling	GOF (autosomal dominant)	Chronic mucocutaneous candidiasis, immunodeficiency, autoimmunity, intracranial calcification
<i>JAK1</i>	Cytokine signalling	ISG signalling	GOF (autosomal dominant)	Eosinophilia, atopy
<i>C1QA</i>	Alternative complement pathway	Immune complexes/CD8 ⁺ T cell metabolism	LOF (autosomal recessive)	SLE
<i>C1QB</i>	Alternative complement pathway	Immune complexes/CD8 ⁺ T cell metabolism	LOF (autosomal recessive)	SLE
<i>C1QC</i>	Alternative complement pathway	Immune complexes/CD8 ⁺ T cell metabolism	LOF (autosomal recessive)	SLE
<i>ACP5</i>	Phosphatase	Phosphorylation of osteopontin	LOF (autosomal recessive)	Spondyloenchondrodysplasia, SLE
<i>PSMB8</i>	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS

Table 1 (cont.) | Genotypes linked to putative type I interferonopathies

Gene	Protein function	Proposed link to type I interferon signalling	Mutation effect	Phenotypic label/features
PSMB4	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS
PSMA3	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS
PSMB9	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS
POMP	Proteasome	Unknown	Dominant negative (autosomal dominant)	PRAAS
PSMB10	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS
PSMG2	Proteasome	Unknown	LOF (autosomal recessive)	PRAAS
PSMB12	Proteasome	Unknown	LOF (autosomal dominant)	Global developmental delay

The table provides an overview of genotypes considered as consistently associated with enhanced type I interferon signalling, with protein function, link to interferon signalling, proposed molecular mechanism and categorization of currently recognized associated clinical phenotypes. ADAR1, double-stranded RNA-specific adenosine deaminase 1; AGS, Aicardi–Goutières syndrome; COPA, coatomer subunit- α ; dNTP, deoxynucleoside triphosphate; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; ER, endoplasmic reticulum; FCL, familial chilblain lupus; GOF, gain of function; ISG, interferon stimulated gene; LOF, loss of function; PRAAS, proteasome-associated autoinflammatory syndrome; RDH, replication-dependent histone; SLE, systemic lupus erythematosus; UPR, unfolded protein response.

some of these genotypes; for example, the severe lung disease seen with mutations in *STING1* and *COPA* is not a feature previously noted in the context of other putative type I interferonopathies. Furthermore, apparently distinct complex diseases, particularly SLE and dermatomyositis, are also characterized by enhanced type I interferon signalling. The basis of such variable expression remains unclear; indeed, the diversity of clinical phenotypes associated with a type I interferon signature might be considered as undermining the type I interferon hypothesis per se (together with the observation of clinical non-penetrance despite enhanced type I interferon signalling — see later). Distinct expression patterns of disease-associated proteins, their protein partners, interferon-inducing signalling components and proteins involved in alternative (‘redundant’) signalling pathways might all be relevant here. Some preliminary light has been shed on this topic recently with the simple observation that while IFN α is present in the CSF and serum of a number of interferon-related diseases, the primary sites of interferon production in AGS (a neurologically focused phenotype) and SAVI (where neurological disease is rare) are, respectively, the CNS and the periphery³⁰. Whereas *STING* signalling is central to seven of nine AGS-associated genotypes and all SAVI cases (FIG. 1), an important distinction is that endogenous nucleic acid ligands activate cGAS–cGAMP–*STING* signalling in AGS, but in SAVI mutant *STING* proteins are constitutively active without a requirement for ligand engagement.

Clinical non-penetrance (or age-related penetrance in some cases) is a common feature of the dominant negative p.Gly1007Arg mutation in ADAR1, the known dominant negative mutations in *TREX1*, and heterozygous mutations in *COPA* and *IFIH1* (dominant negative and gain of function, respectively). In a recent study of 74 individuals harbouring pathogenic lesions in *IFIH1*, 13.5% of these individuals (seven of whom were older than 50 years) were clinically asymptomatic³¹. For those with dominant negative mutations in *COPA*, the rate of clinical non-penetrance is estimated from the literature at around 30%. By contrast, reported carriers of a *STING* gain-of-function mutation are almost invariably

symptomatic, although phenotypic variability (variable expression) can be observed (even within the same family)⁹¹. Of note, while clinical non-penetrance is a feature of MDA5 gain of function, such asymptomatic individuals usually demonstrate a persistent upregulation of ISG transcripts³¹, contrasting with *COPA* syndrome, where the interferon signature is apparently normal or only minimally elevated in asymptomatic carriers⁷². The significance of this observation is unclear.

We draw attention to the fact that while variable expression is well recognized in AGS inherited in an autosomal recessive manner, the rate of clinical non-penetrance in such cases is unknown — because asymptomatic siblings are not typically genotyped. In this regard, we note the report of a woman first developing cutaneous features at the age of 19 years and demonstrating no abnormal neurological features at the age of 32 years in the context of a biallelic p.Ala177Thr mutation in RNase H2b⁹². Broadly speaking, given intrafamilial and interfamilial discrepancies related to the same mutation, such differences in penetrance (and expression) must relate to other factors, genetic or environmental. Although mosaicism might explain occasional cases^{93,94}, non-penetrance is well described in germline inheritance. The possibility of a ‘cumulative’ genetic burden is illustrated by the data from the study of PRAAS mentioned earlier herein⁹⁰. Infection has been noted as a potential trigger of disease in ADAR1-related bilateral striatal necrosis⁹⁵; whether vaccination might act similarly is currently unclear. In this regard, it is important to note that most of the type I interferonopathy-related genes, as well as the key components of the DNA-sensing and RNA-sensing pathways that they regulate, are strongly inducible by interferons. Thus, one can envision a simple gene–environment relationship in which infection could induce the expression of key sensors above a critical threshold, which then causes aberrant detection of self nucleic acids and progression to symptomatic disease⁹⁶. Age at exposure to a given environmental factor might also be important, perhaps reflecting changes in the immune system over time (akin to the situation with the risk of invasive pneumococcal disease in deficiency of IRAK4 and MYD88 (REF. 97)). The question

remains as to whether clinically asymptomatic individuals are at risk of developing later-onset disease. An excellent overview of the general principles underlying penetrance in immunological disease is available⁹⁸.

Mouse models of the type I interferonopathies

Our understanding of the biology of the type I interferonopathies has been informed by a number of mouse models defining the relationships between Mendelian interferonopathy gene products and the innate immune pathways that they regulate. Thus, it is now well established that TREX1, RNase H2 and SAMHD1 are specific regulators of the cGAS–STING DNA-sensing pathway^{99–104}, whereas the RNA-editing enzyme ADAR1 prevents MDA5–MAVS activation by self RNAs^{105–107}. Additionally, mouse data indicate that SAVI-associated mutations activate STING signalling without a requirement for cGAS¹⁰⁸. These elegantly simple relationships are particularly appealing examples of how self versus non-self discrimination is achieved by the innate immune system, and have motivated billions of dollars of investment in the development of pathway-specific inhibitors that hold new promise for the treatment of AGS and other interferonopathies. Importantly, these observations provide a road map for patient stratification that is essential for the deployment of any new therapy. For example, cGAS inhibitors would be predicted as useful in AGS (excluding AGS due to mutations in *ADAR* and *IFIH1*) but not in SAVI, whereas STING inhibition might have therapeutic value in both of these settings. A fascinating and fundamental question is whether the putative immunostimulatory endogenous ligands

underlying the type I interferonopathies are relevant to, and can be used to stratify, complex interferon-associated diseases such as SLE, for which the precise genetic contributions remain obscure^{96,109,110}.

Despite the importance of these models as experimentally tractable systems to define disease mechanisms, they remain an imperfect approximation of the disease phenotypes that are observed in the corresponding human disease states. Of particular note, the neurological involvement so characteristic of AGS has not been convincingly recorded in any murine system. For example, TREX1-deficient mice develop severe inflammatory myocarditis¹¹¹ in the absence of CNS disease. Moreover, *Samhd1*^{-/-} mice present with a mild interferon signature and no tissue disease at all¹⁰⁴, in contrast to AGS due to SAMHD1 loss of function. Finally, *Adar*-mutant mice, which model the most common mutation (p.Pro193Ala) in ADAR1-related AGS, demonstrate kidney and liver dysfunction but no evidence of brain involvement¹¹². Why are these mouse phenotypes so different from the human diseases that they model? We propose two potential explanations. First, the cell types and tissues that express the relevant sensors and essential negative regulators might not overlap perfectly between humans and mice. Second, the source, abundance and tissue distribution of the endogenous nucleic acids that are acted upon by AGS-related enzymes may differ between humans and mice, with the endogenous RNAs that are ADAR1 substrates and MDA5 ligands a particularly illustrative example. Here, recent evidence implicates inverted repeats of Alu elements in non-coding regions of mRNAs as an abundant reservoir of double-stranded RNAs that are edited by ADAR1 and can potentially activate MDA5 in *ADAR*-mutant human cells^{48,113}. However, Alu elements do not exist in the mouse genome. Instead, mice harbour millions of copies of B2 short interspersed nuclear elements, which, like Alu elements, are derived from 7SL non-coding RNA. B2 short interspersed nuclear elements are half the length of Alu elements, and their distribution in the mouse genome does not overlap with that of Alu elements in the human genome. Therefore, the most compelling source of endogenous RNAs relevant for *ADAR* mutation-driven AGS in humans does not exist in mice. A better understanding of the tissue-specific and species-specific triggers of the type I interferonopathies will provide a framework for exploring the biochemistry and cell biology of nucleic acid metabolism and how it relates to other immune diseases.

Treatments

While a set of mutant genotypes associated with an upregulation of interferon signalling clearly exists, a more important question, at least clinically, is the relevance of this interferon upregulation to phenotype, and thus the potential efficacy of anti-interferon therapy (BOX 3). The convergence of most of the type I interferonopathy genotypes on nucleic acid metabolism and sensing, data from mouse models demonstrating a phenotypic dependence on type I interferon receptor signalling^{17,112,114}, overlap of clinical features (for example, intracranial calcification seen in more than half of

Box 3 | Treatments for type I interferonopathies

The type I interferonopathy concept implies shared pathology, and the schema in FIG. 2 suggests common approaches to therapy: including limiting the production or enhancing the removal of putative self nucleic acid stimuli and blocking signalling downstream of such stimuli.

Points for consideration in treating distinct type I interferonopathies

- The relative contribution of interferon-mediated and interferon-independent aspects of a clinical phenotype needs to be kept in mind.
- What is the window of therapeutic opportunity — that is, at what stage in the disease process must treatment start to avoid irreversible tissue damage?
- Is the target disease a progressive or a static disorder? Thus, is treatment useful only early in the disease process, or is there utility in lifelong treatment, or treatment in association with disease flares?
- Variable disease expression, including complete non-penetrance, can make the assessment of therapeutic efficacy difficult on clinical grounds alone, emphasizing the importance of reactive biomarkers.
- Tissue accessibility, such as central nervous system penetration, is important.
- Is there a role for haematopoietic stem cell or discrete organ (for example, the lungs in STING-associated vasculopathy of infancy and COPA syndrome) transplant in any of the type I interferonopathies?
- Randomization and blinded studies can be challenging in rare disorders with early onset and high mortality.
- Where the aim is to block interferon signalling, the risk of infectious susceptibility needs to be taken into account.
- Combinatorial therapy may be beneficial.
- Experimental medicine approaches are likely to be the only way to assess the true value of different therapeutic strategies in humans.

mutant genotypes; as well as the induction of stigmata of the type I interferonopathies in the context of treatment with type I interferon, (for example, REF.¹¹⁵) and the diseases related to discrete negative regulation of the type I interferon receptor discussed earlier herein all support a primary role of enhanced interferon signalling in driving disease (BOX 4). On the other hand, certain mouse data^{116,117}, imperfect correlations between interferon biomarker status and disease penetrance, and the induction of other proinflammatory cytokines beyond the interferon transcriptional programme (for example, REF.¹¹⁸) suggest that interferon signalling might not be central to disease in all cases. In this regard, three groups have recently shown robust STING-dependent antiviral and antitumour activity that is independent of interferon, possibly mediated by NF- κ B^{119–121}. Of course, interferon signalling might contribute to disease, but not necessarily exclusively so, and disease due to *DNASE2* mutations is possibly instructive here. Thus, *DNASE2*-null mice accumulate undigested DNA in the lysosomes of macrophages, which then chronically activates type I interferon production and results in a lethal perinatal anaemia¹²². Deletion of the type I interferon receptor gene rescues *Dnase2a*-knockout mice from this lethal anaemia¹²³, but these double-knockout mice subsequently develop chronic polyarthritis¹²⁴. Both of these embryonic and postnatal phenotypes are cGAS and STING dependent, indicating dual interferon-mediated and non-interferon-mediated pathways that can drive disease downstream of STING. Therefore, the efficacy of interferon blockade therapy might depend on the ‘purity’ of an interferonopathy phenotype; that is, how much of the phenotype is due to interferon upregulation and how much is related to other functions of the protein (for example, the role of BLM in DNA

repair, or the consequence of dysfunction of ATAD3A for oxidative phosphorylation) and/or induction of non-interferon signalling pathways (through, for example, NF- κ B) (FIG. 3).

In general terms, targeted treatments in the type I interferonopathies might aim at limiting the production or enhancing the removal of putative self nucleic acid stimuli and/or blocking signalling downstream of such stimuli. Related to this latter point, a recently developed mouse model of ADAR1 dysfunction was rescued both by crossing it with an *Ifnar1*-knockout mouse and also by treatment with an inhibitor of the integrated stress response (triggered downstream of the eIF2 α kinase PKR)¹¹². However, considering specific treatment approaches already trialled in humans, two are of note. Firstly, premised on a reduction of immunostimulatory DNA derived through a reverse transcription (RNA > DNA) step in the life cycle of endogenous retroelements^{17,125}, Rice et al.¹²⁶ undertook an open-label pilot study of reverse transcriptase inhibitors in AGS. Patients with mutations in *AGS1*, *AGS2*, *AGS3*, *AGS4* or *AGS5* (that is, excluding *ADAR*-mutant and *IFIH1*-mutant genotypes, where disease is mediated via an RNA signalling pathway) were treated with abacavir, lamivudine and zidovudine for 12 months, and interferon status was assessed before, during and after treatment. The results indicated an effect of treatment in reducing interferon signalling, and possibly increasing cerebral blood flow. A follow-up study is now planned (NCT04731103). While the use of reverse transcriptase inhibitors remains experimental, small case reports (for example, REFS^{127–129}) and four larger observational studies^{91,130–132} (summarized in REF.¹³³) have described encouraging results of the inhibition of JAK1 in several type I interferonopathies in a clinical setting. Clear effects on associated systemic and skin disease indicate that these drugs address a relevant biological pathway. However, the effect on neurological features remains more difficult to assess. Notably in this regard, Neven et al.¹³⁴ described the onset of AGS at the age of 15 months in a child with biallelic mutations in *RNASEH2B*, despite treatment with ruxolitinib (a JAK1 and JAK2 inhibitor) starting at the age of 5 months, when the child was asymptomatic. The study authors observed drug concentrations in the CSF to be only 10% of those in blood, suggesting the importance of CNS drug penetration. The observation of apparent neurological benefit in a child with biallelic mutations in *USP18* following an increase in the dosage of ruxolitinib from 5 to 10 mg twice daily might relate to this same point⁸¹.

The future of treatments relevant to the type I interferonopathies holds considerable promise, with the rapid development in the biotechnology industry of inhibitors of cGAS and STING. Inhibitors of the RIG-I-like receptors, including MDA5, have not yet been described, but are of similar potential interest. All told, the confluence of human genetics and mechanistic definition of the type I interferonopathies has set the stage for a precision medicine approach in this field, matching the specific source of aberrant innate immune signalling to targeted therapy.

Box 4 | Does interferon drive disease in the putative type I interferonopathies?

Supporting evidence

- Correlation of enhanced type I interferon signalling with mutant status.
- Clustering of mutant genotypes with a known role in nucleic acid processing, type I interferon signalling, and in negative feedback of interferon-stimulated gene expression.
- Phenotypic resemblance to in utero-acquired infection in certain cases.
- Phenotypic overlap across genotypes.
- Recapitulation of the neuropathology of Aicardi–Goutières syndrome in a transgenic mouse model chronically producing interferon- α (IFN α) from astrocytes.
- The side effect profile of IFN α used therapeutically.
- Phenotypic rescue in certain murine models when crossed with type I interferon receptor-null mice.
- Apparent clinical efficacy of JAK1 inhibitors (premiered on, but not proven to act through, the blocking of type I interferon receptor signalling).

Contradictory evidence

- Clinical non-penetrance despite enhanced type I interferon signalling.
- The absence of an interferon signature (at least in blood) in some individuals with a mutant genotype.
- The diversity of clinical phenotype associated with a type I interferon signature.
- The observation of phenotypes in STING gain-of-function mice that are not dependent on type I interferon.
- Knowledge that non-interferon inflammatory molecules can also be induced by nucleic acid signalling, in particular NF- κ B through STING.

Conclusions

The clustering of mutant genotypes implicated in nucleic acid metabolism and sensing and in negative regulation of type I interferon signalling — in some cases, for example, DNASE2 deficiency and ATAD3A-related disease, identified through agnostic screening for type I interferon upregulation — provides compelling evidence in support of the type I interferonopathy hypothesis. Notable recent insights derived from the definition and study of this rare disease grouping include the identification of physiologically important Golgi apparatus to ER transport of STING involving COPA^{72–74}, the implication of innate immune system activation as a contributor to the phenotype of certain monogenic mitochondrial diseases^{38,61}, the characterization of a separation-of-function mutation in STAT2 specifically affecting its role in limiting IFNAR2 signalling^{78,79} and the observation that disturbed histone stoichiometry due to mutations in *LSM11* and *RNU7-1* enhances the immunostimulatory potential of nuclear DNA⁵³. All of these findings inform possible novel drug targets relevant to the future treatment of diseases associated with enhanced type I interferon signalling.

Many important questions central to a proper understanding of the type I interferonopathies remain, perhaps the most interesting being the precise molecular drivers, nucleic acid or otherwise, of aberrant cytokine production. Of particular note, at the time of writing of this Review, the mechanism by which proteasomal dysfunction induces type I interferon signalling is unresolved, and how mutations in lysosomal ACP5 result in such a highly penetrant Mendelian mimic of SLE — namely, spondyloenchondrodysplasia — is also deserving of more detailed study. Furthermore, the precise contribution of non-interferon-mediated signalling to clinical disease is unclear in many of these mutant genotypes, and is of fundamental relevance when one is considering approaches to their treatment — an issue that may be resolved only through clinical experimentation in humans.

The broader implications deriving from the study of the type I interferonopathies remain to be determined. Most obviously, the link to SLE and dermatomyositis, both associated with enhanced type I interferon signalling, is likely a fertile ground for investigation, with a number of articles highlighting a link between these

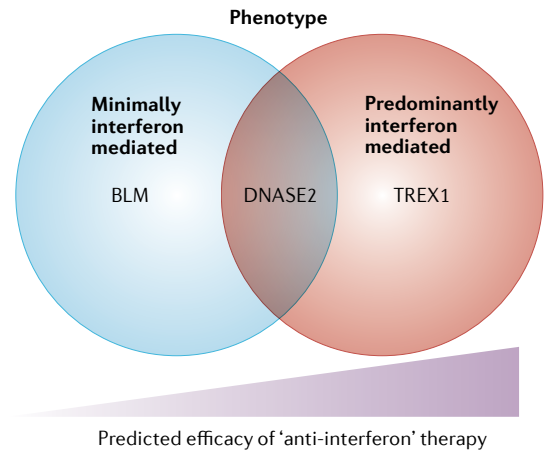


Fig. 3 | Relationship between the relative contribution of interferon-mediated and non-interferon-mediated inflammation to putative type I interferonopathy phenotypes. The effect of ‘anti-interferon’ treatments is expected to depend on the contribution of upregulated interferon signalling to the associated phenotype. Exemplar genotypes are given where the clinical efficacy of such therapies is expected to differ. Other factors (for example, the stage in the disease process at which treatment is started) will likely also be important in determining therapeutic efficacy.

monogenic mutant genotypes and ‘non-syndromic’ systemic lupus erythematosus (for example, REFS^{109,135,136}). Aligned with this point, it is tempting to speculate that polymorphisms in nucleic acid receptors and associated signalling components might confer a selective advantage in fighting infection⁹⁶, noting, for example, that approximately 1 in 300 and approximately 1 in 440 persons of European (non-Finnish) ancestry are heterozygous for the p.Pro193Ala and p.Ala177Thr mutations in ADAR1 and RNase H2B, respectively.

In summary, the past 10 years have witnessed a major expansion in the number of putative type I interferonopathies, knowledge of their pathogenesis and approaches to their treatment. We look forward to further exciting developments in this field in the near-term.

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