The Type I Interferonopathies

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Annu. Rev. Med. 2017. 68:297–315

First published online as a Review in Advance on November 2, 2016

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-050715-104506

Keywords

type I interferon, autoinflammation, autoimmunity, nucleic acid metabolism, nucleic acid sensing, innate immunity

Abstract

Type I interferons (IFNs) play a central role in the immune defense against viral infections. Type I IFN activation is induced by pattern-recognition receptors of the innate immune system that sense pathogen-derived nucleic acids. Cellular responses to type I IFN signaling are orchestrated by a complex network of regulatory pathways that involve both the innate and adaptive immune system. The genetic and molecular dissection of rare Mendelian disorders associated with constitutive overproduction of type I IFN has provided unique insight into cell-intrinsic disease mechanisms that initiate and sustain autoinflammation and autoimmunity and that are caused by disturbances in the intracellular nucleic acid metabolism or in cytosolic nucleic acid–sensing pathways. Collectively, these findings have greatly advanced our understanding of mechanisms that protect the organism against inappropriate immune activation triggered by self nucleic acids while maintaining a prompt and efficient immune response to foreign nucleic acids derived from invading pathogens.

INTRODUCTION: HISTORICAL REMARKS

Type I interferonopathies comprise a genetically and phenotypically heterogeneous group of autoinflammatory and autoimmune disorders characterized by constitutive activation of the antiviral type I interferon (IFN) axis. Our current understanding of the molecular pathology underlying the type I interferonopathies was greatly influenced by advances in the field of innate immunity and human genetics during the past decade. In 2006, Stetson & Medzhitov (1) demonstrated activation of an IFN regulatory factor 3 (IRF3)-dependent innate immune response triggered by cytosolic DNA. That same year, mutations in the genes encoding 3′ repair exonuclease 1 (TREX1) and RNase H2, two then-enigmatic intracellular nucleases, were identified in patients with Aicardi-Goutières syndrome (AGS) by Crow and colleagues (2, 3). In the following years, tremendous progress in immunology led to the discovery of cytosolic nucleic acid–sensing pathways headed by cyclic GMP-AMP synthase (cGAS), retinoic acid–inducible gene 1 (RIG-I), and melanoma differentiation-associated protein 5 (MDA5), which comprise a novel class of ubiquitously expressed germline-encoded pattern recognition receptors (4). These advances in immunology were paralleled by the elucidation of the genetic basis of additional forms of AGS and related Mendelian disorders, such as familial chilblain lupus and STING-associated vasculopathy (5). Together, these findings have revealed novel cell-intrinsic mechanisms leading to autoinflammation and autoimmunity caused by activated type I IFN signaling and have greatly advanced our knowledge on how the organism prevents inappropriate type I IFN activation while maintaining a prompt and efficient response to viral infection. Moreover, these findings have contributed to our understanding of pathomechanisms underlying certain forms of multifactorial systemic lupus erythematosus (SLE).

TYPE I INTERFERON: FRIEND AND FOE ALIKE

The type I IFNs, IFN-α and IFN-β, are the major cytokines of the host immune response against viruses and other intracellular pathogens. Activation of type I IFN is initiated by pattern recognition receptors of the innate immune system that recognize danger signals emanating from pathogen-associated molecular patterns. Whereas bacteria and fungi possess microbe-specific structures for immune recognition that are absent in the host, detection of viruses is primarily achieved through recognition of viral nucleic acids, molecular structures that are also integral components of the host cell. In contrast to Toll-like receptors (TLR3, TLR7, TLR8, TLR9), which detect nucleic acids within endosomes of specialized cells such as dendritic cells or B cells, a distinct and complementary set of nucleic acid–sensing receptors resides within the cytosol of virtually all cells (4).

Figure 1 illustrates type I IFN-dependent nucleic acid–sensing pathways within the cytosol. The central mechanism of cytosolic DNA sensing involves the nucleotidyl transferase cGAS, which upon ligand binding catalyzes the synthesis of a unique second messenger, cyclic GMP-AMP (cGAMP), that subsequently recruits and thereby induces activation of the adapter molecule stimulator of interferon genes (STING) (6–8). Sensing of cytosolic RNA is mediated by the RIG-I-like helicases, RIG-I and MDA5, which signal via mitochondrial antiviral signaling (MAVS) protein (9, 10). Whereas MDA5 senses long dsRNA, RIG-I ligands consist of short dsRNA with a tri- or diphosphate at the 5′ end (9, 11, 12). RIG-I can also recognize viral DNA via the RNA polymerase III pathway, which transcribes DNA into 5′-triphosphate RNA (13, 14). Engagement of STING and MAVS leads to activation of TANK-binding kinase 1 (TBK1) and the IKK kinase complex composed of the IKKα and IKKβ kinases and the NEMO/IKKγ regulatory subunit, which in turn activate the transcription factors IRF3 and nuclear factor-κB (NF-κB), respectively (4). Following translocation into the nucleus, IRF3 induces transcription of type

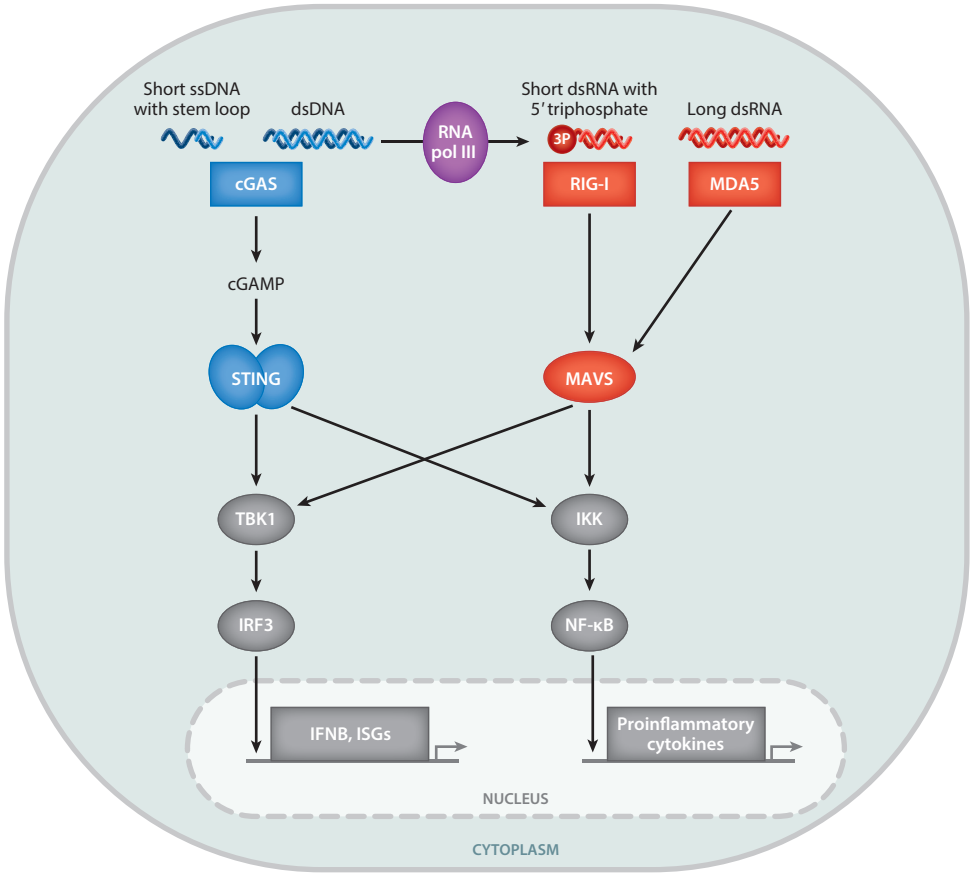

Figure 1

Cytosolic nucleic acid sensing. Cytosolic dsDNA or ssDNA with stem loops are sensed by cGAS. Cytosolic short dsRNA with a 5′ triphosphate or 5′diphosphate is sensed by RIG-I, whereas MDA5 recognizes long dsRNA. RIG-I also recognizes viral DNA via the RNA polymerase III pathway, which transcribes DNA into 5′-triphosphate RNA. cGAS signals via STING; RIG-I and MDA5 signal via MAVS. Both signaling pathways induce TBK1/IRF3-dependent transcription of the *IFNB* gene and ISGs as well as IKK-dependent activation of NF-κB, leading to transcription of proinflammatory cytokines. Abbreviations: cGAS, cyclic GMP-AMP synthase; IKK, inhibitor of nuclear factor κB kinase; IRF3, interferon regulatory factor 3; ISG, interferon-stimulated gene; MAVS, mitochondrial antiviral signaling; MDA5, melanoma differentiation-associated protein 5; NF-κB, nuclear factor κB; RIG-I, retinoic acid–inducible gene I; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1 (TANK, TRAF family member–associated NF-κB activator; TRAF, tumor necrosis factor receptor–associated factor).

I IFN genes and numerous IFN-stimulated genes (ISGs), while NF-κB induces expression of proinflammatory cytokines. Type I IFNs act in an autocrine and paracrine manner by binding to the IFN-α receptor (IFNAR), a cell surface receptor composed of two subunits, IFNAR1 und IFNAR2 (15). Canonical type I IFN signaling activates the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, leading to transcription of the IFN genes and of ISGs. Induction of type I IFN signaling and ISG upregulation endows cells with antiviral capacities in a context-specific manner. Thus, type I IFNs promote apoptosis of infected cells,

alert surrounding cells to the presence of a viral infection, and facilitate antigen presentation as well as maturation and proliferation of lymphocytes, to eliminate infected cells, to restrict viral spread, and to provide protection with minimum damage to the host (4, 15).

Because the capacity of the nucleic acid sensors to differentiate between nonself and self DNA or RNA is limited, a type I IFN response can in principle also be initiated by endogenous nucleic acids. Such inappropriate activation of type I IFN can be detrimental to the host by promoting autoinflammatory responses and a break of immune tolerance, leading to autoimmunity. In fact, type I IFN activation induced by immune recognition of self nucleic acids is a key event in the pathogenesis of type I interferonopathies.

BROADENING THE IMMUNOLOGICAL DISEASE CONTINUUM

The elucidation of the molecular pathology of tumor necrosis factor receptor–associated periodic fever syndrome in 1999 led to the concept of autoinflammation as self-directed inflammation with no involvement of B or T cells and no evidence of infection (16). Although this conceptual framework has been helpful to distinguish autoinflammatory diseases from autoimmune diseases and certain immunodeficiency disorders, advances in immunology and human genetics during the past decade have highlighted that these immune-mediated inflammatory conditions cannot be viewed as mutually exclusive, but rather as part of an immunological disease continuum (17). Indeed, the recent discovery of the type I interferonopathies as autoinflammatory disorders that are caused by a dysfunction of the innate immune system, yet can be accompanied by signs of autoimmunity or infection, has expanded the immunological disease continuum to a remarkable extent.

THE TYPE I INTERFERONOPATHIES

Autoinflammation and Autoimmunity Triggered by Type I Interferon

The type I interferonopathies comprise a growing number of genetically determined disorders that are primarily caused by perturbations of the innate immune system (**Table 1**). The term type I interferonopathy was coined in recognition of an abnormal upregulation of type I IFN as a unifying phenotype of this novel group of diseases (18). Despite a remarkable phenotypic heterogeneity, type I interferonopathies are commonly characterized by systemic autoinflammation and varying degrees of autoimmunity or immunodeficiency. Based on the currently identified molecular defects, a pathogenic type I IFN response can result from (*a*) abnormal accumulation of or abnormal chemical modification of endogenous nucleic acids, (*b*) enhanced sensitivity or ligand-independent activation of nucleic acid sensors or of downstream components of type I IFN signaling pathways, (*c*) impaired negative regulation of nucleic acid–induced type I IFN signaling, or (*d*) defects in pathways that modulate type I IFN responses independent of nucleic acid sensing (**Figure 2**).

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is a systemic inflammatory disorder with onset in early infancy and is the prototypic type I interferonopathy (19, 20). In the majority of cases, AGS presents as a leukoencephalopathy with basal ganglia calcifications and progressive cerebral atrophy, along with lymphocytosis and elevated IFN-α in cerebrospinal fluid (21). The clinical phenotype of AGS resembles congenital viral infection. Infants typically present with a subacute onset of irritability, dystonia, seizures, and fever episodes leading to severe developmental delay and progressive

Table 1 Currently known type I interferonopathies

Disease OMIM symbol	Gene	Inheritance	Protein function
Aicardi-Goutières syndrome (AGS)	*TREX1*	Autosomal recessive, de novo dominant	3′ repair exonuclease; cytosolic DNase
	RNASEH2A	Autosomal recessive	Ribonuclease H2, subunits A, B, C; ribonucleotide excision repair
	RNASEH2B	Autosomal recessive	
	RNASEH2C	Autosomal recessive	
	SAMHD1	Autosomal recessive	SAM domain and HD domain-containing protein 1; dNTP triphosphohydrolase, RNase
	ADAR1	Autosomal recessive, de novo dominant	Adenosine deaminase, RNA-specific; deamination of adenosine to inosine in dsRNA
	IFIH1	Autosomal dominant, de novo dominant	IFN-induced helicase C domain-containing protein 1; pattern recognition receptor for dsRNA
Retinal vasculopathy with cerebral leukodystrophy (RVCL)	*TREX1*	Autosomal dominant	3′ repair exonuclease; cytosolic DNase
Familial chilblain lupus (CHBL)	*TREX1*	Autosomal dominant	Three prime repair exonuclease; cytosolic DNase
	SAMHD1	Autosomal dominant	SAM domain and HD domain-containing protein 1; dNTP triphosphohydrolase, RNase
	STING	Autosomal dominant	Stimulator of interferon genes; IFN-β induction in response to cytosolic DNA
Systemic lupus erythematosus (SLE)	*TREX1*	Multifactorial	3′ repair exonuclease; cytosolic DNase
	RNASEH2A-C	Multifactorial	Ribonuclease H2, subunits A, B, C; ribonucleotide excision repair
	ACP5	Multifactorial	Tartrate-resistant acid phosphatase, type 5; dephosphorylation of osteopontin
	DNASE1	Multifactorial, autosomal dominant	Deoxyribonuclease 1; extracellular DNase
	DNASE1L3	Autosomal recessive	Deoxyribonuclease 1-like 3; extra- and intracellular DNase
	C1QA-C	Multifactorial, autosomal recessive	Complement component 1q; fixation of immunoglobulin
	C4	Multifactorial, autosomal recessive	Complement component 4; fixation of immunoglobulin
STING-associated vasculopathy, infantile-onset (SAVI)	*STING*	Autosomal dominant, de novo dominant	Stimulator of interferon genes; IFN-β induction in response to cytosolic DNA
Singleton-Merten syndrome (SGMRT)	*IFIH1*	Autosomal dominant	IFN-induced helicase C domain-containing protein 1; pattern recognition receptor for dsRNA
	RIGI	Autosomal dominant	Retinoic acid–inducible gene 1; pattern recognition receptor for dsRNA
Spondyloenchrondro-dysplasia (SPENCD)	*ACP5*	Autosomal recessive	Tartrate-resistant acid phosphatase, type 5; dephosphorylation of osteopontin
ISG15 deficiency	*ISG15*	Autosomal recessive	Interferon-stimulated gene (ISG) 15; ubiquitin-like protein, modifies proteins by ISGylation

(*Continued*)

Table 1 (*Continued*)

Disease OMIM symbol	Gene	Inheritance	Protein function
USP18 deficiency	*USP18*	Autosomal recessive	Ubiquitin-specific protease 18; de-ISGylation
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)	*PSMB8*	Autosomal recessive	Proteasome subunit β5i; antigen processing in immunoproteasome
	PSMB4	Autosomal recessive	Proteasome subunit β7; antigen processing in immunoproteasome
	PSMA3	Autosomal recessive	Proteasome subunit α7; antigen processing in immunoproteasome
	PSMB9	Autosomal recessive	Proteasome subunit β1i; antigen processing in immunoproteasome
	POMP	Autosomal dominant	Proteasome maturation protein; formation of immunoproteasome
X-linked reticulate pigmentary disorder (XLRPD)	*POLA1*	Autosomal recessive	DNA polymerase α; synthesis of RNA-DNA primer during DNA replication
Panarteritis nodosa, childhood-onset (PAN)	*CECR1*	Autosomal recessive	Adenosine deaminase 2; extracellular adenosine deaminase

microcephaly. Some patients develop signs that are also observed in patients with SLE, including hepatic disease, arthritis, thrombocytopenia, lymphopenia, and antinuclear antibodies, as well as cold-induced cutaneous chilblain lesions (22, 23). In contrast to IFN-α in cerebrospinal fluid, which tends to gradually decrease during the course of the disease, ISGs are constitutively upregulated in the peripheral blood of AGS patients (24). Indeed, this IFN signature has proven a useful marker for the differential diagnosis of AGS. There can be striking intrafamilial variability in AGS, with one sibling exhibiting severe neurological impairment and another with only mild spasticity and normal intellect (25, 26). AGS is a genetically heterogeneous disorder caused by mutations in at least seven distinct genes. Their corresponding genetic loci are termed AGS1 to AGS7 (**Table 1**, **Figure 2**).

TREX1 (AGS1; OMIM 225750) encodes 3′ repair exonuclease 1, a cytosolic DNase with high specificity for ssDNA. Loss-of-function mutations of *TREX1* cause intracellular accrual of ssDNA metabolites derived from diverse biological processes including granzyme A–mediated apoptosis, DNA replication and repair, and the reverse transcription of retroelements (2, 27–30). *Trex1*$^{-/-}$ mice develop type I IFN-dependent autoimmune disease initiated in nonhematopoietic cells and succumb to heart failure (30, 31). In TREX1 deficiency, unmetabolized ssDNA species are recognized as danger signals and trigger a type I IFN response in a cGAS/TBK1/IRF3-dependent manner (29, 32, 33). TREX1 was also shown to be exploited by human immunodeficiency virus type 1 (HIV-1): Degradation of reverse transcripts of its RNA genome by TREX1 prevents an antiviral response, promoting viral replication (34). In the majority of cases, patients with AGS1 harbor biallelic loss-of-function mutations of *TREX1* (2). In addition, rare cases with heterozygous de novo *TREX1* mutations have been described (22, 35, 36).

RNASEH2A (AGS4; OMIM 610333), *RNASEH2B* (AGS2; OMIM 610181) and *RNASEH2C* (AGS3; OMIM 610329) encode the three subunits of the ribonuclease H2 (RNase H2) complex, which degrades RNA within an RNA:DNA hybrid or cleaves the phosphodiester bond 5′ of a single ribonucleotide embedded within a DNA duplex. Biallelic loss-of-function mutations in any of the three RNase H2 subunits can cause AGS (3). RNase H2 functions in genome surveillance by removing misincorporated ribonucleotides from genomic DNA (37–39). A lack of

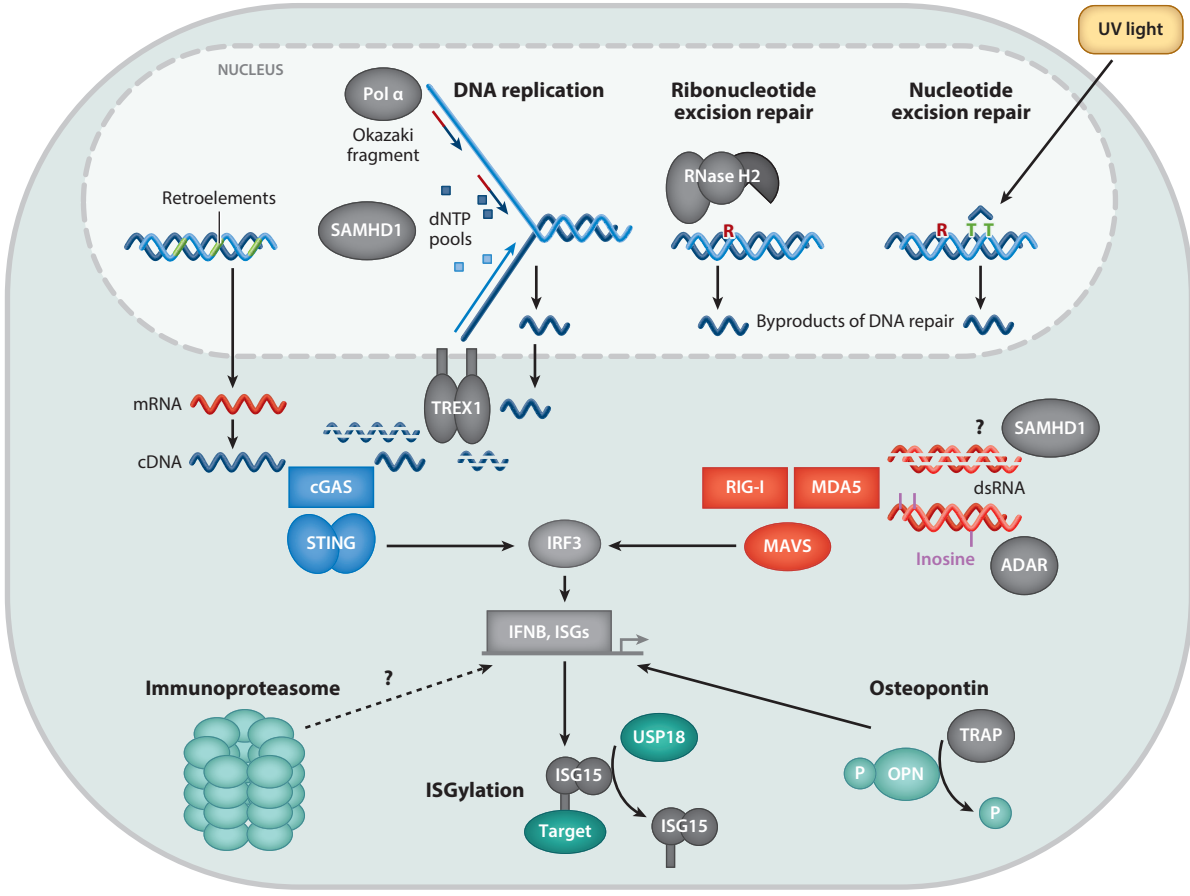

Figure 2

Cellular functions of genes causing type I interferonopathies. TREX1 is a cytosolic DNase that degrades ssDNA derived from retroelements or byproducts of DNA repair. Undegraded ssDNA metabolites are recognized by cGAS. RNase H2 removes ribonucleotides from genomic DNA. The presence of ribonucleotides in genomic DNA enhances photodimerization of adjacent pyrimidines nearby, which are repaired by nucleotide excision repair. A lack of RNase H2 promotes DNA damage, leading to enhanced formation of DNA repair metabolites. Pol α initiates DNA replication by synthesizing the initial RNA-DNA primer. Pol α deficiency likely causes replication fork stalling, leading to DNA damage. SAMHD1 regulates dNTP pools required for DNA synthesis during replication in a cell cycle–dependent manner. Loss of SAMHD1 causes cell cycle arrest and DNA damage. SAMHD1 also has RNase activity. ADAR edits dsRNA by deamination of adenosine to inosine. This chemical modification prevents recognition of dsRNA by MDA5. Activating mutations in STING, RIG-I and MDA5 lead to enhanced type I IFN signaling. The immunoproteasome functions in cellular stress responses and antigen processing. How this is linked to type I IFN activation is currently unknown. ISG15 modifies target proteins by ISGylation; ISG15 is removed from its targets by USP18. ISG15 and USP18 act as negative regulators of type I IFN signaling. TRAP inactivates OPN by dephosphorylation. OPN is a cytokine that promotes TLR-dependent type I IFN production. Abbreviations: ADAR, adenosine deaminase, RNA-specific; dNTP, deoxynucleoside triphosphate; IFN, interferon; ISG, interferon-stimulated gene; MDA5, melanoma differentiation-associated protein 5; OPN, osteopontin; RIG-I, retinoic acid–inducible gene I; SAMHD1, SAM domain and HD domain-containing protein 1; STING, stimulator of interferon genes; TLR, Toll-like receptor; TRAP, tartrate-resistant acid phosphatase; TREX1, 3′ repair exonuclease 1; USP18, ubiquitin-specific protease 18.

ribonucleotide excision repair renders genomic DNA susceptible to DNA strand breaks. Complete RNase H2 deficiency in mice is embryonic lethal owing to a massive p53-dependent DNA damage response leading to apoptosis (37, 38). In AGS patients with hypomorphic *RNASEH2A-C* mutations, enhanced levels of embedded ribonucleotides in genomic DNA cause low-level DNA damage leading to a chronic DNA damage response and senescence (40, 41). This is accompanied by cGAS-dependent type I IFN activation, possibly induced by DNA repair metabolites (42, 43).

SAMHD1 (AGS5; OMIM 612952; SAM domain and HD domain-containing protein 1) acts as a dGTP-dependent triphosphohydrolase, which converts deoxynucleoside triphosphates (dNTPs) to the constituent deoxynucleoside and inorganic triphosphate (44). AGS5 is caused by biallelic loss-of-function mutations of *SAMHD1* (45). SAMHD1 restricts infection of myeloid cells with HIV-1 by depleting the dNTP pools required for reverse transcription of the viral RNA genome (46). It also binds to nucleic acids and exhibits significant nuclease activity (47–49), which may prevent accumulation of yet undefined immunostimulatory nucleic acids. SAMHD1 is regulated in a cell cycle–dependent manner by cyclin A/CDK1-dependent phosphorylation (50, 51). Imbalances of the intracellular dNTP pools in SAMHD1-deficient cells causes genome instability with low-level DNA damage leading to chronic DNA damage signaling along with type I IFN activation, which may account for an increased malignancy risk observed in SAMHD1 deficiency (51, 52).

ADAR (AGS6; OMIM 615010; adenosine deaminase, RNA-specific) catalyzes the deamination of adenosine to inosine in dsRNA. Patients with AGS6 were shown to carry biallelic as well as heterozygous de novo mutations (53). ADAR-mediated posttranscriptional modification of RNA by adenosine-to-inosine editing was shown to prevent MDA5-dependent sensing of endogenous dsRNA as nonself (54).

IFIH1 (AGS7; OMIM 615846; interferon induced with helicase C domain 1) encodes MDA5, a cytoplasmic sensor for long dsRNA (9). AGS7-causing *IFIH1* mutations are inherited in an autosomal dominant manner with reduced penetrance or may arise de novo (55). They act as gain-of-function mutations and exhibit an increased affinity for dsRNA leading to enhanced type I IFN signaling (55).

Retinal Vasculopathy with Cerebral Leukodystrophy

Retinal vasculopathy with cerebral leukodystrophy (RVCL; OMIM 192315) is an autosomal dominant disorder with onset in adolescence and early adulthood. Patients present with progressive loss of vision, cerebrovascular disease, and dementia. Some patients also develop migraine, glomerulopathy, and Raynaud's disease. RVCL is caused by heterozygous *TREX1* mutations that lead to C-terminal truncation of TREX1 with preservation of the N-terminal DNase domain (**Table 1**) (56). Patients with RVCL exhibit variable signs of autoimmunity as well as an IFN signature in blood consistent with an inflammatory process (57).

Familial Chilblain Lupus

Familial chilblain lupus is a monogenic form of cutaneous lupus erythematosus with onset in early childhood. It is characterized by cold-induced bluish-red skin lesions in acral locations such as the fingers, toes, nose, cheeks, and ears (58). Some patients develop arthralgia, antinuclear antibodies, immune complexes, and lymphopenia. Histological findings include perivascular inflammatory infiltrates with increased mucin formation and deposits of immunoglobulins or complements along the basement membrane (58). Constitutive type I IFN activation is evident from increased expression of myxovirus resistance protein 1 (MxA) in lesional skin as well as an upregulation of IFN-stimulated genes in peripheral blood cells (59). Familial chilblain lupus is caused by

heterozygous *TREX* mutations (CHBL1; OMIM 610448) (35, 60). In addition, in two families with chilblain lupus, heterozygous mutations in *SAMHD1* (CHBL2; OMIM 614415) and STING, respectively, were reported (**Table 1**) (61, 62).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, relapsing autoimmune disease characterized by fevers, fatigue, and multiple organ manifestations including dermatitis and arthritis, which occur in most patients, as well as glomerulonephritis, serositis, central nervous system involvement, and perturbations of the hematopoietic system (63). Loss of self-tolerance resulting in formation of autoantibodies, which are deposited as immune complexes in tissues and thereby induce inflammation, is regarded as a key mechanism in SLE pathogenesis. Indeed, antinuclear antibodies that target ubiquitous nuclear antigens including DNA are a hallmark of SLE. Unlike the monogenic type I interferonopathies, SLE is a multifactorial disease, in which the interaction of multiple genetic and environmental factors determines disease susceptibility (64). Numerous genes with diverse roles in both innate and adaptive immunity have been linked to SLE, but there is substantial evidence for a central role of type I IFN in SLE pathogenesis (65–68). This is also reflected by the finding of an IFN signature in peripheral blood cells in patients with SLE (69). In fact, SLE was the first disease suspected to be caused by inappropriately increased type I IFN activity. Notably, rare variants of the AGS-causing genes *TREX1*, *RNASEH2A-C*, and *ACP5* confer an increased risk for SLE (**Table 1**), underpinning the relevance of cell-intrinsic mechanisms of nucleic acid–induced type I IFN activation in SLE (41, 70–72). In RNase H2-deficient cells, the presence of ribonucleotides in genomic DNA promotes UV-light-induced DNA damage (**Figure 2**), which may explain the high prevalence of photosensitivity in SLE patients carrying *RNASEH2* variants (41). Moreover, mutations in nucleases responsible for the removal of extracellular DNA, such as DNase 1 or DNase 1L3, as well as mutations in the complement components C1q or C4 required for clearance of nucleic acid–containing immune complexes, are also associated with SLE (**Table 1**) (73–75).

STING-Associated Vasculopathy, Infantile-Onset

STING-associated vasculopathy, infantile-onset (SAVI; OMIM 615934), is an autoinflammatory vasculopathy characterized by ulcerating acral skin lesions located at the fingers, toes, ears, and nose (76). Many patients develop fever episodes and inflammatory interstitial lung disease that may lead to lung fibrosis. Similar to chilblain lesions observed in patients with AGS or chilblain lupus, skin lesions in SAVI patients are aggravated by cold. Lesional skin shows prominent vascular inflammation with occasional deposition of IgM and C3. Some patients demonstrate variable or transient autoantibody titers. SAVI is caused by heterozygous de novo mutations in *STING*, which encodes a key adaptor signaling molecule of the cGAS-dependent DNA sensing pathway (**Table 1**, **Figure 2**) (76). Mutations result in a gain of function leading to constitutive type I IFN activation, even in the absence of stimulation by cGAMP. Consistent with this, patients also show an IFN signature as well as increased levels of IFN-induced cytokines in blood. In addition, a single family with SAVI and lupus-like features segregating a dominant *STING* mutation was reported (77).

Singleton-Merten Syndrome

Singleton-Merten syndrome is characterized by progressive calcifications of large vessels, dental anomalies with periodontal disease, alveolar bone loss, skeletal abnormalities, and osteoporosis. In

addition, patients may suffer from psoriasis, photosensitivity, early-onset glaucoma, and recurrent respiratory infections. Singleton-Merton syndrome is inherited in an autosomal dominant manner and caused by heterozygous gain-of-function mutations in *IFIH1* (SGMRT1; OMIM 182250) or *RIGI* (SGMRT2; OMIM 616298) encoding cytosolic pattern recognition receptors for dsRNA resulting in constitutive type I IFN activation (**Table 1**, **Figure 2**) (78, 79).

Spondyloenchondrodysplasia

Spondyloenchondrodysplasia (SPENCD; OMIM 271550) is a skeletal dysplasia characterized by enchondromatous nonossifying metaphyseal and vertebral bone lesions leading to irregular metaphyses, particularly involving the distal radii, and platyspondyly. Patients exhibit basal ganglia calcification with varying degrees of neurological impairment, including spasticity and developmental delay. In addition, signs of systemic autoimmunity, such as arthritis, antinuclear antibodies, and recurrent infections, are commonly observed. SPENCD is inherited as an autosomal recessive trait and caused by biallelic mutations of *ACP5* encoding tartrate-resistant acid phosphatase (TRAP) (80, 81). TRAP dephosphorylates and thereby inactivates osteopontin, a cytokine that regulates bone formation and immune responses. Secreted osteopontin facilitates attachment of osteoblasts and osteoclasts to the extracellular matrix during osteogenesis, and intracellular osteopontin is essential for TLR9-dependent IFN-α production in plasmacytoid dendritic cells (82). In patients with SPENCD, constitutively activated osteopontin is thought to be responsible for increased bone resorption and immune dysregulation resulting in skeletal abnormalities and overproduction of type I IFN (**Table 1**, **Figure 2**) (80, 81).

Interferon-Stimulated Gene 15 Deficiency

Interferon-stimulated gene 15 deficiency (ISG15 deficiency; OMIM 61626) was first described as an autosomal recessive immunodeficiency disorder with increased susceptibility to mycobacterial disease (83). Patients were subsequently noted to be relatively resistant to viral infection and to exhibit an IFN signature in blood. Like patients with AGS, ISG15-deficient patients develop basal ganglia calcification consistent with an inflammatory vascular process (84). ISG15 deficiency is caused by biallelic mutations in *ISG15*, which encodes a type I IFN-induced ubiquitin-like protein that modifies target proteins by ISGylation (83, 84). Absence of ISG15 in patient cells prevents the accumulation of ubiquitin-specific protease 18 (USP18), which acts as a negative regulator of type I IFN signaling by removing ISG15 from its conjugated proteins, resulting in the enhancement of type I IFN responses (**Table 1**, **Figure 2**) (84). Collectively, these findings demonstrate a nonredundant role of ISG15 as an IFN-γ-inducing molecule during mycobacterial infection, whereas its primary role in antiviral immunity is to mediate an USP18-dependent negative regulation of the type I IFN axis.

Ubiquitin-Specific Protease 18 Deficiency

Ubiquitin-specific protease 18 deficiency (USP18 deficiency; OMIM 607057) is characterized by microcephaly, enlarged ventricles, cerebral calcification, and, occasionally, systemic features at birth (85). In addition, patient cells exhibit type I IFN activation. The clinical features resemble congenital viral infection or AGS. The disorder is caused by loss-of-function recessive mutations of *USP18*, encoding ubiquitin-specific protease 18, which removes ISG15 from its conjugated proteins (**Table 1**, **Figure 2**) (85).

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE; OMIM 256040) is an autosomal recessive autoinflammatory disorder with onset in infancy characterized by annular erythematous skin lesions with panniculitis-induced lipodystrophy, hepatomegaly, and arthralgias. Patients may also suffer from recurrent fever, joint contractions with muscle atrophy, and basal ganglia calcification, and their blood cells exhibit enhanced ISG expression as well as constitutive STAT1 phosphorylation (86). CANDLE constitutes a spectrum of proteasome-associated autoinflammatory syndrome (PRAAS) and is caused by either monogenic or digenic inheritance of loss-of-function mutations in immunoproteasome and constitutive proteasome subunits (**Table 1**, **Figure 2**). Biallelic mutations in *PSMB8* and *PSMB4*, encoding the inducible subunit β5i and the constitutive subunit β7, respectively, as well as additive heterozygous mutations involving either the immunoproteasome subunits *PSMB8* (β5i) or *PSMB9* (β1i) and the constitutive proteasome subunits *PSMA3* (α3) or *PSMB4* (β7), respectively, have been identified in CANDLE patients (86–88). In addition, an autosomal dominant mutation in *POMP*, encoding proteasome maturation protein, which facilitates sequential assembly of proteasome subunits, has been described in a single patient (88). The immunoproteasome is involved in processing of major histocompatibility complex class-I restricted T cell epitopes in antigen-presenting cells and influences cytokine production and T cell function. These findings suggest that cellular stress responses due to proteasome dysfunction can lead to chronic type I IFN signaling by hitherto unknown mechanisms.

X-Linked Reticulate Pigmentary Disorder

X-linked reticulate pigmentary disorder (XLPDR; OMIM 301220) is a rare genodermatosis with systemic manifestations beginning in early childhood (89). Males present with reticulate hyperpigmentation of the skin and distinct facial features as well as recurrent infections mainly involving the respiratory and gastrointestinal tracts. In addition, corneal dyskeratosis and hypohidrosis are observed. Females develop linear hyperpigmentation following the lines of Blaschko, without any systemic signs. XLPDR was recently shown to be caused by a recurrent intronic mutation in *POLA1* leading to missplicing (90). *POLA1* encodes the catalytic subunit of DNA polymerase α (Pol α), which in complex with primase synthesizes the short RNA-DNA primer required for initiating DNA synthesis during DNA replication (**Table 1**, **Figure 2**). Patient fibroblasts were shown to exhibit an IFN signature suggesting a cell-intrinsic mechanism of type I IFN activation. This was attributed to reduced formation of cytosolic DNA duplexes consisting of one DNA strand and one RNA-DNA strand as synthesized by the Pol α/primase complex. These duplexes were unexpectedly reported to downregulate antiviral gene expression (90). Given the essential role of Pol α in replication, it is also possible that byproducts of DNA repair at sites of stalled replication forks may actually account for type I IFN activation.

Childhood-Onset Polyarteritis Nodosa—ADA2 Deficiency

Childhood-onset polyarteritis nodosa (PAN; OMIM 615688) is an autosomal recessive systemic vascular inflammatory disorder affecting mainly the brain and skin. In addition to fever, necrotizing vasculitis of the gastrointestinal tract and renal aneurysms as well as varying degrees of immunodeficiency and autoimmunity have been described. PAN is caused by biallelic mutations of *CECR1* (cat eye syndrome chromosome region, candidate 1), encoding extracellular adenosine

deaminase 2 (ADA2), which deaminates adenosine to inosine and has been implicated in growth, development, and innate immunity (91, 92). Patients with ADA2 deficiency exhibit constitutive type I IFN activation in blood, although the underlying mechanisms remain to be investigated (93). In addition, biallelic *CECR1* mutations have been reported in a single family with Sneddon syndrome, which has a later onset than PAN (94).

REVISITING THE WASTE DISPOSAL HYPOTHESIS

The waste disposal hypothesis of SLE pathogenesis refers to the role of complement in the removal of immune complexes consisting of self antigens derived from dying cells (75). On the one hand, complement activation by immune complexes deposited in the capillary bed marks the effector inflammatory phase of the autoimmune response. On the other hand, reduced complement activity may promote presentation of autoantigens to the immune system in the context of inflammatory injury. In support of this hypothesis, deficiencies of the complement components C1q and C4 are associated with a high risk for SLE (75).

Clearance of Extracellular Nucleic Acid Waste

Formation of autoantibodies targeting nucleic acids is initiated by virus-induced IFN-α, which, in a susceptible individual, can drive a self-perpetuating feedback loop that stimulates maturation and proliferation of autoreactive B cells (68). These autoantibodies form immune complexes with self nucleic acids from dying cells. Following Fcγ receptor-mediated endosomal uptake of immune complexes by dendritic cells, the internalized nucleic acids subsequently activate TLR signaling to stimulate more IFN-α-production, further promoting a loss of tolerance and autoimmunity (**Figure 3**) (68).

This chain of events can be initiated by different mechanisms, including, for example, defects of central T cell tolerance due to impaired apoptosis, uncontrolled T cell costimulation resulting from inappropriate expression of costimulatory receptors, and insufficient degradation of extracellular DNA waste due to reduced activity of serum DNase I (**Figure 3**). A lack of DNase I in mice or humans has been shown to promote SLE (73, 95). Extracellular DNA waste may be derived not only from dying cells or immune complexes but also from neutrophil extracellular traps containing oxidized mitochondrial DNA (**Figure 3**) (96, 97).

Clearance of Intracellular Nucleic Acid Waste

Although perturbations in the removal of extracellular nucleic acid waste primarily trigger type I IFN signaling by noncell autonomous pathways, intracellular nucleic acids can also elicit antiviral immune responses in a cell-intrinsic manner. The host organism has, therefore, evolved diverse mechanisms to prevent detrimental immune recognition of self nucleic acids that are produced during physiological metabolic processes. TLR-mediated sensing of DNA and RNA derived from endocytosed cell debris or in complex with autoantibodies or other proteins is confined to the endosomal compartment (**Figure 3**). In addition, DNA taken up by lysosomes is subject to degradation by lysosomal DNase II. Complete DNase II deficiency in mice is embryonic lethal owing to excessive type I IFN production by macrophages, which are unable to digest nuclear DNA expelled from erythroid precursor cells (98). Interestingly, this phenotype can be rescued by concomitant deletion of cGAS or STING, suggesting that large amounts of undegraded lysosomal DNA exceeding a certain threshold can leak into the cytosol (99, 100). Similarly, mitochondrial

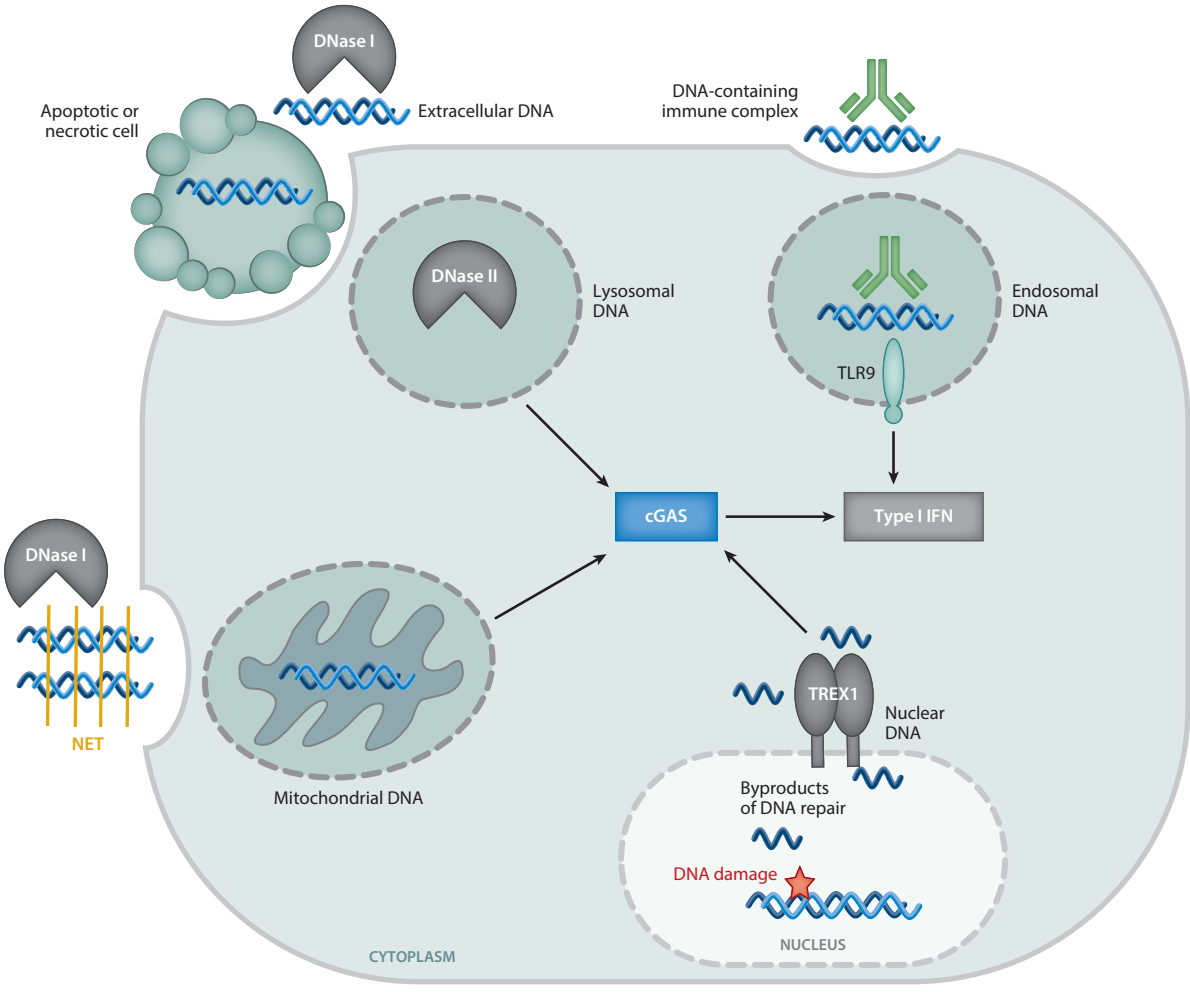

Figure 3

Pathways of DNA waste removal. Extracellular DNA derived from dying cells or contained in immune complexes or in neutrophil extracellular traps is degraded by serum DNase I. DNA taken up by lysosomes is degraded by lysosomal DNase II. DNA-containing immune complexes internalized into endosomes via either the Fcγ receptor or the B cell receptor activate TLR-dependent type I IFN signaling. Cytosolic DNA derived from byproducts of DNA repair is recognized by cGAS. This is prevented by nucleolytic degradation of nuclear DNA by TREX1, which is anchored within the outer nuclear membrane. Likewise, mitochondrial DNA as well as lysosomal DNA can leak into the cytosol under certain stress situations, leading to activation of cGAS-mediated immune recognition. Abbreviations: cGAS, cyclic GMP-AMP synthase; IFN, interferon; TLR, Toll-like receptor; TREX1, 3′ repair exonuclease 1.

stress has been shown to promote aberrant packaging of mitochondrial DNA, which can escape the mitochondrion and prime a cGAS-dependent antiviral response (101). Finally, short ssDNA metabolites, which continuously arise during repair of DNA damage induced by endogenous and environmental genotoxic stress, can to leak into the cytosol and activate cGAS-mediated type I IFN signaling (29), confirming the role of cGAS as universal sensor of cytosolic DNA. This is prevented by TREX1, a tail-anchored protein that acts as a sentinel nuclease patrolling the border

of the nuclear membrane to degrade nuclear DNA leaking into the cytosol (29). Collectively, these findings highlight the eminent role of proper cellular waste management in immune homeostasis and extend the waste disposal hypothesis to include extracellular as well as intracellular waste.

TRANSLATIONAL ASPECTS: TARGETING TYPE I INTERFERON

Type I interferonopathies are chronic multisystem diseases causing significant and severe morbidities. The inflammatory etiology of type I interferonopathies indicates that they are amenable to immunomodulatory treatment. Based on our current knowledge of the molecular pathogenesis of type I interferonopathies, targeting IFN-α/β, the IFN-α receptor (IFNAR), or the JAK/STAT pathway to inhibit the pathogenic type I IFN response might be therapeutically effective. Indeed, first observations in patients with STING-associated SAVI or chilblain lupus treated with the JAK inhibitor ruxolitinib or tofacitinib, respectively, are promising (62, 102). A first clinical trial (NCT01724580) with the JAK inhibitor baricitinib in patients with CANDLE or SAVI is under way. Another ongoing study (NCT02363452) addresses the potential therapeutic efficacy of antiretroviral agents in AGS patients with TREX1 deficiency, which aims at inhibiting reverse transcription of retroelements. Undoubtedly, further advances will also foster the development of novel compounds targeting components of the type I IFN signaling axis such as cGAS, TBK1, and STING.

CONCLUSIONS

Understanding the cellular and molecular functions of the genes causing type I interferonopathies was greatly accelerated by the discovery of the cytosolic nucleic acid sensors cGAS, RIG-I, and MDA5, which act in the first line of defense against viruses. Indeed, these scientific advances have unraveled a set of nucleic acid–metabolizing enzymes that either contribute to the formation of immunostimulatory nucleic acids, such as RNase H2 and SAMHD1, or prevent innate immune responses by degrading or modifying self nucleic acids, such as TREX1 and ADAR. However, the precise role of other disease genes encoding certain proteasome subunits and the extracellular adenosine deaminase 2 in type I IFN signaling remains to be investigated. Antiviral responses have both immediate and long-term effects and must be tightly orchestrated in time and space to be targeted and effective. Host, pathogen, and environmental factors regulate cellular responses to type I IFN signaling and determine whether pathogens are cleared effectively or chronic infection or autoimmune disease ensues. An antiviral immune response launched in the wrong place and/or at the wrong time can cause damage to the host, so the organism must have some efficient means to overcome limitations in pattern recognition. This can be achieved by confinement of nucleic acid species to distinct cellular compartments away from the cytosolic nucleic acid–sensing machinery, either through clearance of nucleic acid waste by nucleolytic degradation or through structural or chemical modification of nucleic acid ligands. Collectively, these findings have provided further insight into mechanisms that prevent inappropriate type I IFN activation yet ensure a prompt and efficient response to viral infection. This knowledge will also help define molecules and pathways that could potentially be targeted for specific therapeutic intervention in the future.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by grants from the Deutsche Forschungsgemeinschaft (Clinical Research Group 249). I apologize to those authors whose work has not been cited owing to space restrictions.

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