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The role of nucleic acid sensors and type I IFNs in patient populations and animal models of autoinflammation

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A spectrum of human autoinflammatory conditions result from defects in cytosolic nucleic acid clearance or overexpression of the nucleic acid sensor STING. These patients often develop severely debilitating lesions and invariably show robust IFN signatures that have been attributed to the cGAS/STING signaling cascade and type I IFN. However, murine models that recapitulate major features of these syndromes have now shown that autoinflammation is more likely to depend on type II IFN/IFNgamma or type III IFN/IFNlambda, and further revealed a critical role for Th1 cells in tissue damage and the persistence of inflammation. These studies provide important insights about the types of IFNs, and the interplay of the innate and adaptive immune systems mediated by these IFNs, that can initiate and maintain the corresponding human diseases. They further point to type II/III IFNs and effector T cells as targets for more effective therapeutic strategies in the treatment of these patient populations.

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Introduction

Microbial nucleic acids (**NA**) are readily detected by a diverse collection of NA sensors that routinely survey cells for signs of infection or tissue damage. Such RNA and DNA sensors play a key role in host defense as they both curb pathogen replication and initiate beneficial repair responses to tissue injury [1]. However, it is becoming increasingly clear that these sensors also recognize endogenous (mammalian) nucleic acids and thereby activate programs that result in autoimmune or autoinflammatory diseases. The connection between NA sensors and sterile inflammation was first shown for the endosomal Toll-like receptors, TLR9 and TLR7 [2,3], and more recently extended to cytosolic DNA and RNA sensors [4]. In healthy individuals, NA sensor activation by endogenous ligands is routinely limited by sequestration of these NA in either the nucleus or mitochondria where they cannot engage receptors located in the cytosol or endolysosomal compartments. However this barrier can be breached by lysosome instability, defects in autophagosome formation, retroelement activity, DNA damage or DNA replication [4–8]. In addition, the inappropriate accumulation of mammalian NAs is constrained by nucleases located outside of cells (DNase I or DNase IL3), within the phagolysosomal compartment (DNase II) or in the cytosol (DNase III/Trex1, RNaseH2) that further ensure that self-ligands do not aberrantly trigger DNA sensors. Thus, autoinflammation can result from gain-of-function mutations in the sensors *per se*, or loss of function mutations in enzymes required for NA degradation or metabolism that normally limit the availability NA ligands.

Autoinflammatory conditions dependent on nucleic acid sensors

Monoclonal type I interferonopathies

The failure to properly degrade extracellular DNA derived from cell debris has been implicated in SLE-like conditions in patient populations and mice deficient in DNaseI or DNAseIL3 expression [9–13]. As with other models of SLE, it is generally agreed the subsequent NA activation of endosomal TLRs, working through a MyD88/IRAK/Traf6 signaling complex, activate both NFκB and IRF5/7 pathways to induce the production of proinflammatory cytokines and type 1 IFNs. In addition, a spectrum of autoinflammatory diseases are initiated through cytosolic NA sensors. For example, the RNA sensors MDA5 and RIG-I converge on the cytosolic mitochondria-associated protein MAVS to activate NFκB and type I IFN programs, and mice expressing a self-activating mutation in MDA5 develop a lupus-like disease in mice that is dependent on MAVS [14]. The DNA sensor cGAS (cyclic GMP-AMP synthase) is a cytosolic nucleotidyl transferase that detects dsDNA and generates a novel second-messenger 2'–5'cyclic GMP-AMP (cGAMP). cGAMP binds the ER-associated signaling intermediate STING causing its dimerization and the subsequent activation of TBK1/IRF3 and IKK/NFκB pathways, resulting in the induction of type I IFNs

and proinflammatory cytokines, respectively [15]. The cGAS/STING pathway has been increasingly implicated in a range of autoinflammatory conditions. Examples or relevant loss of function (LOF) and gain of function (GOF) mutations identified in patient populations and the corresponding gene targeted mouse lines are summarized in Table 1. In accordance with the strong IFN signature associated with each of these diseases, they have been categorized as monoclonal type I interferonopathies [16]. However, as the animal models have now revealed (see below), additional IFNs or IFN-independent pathways are also likely to contribute to the range of clinical manifestations exhibited by patient populations.

Loss of function mutations in Trex1 associated with autoinflammation

Overactivation of NA sensors can lead to a broad spectrum of debilitating autoinflammatory human diseases. One example involves children that develop ***Aicardi–Goutiéres syndrome (AGS)***. These patients share a spectrum of overlapping clinical manifestations that include early onset neurological disorders associated with sterile inflammation of the central nervous system, deforming arthropathies and vascular lesions of the hands and toes [17]. A subset of AGS patients have loss of function mutations in the cytosolic DNase Trex1, a 3'–5' exonuclease that degrades DNA accumulated in the cytosol. These patients fail to adequately degrade DNA leading to DNA accrual in the cytosol and the production of excessive levels of type I interferon [18]. Mutations in additional nucleases or enzymes involved in NA metabolism such as the RNase H2 complex, SAMHD1, and ADAR-1 have also been implicated in AGS [17,19–22].

Murine models have been used to explore the molecular mechanisms that drive autoinflammation in Aicardi–Goutiéres patients [23–27]. Trex1$^{-/-}$ mice have been the most useful. They initially present with an inflammatory myocarditis, associated with high expression of a range of IFN-stimulated genes, that is dependent on IRF3 and the type I IFN receptor (**IFNaR**). They subsequently develop inflammation of other organ systems including skeletal muscle, stomach, and skin, although there is no evidence of the CNS inflammation that is prominent in many of the AGS-afflicted children [23,28,29]. Nevertheless, the association between Trex1 dysfunction, systemic inflammation and type I IFN established the model as a useful tool for exploring the molecular mechanisms responsible for inflammation. It was then shown that STING deficiency completely ablated the production of type I IFNs and systemic inflammation in these mice and that cytokine production by STING-sufficient myeloid and stromal cells played a key role in disease progression [29,30]. Tissue inflammation also depended on the presence of lymphocytes as Rag-deficient and T cell-deficient Trex1$^{-/-}$ mice showed prolonged survival [23,29]. In accordance with the strong IFN signature in the patient populations and the genetic evidence linking type I IFNs to inflammation in the murine model, AGS patients are a prime example of monoclonal type I interferonopathy.

Table 1

Disease manifestations in patient and murine populations with NA-sensor-dependent autoinflammation

Disease	Mutated protein	Patient manifestations	Murine model manifestations	Murine model PRR dependency
SLE	DNase I L3 (LOF) DNase I (LOF)	ANA, glomerulonephritis, IgG deposition, lymphocyte hyperactivation	ANA, splenomegaly, glomerulonephritis, IgG deposition, lymphocyte hyperactivation	MyD88
	MDA5 (GOF)		ANA, IgG deposition, glomerulonephritis	MAVS
Aicardi–Goutieres	TREX1	Leukodystrophy, intracranial calcifications, thrombocytopenia, hepatomegaly, chilblain-like skin lesions	Myocarditis and additional multi-organ inflammation, ANAs	
	RNase2A,2B,2C		Embryonic lethal	STING
	SAMHD1		No phenotype	
	ADAR		Embryonic lethal	MAVS
SAVI	STING (GOF)	Systemic inflammation, lymphopenia, vasculopathy, pulmonary fibrosis	Systemic inflammation, lymphopenia, pulmonary fibrosis	STING
DNase II deficiency	DNase II (LOF)	Anemia, splenomegaly, liver fibrosis, extramedullary hematopoiesis, arthropathy, glomerulonephritis	Embryonic lethality due to anemia	STING
	DNase II (LOF) x IFNAR KO		Late onset of inflammatory arthritis	STING, AIM2
			Early onset of systemic inflammation	Unc93B1
			Excessive accumulation of bone in BM and spleen	STING, Unc93B1

Loss of function mutations in DNaseII associated with autoinflammation

DNaseII-deficiency represents another example of LOF nuclease activity that results in autoinflammation. In the case of DNaseII, the animal models were originally developed by Nagata and coworkers many years before human DNaseII-deficient patients were identified. They found that loss of DNaseII results in embryonic lethality driven by excessive levels of type I IFN and the ensuing development of severe anemia [31,32]. DNaseII$^{-/-}$ IFNaR$^{-/-}$, DNaseII$^{-/-}$ STING$^{-/-}$, and DNaseII$^{-/-}$ cGAS$^{-/-}$ double knockout mice survive, implicating cGAS/STING-driven type I IFN production as the cause of prenatal death [31,33,34]. However, the DNaseII$^{-/-}$ IFNaR$^{-/-}$ mice are not disease-free. They develop a late onset inflammatory arthritis that is STING-dependent but presumably due to inflammatory cytokines downstream of the NFκB activated pathway [35]. The inflammasome-forming cytosolic DNA sensor AIM2 is also involved in the arthritic process [36], and may be responsible for the high levels of IL-1 that contribute to the arthritic phenotype.

Rodero *et al.* subsequently identified 3 patients whose autoinflammatory conditions were associated with LOF mutations in DNaseII [37]. These individuals were characterized by an IFN signature in PBMCs, anemia, elevated erythroblast counts, and hepatosplenomegaly, all indicative of extrameduallary hematopoiesis. They also developed membranous glomerulonephritis, liver fibrosis, and a type of deforming arthropathy previously described in other patients with monoclonal type I interferonopathies.

Remarkably, in addition to the joint inflammation described above that develops at ~5–6 months of age, DNaseII$^{-/-}$ IFNaR$^{-/-}$ mice also develop an early onset systemic autoinflammatory condition that has remarkable similarities to the DNaseII LOF patients [38,39]. Shared clinical manifestations include pancytopenia, high serum titers of proinflammatory cytokines and chemokines, splenomegaly associated with extramedullary hematopoiesis, autoantibody production and liver fibrosis. However, these clinical manifestations cannot be due to type I IFNs (due to lack of the appropriate receptor) and are also not dependent on STING [39,40]. Unexpectedly, they depend on expression of functional Unc93B1, a chaperone for endosomal TLRs, implicating these TLRs in many aspects of the autoinflammation apparent in the murine model. T lymphocytes again play a critical role in disease pathogenesis. Although DNaseII$^{-/-}$ IFNaR$^{-/-}$ mice are lymphopenic, the residual T cells are highly active and carry a type II IFNγ signature. Moreover, IFNγR-deficiency prevents the development of activated T cells and splenomegaly, and also limits additional features of autoinflammation in the periphery. Nevertheless, the BM of IFNγR$^{-/-}$ mice is still perturbed.

STING gain of function mutations associated with autoinflammation and the role of type I IFN

A spectrum of GOF mutations in STING have been identified in over 25 patients who develop an autoinflammatory disease now designated SAVI (STING-associated vasculopathy with onset in infancy) [41–44]. SAVI patients exhibit early onset systemic inflammation, associated with an IFN signature, lymphopenia, severe skin vasculopathy and interstitial lung disease that can result in pulmonary fibrosis and respiratory failure. These SAVI mutations lead to spontaneous dimerization and activation of STING that occurs independently of cGAS. On the basis of the association between STING and the induction of type I IFNs, these patients have been considered another example of monoclonal type I interferonopathy [16]. Despite the severe phenotypes of many SAVI patients, identical mutations in different individuals can have very different clinical presentations [45,46]. Thus, a better understanding of how, when and where overactivation of STING causes sterile inflammation is clearly needed.

The two most common mutations in SAVI N154S and V155M have been modeled in mice (N153S and V154M) to explore these questions [47,48]. Both models exhibit decreased survival rates, spontaneous IFN signatures, elevated serum cytokine levels, T cell and B cell lymphopenia, splenomegaly, and lung inflammation. A direct comparison of both mutations in the same colony revealed significantly differences in activation levels both *in vitro* and *in vivo*; the V154M mutation has more robust STING activity and the V154M mutant mice develop a more severe disease phenotype where lung inflammation progresses to lung fibrosis [49]. However, quite unexpectedly, disease outcome in both strains of SAVI mice is completely unaffected by IRF3-deficiency or IFNaR-deficiency [48–50], and therefore independent of type I IFNs. These discoveries raise important questions about the source and/or impact of the IFN signature in SAVI patients. Type III IFNs (IFNλ) are members of the IL-10 family that, like type I IFNs, play an important role in anti-viral immunity following engagement of NA-sensing receptors and activate similar Jak/STAT pathways [51,52]. However, in contrast to the ubiquitously expressed type I IFN receptor, expression of the type III IFN receptor is more limited and found predominantly on epithelial cells where it plays a unique role in the protection of barrier surfaces [53]. Intriguingly, intranasal administration of cyclic dinucleotide induced production of both IFNγ and IFNλ in the lung, without inducing IFNβ [54]. In addition, IFNλ has been implicated in kidney fibrosis in patients with lupus nephritis [55]. IFNλR expression has also been found on neutrophils, DCs, and lupus B cells [56–58]. Moreover, there is evidence of increased serum IFNγ titers and increased numbers of IFNγ-producing T cells in SAVI patients [59]. Therefore, the origin of the IFN signature in patient

populations with autoinflammatory conditions warrants further attention and may include IFNλ produced by a variety of cell types as well as IFNγ produced by either T cells or NK cells.

T cells in autoinflammation

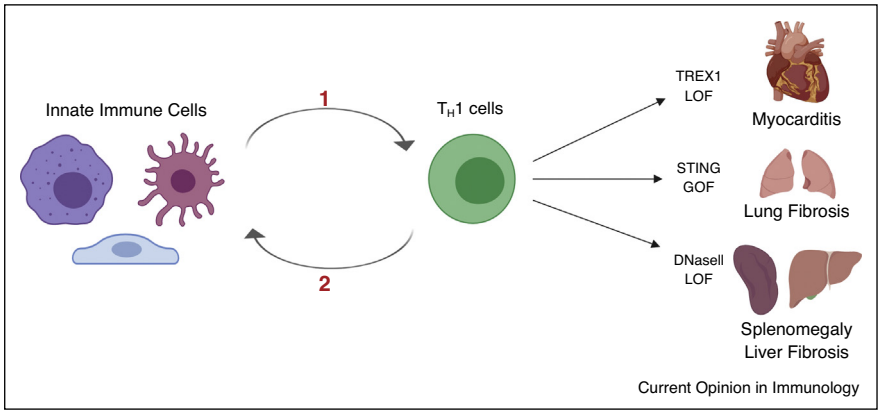
The STING signaling cascade has been extensively studied in myeloid cells, but STING is also expressed by both T cells and B cells where its activity has been less well explored. Larkin *et al.* first showed that STING agonists induced both type I IFN and an ISG in T cells, but also activated cell stress and death pathways; these outcomes were amplified by co-engagement of the TCR [60]. Recent studies from Wu *et al.* have further identified a novel UPR motif in STING and shown that the SAVI mutation renders T cells hyperresponsive to TCR-induced ER-stress and ensuing cell death through this UPR motif [61]. This function of STING most likely accounts for the T cell lymphopenia consistently observed in SAVI mice and may also contribute to loss of B cells. Nevertheless, limited numbers of T cells persist in these mice as activated effector cells and T cells are required for lung pathology [61].

The surviving T cells in lymphopenic DNaseII$^{-/-}$ IFNaR$^{-/-}$ mice also bear markers of activation. Quite unexpectedly, activated DNaseII$^{-/-}$ IFNaR$^{-/-}$ CD4 T cells have the capacity to transfer the Unc93B1-dependent phenotype to DNase-sufficient Rag1$^{-/-}$ mice where they induce BM inflammation, limit pro-B cell development and induce extramedullary hematopoiesis and splenomegaly. As mentioned above, DNaseII$^{-/-}$ IFNaR$^{-/-}$ T cells do not become activated in IFNγR-deficient mice and IFNγR-deficient mice cannot transfer autoinflammation. Nevertheless, CD11b^{+} cells are expanded in the BM of IFNγR-deficient mice. Together these studies point to a feed forward loop, in which aberrant activation of DNaseII$^{-/-}$ antigen presenting cells provokes the development of a pathogenic T cell subset that not only mediates tissue pathology but is also fully capable of inducing the development of hyperactive APCs in DNase-sufficient mice and thereby reinitiating the autoinflammatory program (Figure 1).

Conclusions

Mutations that impact either the expression or trafficking of NA sensors or result in the inappropriate accumulation of their NA ligands can lead to an ever-growing list of severe autoinflammatory syndromes associated with an interferon signature. Since these patients frequently exhibit a robust interferon signature, and develop overlapping clinical manifestations of disease, they are often categorized under the general term of monoclonal interferonopathy. Activation of the cGAS/STING cytosolic DNA sensing pathway of and the ensuing production of type I IFNs have been increasingly implicated in the development of these interferonopathies. However, murine models of autoinflammation have provided important mechanistic insights and shown that type I IFN signaling is not required for many of the clinical manifestations that recapitulate the corresponding human syndromes. Moreover, the animal models have further demonstrated the critical role of the adaptive immune system, and in particular a Th1-like CD4 subset, in the reinitiation as well as the pathological outcomes of autoinflammation. This paradigm may well extend to other examples of autoinflammation, and if so, therapeutic strategies for the treatment of patients with 'Monoclonal Interferonopathies' will need to target both the initiating innate immune and also the sustaining adaptive immune compartments in order to prevent the recurrence of inflammation.

Figure 1



Autoinflammation results from hyperactivation of nucleic acid sensors in hematopoietic and non-hematopoietic components of the innate immune system. Aberrantly activated antigen presenting cells in turn stimulate cell reactive T cells to differentiate into Th1 effector cells that can both mediate tissue damage and also reinitiate autoinflammation in naïve recipients.

Conflictof interest statement

Nothing declared.

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