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EDITORIAL

Nucleic acid-mediated autoinflammation and autoimmunity—type I interferonopathies

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Type I interferons (IFN), IFN-α, and IFN-β play a central role in the immune defense against viral infections. While IFN-α is mainly secreted by plasmacytoid dendritic cells, IFN-β can be produced by almost every cell. Type I IFNs are induced by engagement of pattern recognition receptors of the innate immune system that recognize danger signals originating from pathogen-derived molecular patterns. Detection of viral infection by the host organism is primarily achieved through recognition of viral nucleic acids. Within the cytosol, dsDNA, and ssDNA are sensed by the nucleotidyl transferase cyclic GMP-AMP synthase (cGAS), which catalyzes the synthesis of the second messenger cyclic GMP-AMP (cGAMP) leading to activation of the adapter molecule STING (Fig. 1) [1, 2]. Cytosolic dsRNA is recognized by the RNA helicases retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), which recruit the mitochondrial antiviral signaling (MAVS) adapter protein [3]. Both STING and MAVS activate interferon stimulatory factor 3 (IRF3) through phosphorylation by TANK-binding kinase 1 (TBK1) resulting in the transcriptional activation of the interferon genes and of numerous interferon-stimulated genes (ISGs). Collectively, these transcriptional responses induce an antiviral state and enable cells to restrict viral spread and to eliminate infected cells through modulation of innate and adaptive immune responses (Fig. 1). Binding of type I IFNs to the interferon-α receptor (IFNAR), a cell surface receptor composed of two subunits, activates the Janus kinase (JAK)—signal transducer and activator of transcription (STAT) pathway—leading to transcription of ISGs [4]. Importantly, a complex interplay of host, pathogen, and environmental factors modulates the innate and adaptive immune responses to type I IFN signaling and determines whether pathogens are cleared effectively or chronic infection or autoimmune disease ensues. Consequently, inappropriate activation of the type I IFN system can be detrimental to the host by promoting inflammatory responses and a break of immune tolerance leading to autoimmunity.

While the pattern recognition receptors, cGAS, RIG-I, and MDA5, alert the host to viral infection by sensing viral nucleic acids, their capacity to differentiate between nonself and self DNA or RNA is limited. As a result, a type I IFN response can in principle also be initiated by endogenous nucleic acids, which means that the host organism must be equipped with efficient means to prevent inappropriate type I IFN activation by self nucleic acids. Indeed, type I IFN activation induced by immune recognition of self nucleic acids is central to the pathogenesis systemic lupus erythematosus (SLE), a chronic relapsing autoimmune disease that can virtually affect any organ system [5].

The elucidation of the molecular pathology of rare Mendelian disorders associated with inappropriate activation of the type I IFN axis has provided novel insight into cell-intrinsic disease mechanisms underlying autoinflammation and autoimmunity. Collectively, these disorders are referred to as type I interferonopathies, a term coined by Yanick

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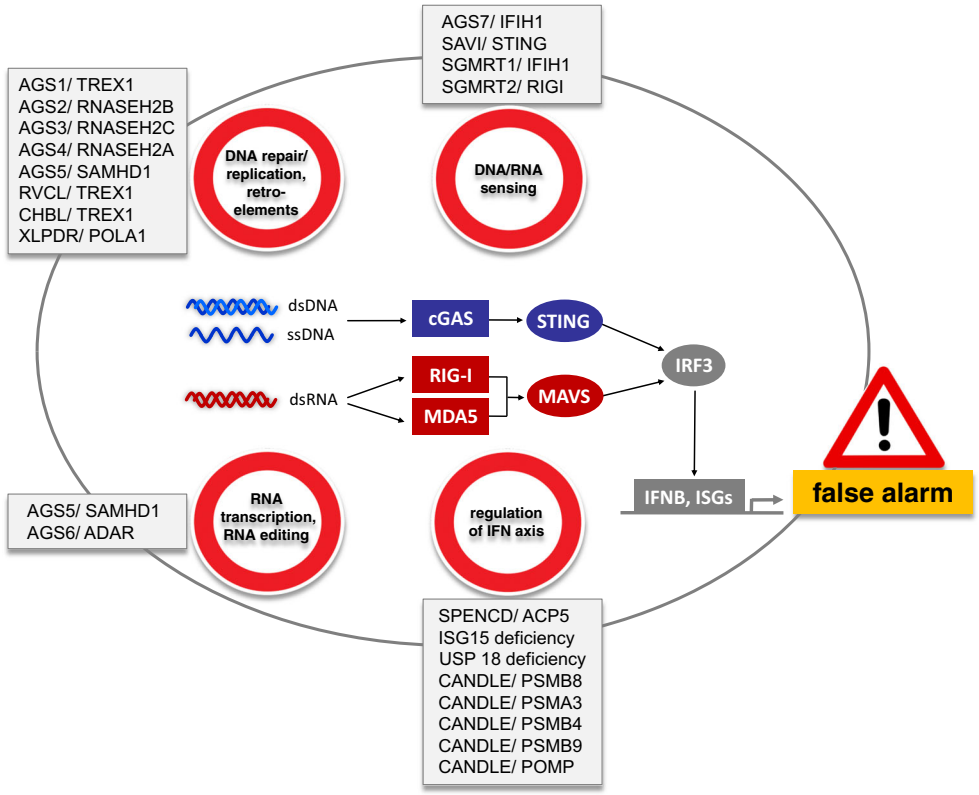

Fig. 1 Disease pathways leading to nucleic acid-induced type I IFN activation. Deficiency in the DNase TREX1 results in cytosolic accumulation of ssDNA derived from aberrant DNA replication intermediates, DNA repair metabolites, or reverse transcription of retroelements. Defective removal of ribonucleotides from genomic DNA due to RNase H2 (*RNASEH2A*, *RNASEH2B*, *RNASEH2C*) deficiency or imbalanced deoxynucleotide (dNTP) pools due to SAMHD1 deficiency, respectively, causes genome instability leading to enhanced formation of DNA repair metabolites. Similarly, a lack of DNA polymerase α (*POLA1*) is thought to result in the build-up of RNA:DNA hybrids. The DNA by-products of these pathways act as danger signals that activate cGAS-dependent type I IFN signaling. The RNase activity of SAMHD1 may also prevent accumulation of yet unknown immunostimulatory RNA species. Editing of endogenous dsRNA by the deaminase ADAR prevents MDA5-mediated sensing of dsRNA as nonself. Gain-of-function mutations in the dsRNA sensors RIG-I and MDA5 (encoded by the *IFIH1* gene) or in the cGAMP-binding adaptor molecule STING leads to inadequately or constitutively increased type I IFN signaling. Loss of tartrate-resistant acid phosphatase (encoded by the *ACP5* gene) or of interferon-stimulated protein 15 (*ISG15*) or ubiquitin-specific protease 18 (*USP18*) alters pathways that negatively regulate the type I interferon axis. Deficiency of components of the immunoproteasome (*PSMB8*, *PSMA3*, *PSMB4*, *PSMB9*, *POMP*) causes chronic type I IFN activation by yet unknown mechanisms that may involve antigen presentation. *AGS* Aicardi-Goutières syndrome, *RVCL* retinal vasculopathy with cerebral leukodystrophy, *CHBL* familial chilblain lupus, *XLPDR* X-linked reticulate pigmentary disorder, *SAVI* STING-associated vasculopathy, infantile-onset, *SGMRT* Singleton-Merton syndrome, SPENCD spondyloenchrondrodysplasia, *CANDLE* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

Crow in 2011 [6]. Type I interferonopathies comprise a growing number of genetically determined disorders that are caused by a dysfunction of the innate immune system. While the clinical spectrum of the type I interferonopathies is highly variable and broad, neurological and cutaneous manifestations represent the most salient findings [7, 8]. In addition, signs of immunodeficiency with recurrent infections can be observed in certain disease entities [9–11]. Although the implicated genes exert diverse biological functions, the associated disease pathways converge to a common route which is inappropriate overproduction of type I IFN (Table 1) [8]. Thus, chronic type I IFN activation results from defects in the metabolism or the immune recognition of intracellular nucleic acids or in altered pathways that regulate the type I IFN axis (Fig. 1). Deficiency in the nucleases TREX1 or RNase H2, a lack of the triphosphohydrolase activity of SAMHD1 or loss of the DNA polymerase α results in abnormal accumulation of nucleic acids emanating from DNA repair/replication or the life cycle of retroelements causing a spectrum of phenotypes including Aicardi-Goutières syndrome (AGS), retinal vasculopathy with cerebral leukodystrophy (RVCL), familial chilblain lupus (CHBL), or X-linked reticulate pigmentary disorder (XLPDR) [11–17]. Similarly, a lack of the RNA-specific deaminase ADAR or loss of the RNase activity of SAMHD1 alters the chemical properties of RNA or causes accumulation of RNA species which triggers type I IFN activation [18, 19]. Enhanced sensitivity or ligand-independent activation of the nucleic acid sensors RIG-I or MDA5 (encoded by the *IFH1* gene) or of the signal adaptor STING underlies Singleton-Merton syndrome (SGMRT1,

Table 1 Genes implicated in type I interferonopathies

Gene	Protein function	Phenotypes
TREX1	Three prime repair exonuclease	Aicardi-Goutières syndrome
	Cytosolic DNase	Retinal vasculopathy with cerebral leukodystrophy
		Familial chilblain lupus
		Systemic lupus erythematosus
RNASEH2A	Ribonuclease H2, subunits A, B, C	Aicardi-Goutières syndrome
RNASEH2B	Ribonucleotide excision repair	Systemic lupus erythematosus
RNASEH2C		
SAMHD1	SAM domain and HD domain-containing protein 1	Aicardi-Goutières syndrome
		Familial chilblain lupus
	dNTP triphosphohydrolase, RNase	Systemic lupus erythematosus
ADAR1	Adenosine deaminase, RNA-specific	Aicardi-Goutières syndrome
	Deamination of adenosine to inosine in dsRNA	
IFIH1	IFN-induced helicase C domain-containing protein 1	Aicardi-Goutières syndrome
	Pattern recognition receptor for dsRNA	Singleton-Merten syndrome
STING	Stimulator of interferon genes	STING-associated vasculopathy, infantile-onset Familial chilblain lupus
	IFN-β induction in response to cytosolic DNA	
ACP5	Tartrate-resistant acid phosphatase, type 5	Spondyloenchrondrodysplasia
	Dephosphorylation of osteopontin	
RIGI	Retinoic acid-inducible gene 1	Singleton-Merten syndrome
	Pattern recognition receptor for dsRNA	
ISG15	Interferon-stimulated gene 15	ISG15 deficiency
	Ubiquitin-like protein, modifies proteins by ISGylation	
USP18	Ubiquitin-specific protease 18	USP18 deficiency
	de-ISGylation	
PSMB8	Proteasome subunit β5i	CANDLE syndrome
	Antigen processing in immunoproteasome	(chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature)
PSMB4	Proteasome subunit β7	
	Antigen processing in immunoproteasome	
PSMA3	Proteasome subunit α7	
	Antigen processing in immunoproteasome	
PSMB9	Proteasome subunit β1i	
	Antigen processing in immunoproteasome	
POMP	Proteasome maturation protein	
	Formation of immunoproteasome	
POLA1	DNA polymerase α	X-linked reticulate pigmentary disorder
	Synthesis of RNA:DNA primers during DNA replication	

SGMRT2), AGS and STING-associated vasculopathy (SAVI), respectively [20–23]. Finally, dysregulation of pathways that modulate type I IFN signaling can cause ISG15 or USP18 deficiency, spondyloenchondrodysplasia, or CANDLE syndrome [10, 24–26].

Taken together, the discovery of cytosolic sensing pathways along with the genetic dissection of the type I interferonopathies has revealed novel mechanisms that protect the organism against inappropriate immune activation caused by self nucleic acids, while maintaining a prompt and efficient immune response to foreign nucleic acids. These scientific advances not only provide a set of molecules and pathways such as IFN-α/β, the IFNAR receptor, or the JAK/STAT pathway that could already potentially be targeted for specific therapeutic intervention, but will also foster the development of novel compounds targeting other components of the type I IFN axis such as cGAS, TBK1, and STING.

The review by Andrea Ablasser and Muhammed Gulen focuses on the role of cGAS in DNA sensing mechanisms and its role in disease processes leading to autoimmunity and cancer [27]. Carl Walkley and Jacki Heraud-Farlow review the role of the deaminase ADAR in the discrimination of

foreign and self RNA molecules by MDA5 through chemical modification of dsRNA by deamination [28]. Lars Rönnblom and Maija-Leena Eloranta give an overview on the multifaceted roles of type I IFN in the pathogenesis of SLE, which unlike the monogenic type I interferonopathies is a complex multifactorial disorder [29]. Last but not the least, Raphaela Goldbach-Mansky and her colleagues review the genetic and clinical findings of the type I interferonopathies SAVI and CANDLE in contrast to AGS and monogenic forms of SLE and provide insight into the underlying disease mechanisms [30].

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