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Review article

Shaping the spectrum — From autoinflammation to autoimmunity

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ABSTRACT

Historically, autoimmune-inflammatory disorders were subdivided into autoinflammatory vs. autoimmune diseases. About a decade ago, an immunological continuum was proposed, placing "classical" autoinflammatory disorders, characterized by systemic inflammation in the absence of high-titer autoantibodies or autoreactive T lymphocytes, at the one end, and autoimmune disorders at the other end. We provide an overview of recent developments and observations, filling in some of the gaps and showing strong interconnections between innate and adaptive immune mechanisms, indicating that disorders from both ends of the immunological spectrum indeed share key pathomechanisms. We focus on three exemplary disorders: i) systemic juvenile idiopathic arthritis representing "classical" autoinflammatory disorders; ii) psoriasis, a mixed pattern disease; and iii) systemic lupus erythematosus, a prototypical autoimmune disease. We summarize scientific observations suggesting that, depending on disease stages and/or duration, individualized treatment targeting innate or adaptive immune mechanisms in disorders from either end of the immunological spectrum may control disease activity.

Contents

1. Introduction

Under physiological conditions, immune responses are induced by pathogens or other danger signals and conducted by immune and/or sometimes epithelial cells. The immune system can be subdivided into two parts, the developmentally more ancient *innate immune system*, and the evolutionarily younger *adaptive* or *acquired immune system* [1–5].

The innate immune system comprises a number of non-specific defense mechanism, constituting the "first line of defense" against pathogens. Innate mechanisms include both cellular and humoral components, which are involved in the detection and elimination of danger signals. Targets of the innate immune system can be of microbial origin (pathogen-associated molecular patterns, PAMPs) but also host molecules (danger-associated molecular patterns, DAMPs) [1,2,6]. Innate immune mechanisms are manifold and our understanding of their molecular composition and function is continuously expanding. Central molecules of innate immune mechanisms include Toll-like receptors (TLRs), Nod-like receptors (NLRs), scaffolding proteins, such as the caspase recruitment domain (CARD) family of proteins, and cytosolic DNA-sensing molecules, inflammatory multi-protein complexes, referred to as inflammasomes, the complement system, and others. Cellular components of the innate immune system comprise monocytes and macrophages, neutrophilic granulocytes, natural killer (NK) cells, and dendritic cells (DC). However, also non-immune cells, e.g. epithelial

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cells, express molecules that are considered part of the innate system, including TLR4/5, CARD family proteins, and inflammasome components [1–7].

The adaptive immune system is evolutionary younger and exclusive to vertebrates. Adaptive immune mechanisms create the immunological memory to pathogens in response to an initial contact. This results in a rapid and enhanced response to subsequent exposures. In contrast to inflammation mediated by the innate immune system, acquired immune responses are highly specific and can provide long-lasting protection from pathogens. Specificity to pathogens, spatiotemporal or regional control, and the limitation of inflammatory responses is necessary to prevent tissue damage, and is mediated by cells of the adaptive immune system (B and T cells), which provide humoral and cellular immune responses to "intruders" [8–11].

Following the definition suggested by Kastner et al., autoinflammatory disorders are characterized by seemingly unprovoked systemic inflammation in the absence of high-titer autoantibodies and autoreactive T lymphocytes [12,13]. More recently, however, the definition was expanded by the observation that external factors, including the environment, infections, temperature, etc., may promote flares, alter the phenotypes, and/or directly contribute to pathogenesis [1,3,4,14]. Thus, historically autoinflammatory disorders used to be strictly separated from autoimmune disorders, in which adaptive immune cells (B and/or T lymphocytes) largely contribute to the pathophysiology. About a decade ago, McDermott and McGonagle proposed a classification of immunological diseases with prototypical, mostly monogenic autoinflammatory disorders at the one end, and classical autoimmune disorders at the other end of an immunological spectrum [13]. Over the recent years, a number of monogenic and polygenic common and rare disorders have been identified, providing advanced insight into the pathophysiology of autoinflammatory and autoimmune disorders, further establishing the interplay between the two "parts" of the immune system in complex systems (such as the human body) [4,14,15]. Furthermore, genome-wide association studies, molecular imaging techniques, gene function studies, and the identification of tissue-specific factors in some disorders provided insights into the relative contribution of innate and adaptive immune mechanisms to some non-infectious immunological disorders, aided in gaining a better understanding of autoimmune/inflammatory conditions, and scientifically verified the hypotheses of McGonagle et al. Here, we provide an update on molecular pathomechanisms contributing to the immunological continuum, focusing on three exemplary disorders: i) the "classical" autoinflammatory disease systemic juvenile idiopathic arthritis (sJIA), ii) the mixed-pattern disorder psoriasis, and iii) the prototypical autoimmune disease systemic lupus erythematosus [16] and what we learned from rare monogenic disorders. The goal of this manuscript is not to deliver an all-embracing review of molecular pathomechanisms of single disorders, however, to provide an overview of recent developments in three "model disorders", focusing on proposed or established interconnections between innate and adaptive immune mechanisms in autoimmune-inflammatory disorders.

2. Classical autoinflammatory disorders: sJIA

The systemic form of juvenile idiopathic arthritis (sJIA) is a prototypical autoinflammatory disorder [17,18]. During its early and highly acute phase it is characterized by clinical signs of inflammation including fevers, skin rash, lymphadenopathy, hepatosplenomegaly, and/or serositis [17,19–21]. Particularly in this early inflammatory stage, sJIA is characterized by the absence of autoreactive T cells and high-titer autoantibodies, thus following the "traditional" definition of autoinflammation. Arthritis, though being a diagnostic criterion, is frequently absent during the acute highly inflammatory phase and may occur later during the course of disease. Potentially due to early diagnosis and treatment initiation, only about one third of sJIA patients fulfill the diagnostic criteria proposed by the International League of Associations for Rheumatology (ILAR) (Table 1) [17,19–21]. Up to one third of patients do generally not fulfill the criterion of quotidian fevers, while another third may not develop arthritis, potentially secondary to early aggressive treatment [17,22–24].

Table 1
International League of Associations for Rheumatology (ILAR) criteria for the diagnosis of systemic JIA [25].

Major criteria (*both obligatory*)
Quotidian fever on 3 subsequent days over 2 weeks
Arthritis (any number of joints)
Minor criteria (*at least one must be present*)
Evanescent rash
Generalized lymphadenopathy
Hepato-/splenomegaly
Serositis

To date, the pathophysiology of sJIA is only incompletely understood. Since familial clusters do not commonly occur, all ethnicities and both genders are affected with only slight variations between geographic regions, a combination of both genetic and environmental factors seem to contribute to disease pathogenesis. Polymorphisms in a number of genes have been reported associated with sJIA [17]. However, mutations in sJIA-associated genes are by themselves not strong enough to confer disease. Of note, mutations in genes associated with other monogenic autoinflammatory disorders, including cryopyrin-associated periodic syndromes (CAPS: *NLRP3*), Blau syndrome (*NOD2*), Familial Mediterranean fever (FMF: *MEFV*), or Periodic fever (PFAPA: *PSTPIP1*) have not been detected [17]. Genetic associations exist with a number of genes encoding for pro-inflammatory molecules, including cytokines (*IL1*, *IL6*, and *IL20*) and chemokines (*IL8* and *MIF*), anti-inflammatory or immune-modulating genes, including cytokines (*IL10*) and cytokine receptors (IL1R) (Table 2) [17]. Altogether, polymorphisms in those genes may contribute to the pro-inflammatory phenotype in sJIA. Of note, all of the aforementioned genes are associated with innate immune responses and exert effects on a large variety of immune and non-immune cells. Providing a pro-inflammatory microenvironment also affects lymphocytes, potentially contributing to the generation of specialized effector T cell phenotypes [7]. In this context, the "window-of-opportunity" hypothesis has been proposed and offers an interesting explanation for the changing phenotype from systemic inflammatory symptoms (fever, rash) to more organ-specific complications (e.g. destructive polyarthritis) over the disease course [26]. Thus, the authors proposed that during the acute early phase, the activation of innate immune cells resulting in innate pro-inflammatory cytokine expression holds the potential of early and aggressive intervention through cytokine blockade (e.g. with recombinant IL-1 receptor antagonist: anakinra; antil-IL-1 antibodies: canakinumab; anti-IL-6 receptor antibodies: tocilizumab). Early and aggressive disease control may prevent chronically destructive arthritis and other long-term sequelae. Case reports and case series promise potential of this approach [22–24,27,28]. However, further research, including controlled clinical trials are warranted to scientifically prove the window-of-opportunity concept.

3. Mixed pattern disorders: psoriasis

Psoriasis is an immunologically mediated disease that covers a range of subtypes or disease-stages representing mixed patterns of dysregulated innate and/or adaptive immune responses (Fig. 1) [38–40]. Early psoriasis but also highly active disease during flares sometimes presents with pustulous lesions, which entail dermal infiltrates with innate immune cells, including neutrophilic granulocytes, monocytes/macrophages, activated mast cells, as well as classical dendritic and plasmacytoid dendritic cells (pDCs). Predominantly expressed

Table 2
Genetic associations in systemic JIA.

Associated gene	*(Suspected) effect*	*Gene product*	*Gene function*
IL1 [29] (rs6712572, rs2071374, rs1688075)	Increased expression	Interleukin-1	Pro-inflammatory cytokine
IL1R (rs12712122)	Increased signaling	Interleukin-1 receptor	Cytokine receptor
IL6 [30,31] (rs1800795)	Increased expression	Interleukin-6	Pro-inflammatory cytokine
IL20 [32] (rs1400986)	Increased expression	Interleukin-20	Pro-inflammatory cytokine
TNF [33]	Increased expression	Tumor necrosis factor-alpha	Pro-inflammatory cytokine
MIF [34,35] (rs755622)	Increased expression	Macrophage migration inhibitory factor	
IL10 [32,36] (rs1800896)	Reduced Expression	Interleukin-10	Immune-modulating cytokine
LACC1 [37] (p.Cys43Tyrfs*6)	Truncated protein	Laccase domain-containing 1 protein	unknown

cytokines are IL-1-related cytokines, including IL-1α, IL-1β, IL-36, TNF-α, and the type I interferon IFN-γ. Cytokines are mainly produced by immune cells, but also keratinocytes (particularly IL-1alpha) [38,39]. At early stages, T lymphocytes are rare or completely absent in affected skin (Fig. 3A). Of note, the pro-inflammatory cytokine TNF-α has been demonstrated to induce the expression of adhesion molecules on endothelial cells which then results in the recruitment of further immune cells, forming micro-abscesses, and the emigration of cells to epidermal layers [38,39]. Recent reports indicate a central role of the innate molecule caspase recruitment domain family member (CARD)14 [41–43]. Gain-of-function mutations in the *CARD14* gene have been demonstrated to cause rare cases of familial psoriasis, referred to as PSOR2 [43]. Furthermore, single nucleotide polymorphisms (SNPs) in *CARD14* significantly more frequently occur in individuals with common multifactorial psoriasis and have been demonstrated to result in enhanced protein expression [42]. The CARD14 protein is expressed in keratinocytes and dermal endothelial cells in the affected skin and functions as scaffolding protein for NFκB, mediating NFκB activation and its nuclear translocation [42]. The transcriptional regulatory factor NFκB positively regulates the expression of chemokines (including IL-8, CXCL10, and CCL2), and pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α) which in turn contribute to the recruitment of aforementioned immune cells (Fig. 1A) [17]. The importance of an intact signal-specific regulation of NFκB activation for immune homeostasis was further underscored by most recent reports on defective NFκB activation in the immune deficiency syndrome NEMO (reduced NFκB activation) [44], and deficiency of the NFκB regulatory protein A20 (increased NFκB activation), both conditions resulting in systemic autoinflammation [45]. In NEMO patients, reduced NFκB activation contributes to immune deficiency, resulting in recurring infections, and in a subset of patients, concurrent inflammatory symptoms, including arthritis, colitis, and dermatitis. Both NFκB-associated disorders are characterized by systemic inflammation and inflammatory skin disease through uncontrolled pro-inflammatory cytokine expression. The exact role of DCs and particularly pDCs during early stages of psoriasis remain unclear, however, offer promising pathophysiological hypotheses [38,39]. Plasmacytoid DCs have been demonstrated to play a role during the differentiation of Th1 and Th17 effector T cell subsets, which play a role during later disease stages in psoriasis (see below) [7,38,39,46]. Furthermore, pDC-derived IFN-α limits the expression of IL-1-associated cytokines and inflammasome activation in macrophages and monocytes, thus contributing to disease progression to stages in which primarily adaptive immune mechanisms drive inflammation [38,39].

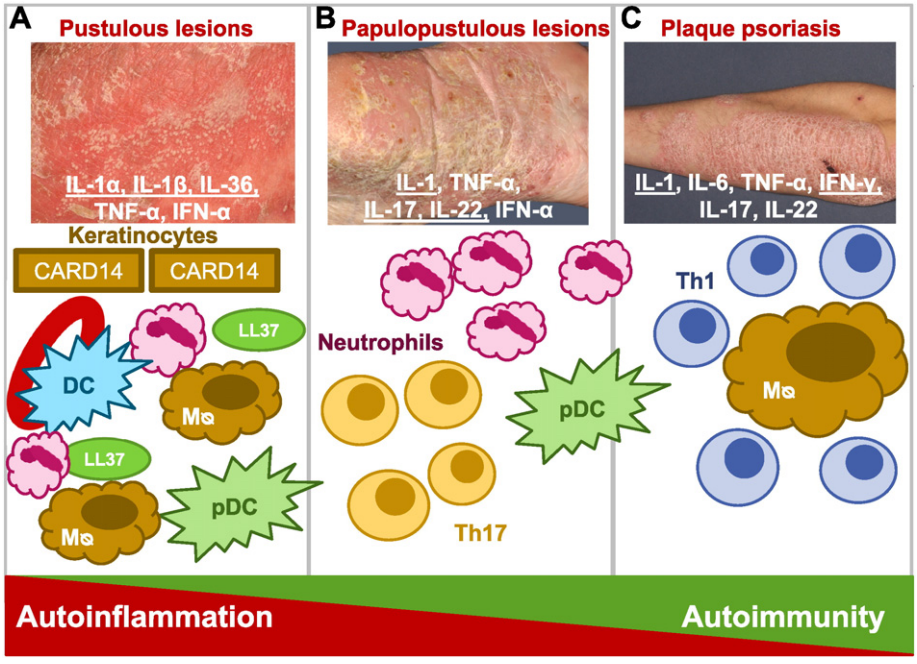

Fig. 1. Innate and adaptive immune mechanisms in psoriasis. A) During early stages or in highly active disease, some psoriasis patients exhibit pustulous lesions, which are characterized by infiltrates of innate immune cells, including neutrophils, dendritic cells (DC), macrophages/monocytes (Mφ), and plasmacytoid DC (pDC). Innate immune cells provide an IL-1-related cytokine microenvironment (inset in clinical picture) [38–40]. In a subset of psoriasis patients, gain of function mutations in *CARD1* result in enhanced cytokine expression in keratinocytes, and increased expression of chemokines in endothelia (red ring structure) [42,43]. The innate protein LL37 acts as a T cell antigen in psoriasis, resulting in effector T cell recruitment and activation [50]. B) In papolopustulous psoriasis lesions, cells of the adaptive immune system, mostly Th17 cells infiltrate the skin, and T cell effector cytokine expression plays a more predominant role (inset in clinical picture) [38–40]. C) Most psoriasis patients develop plaque psoriasis. In plaque psoriasis, Th1 cells are the predominant cellular infiltrate and Th1 cytokine expression can be detected (inset in clinical picture) [38–40].

During the progression of psoriasis, affected individuals can develop papulous or papulopustulous lesions. Of note, in some cases (particularly in palmopustular psoriasis) papulopustular psoriasis may reflect its own disease entity that can also be associated with other autoinflammatory disorders, such as chronic nonbacterial osteomyelitis (CNO) [47–49]. In papulopustulous lesions, neutrophilic infiltrates persist and continue producing IL-1-associated cytokines (Fig. 1B) [38,39]. However, during this stage of disease, lymphocyte infiltrates and effector lymphocyte-derived pro-inflammatory cytokines can be detected, resembling the coexistence of mainly innate inflammatory responses and adaptive *T*-cell driven immunity. T cell infiltrates during this stage mainly consist of Th17 effector cells, producing IL-17 family cytokines, and IL-22 [38–40,46]. Of note, DCs, and IL-1 family cytokines both play a role during the priming and differentiation of Th17 cells [7].

Later, the majority of patients develop plaque psoriasis over the course of disease, which is characterized by infiltrates of Th1 effector T cells, producing IFN-γ, IL-12, and TNF-α, and IL-1 producing monocytes and macrophages. Th17 cells may still be present, but less frequent when compared to earlier disease stages (Fig. 1C) [38,39,41,46]. In addition to the aforementioned cellular and humoral contributions of innate immune cells to the generation of autoreactive effector T cell responses, the innate peptide LL37 may be of central importance [50,51]. LL37 is an antimicrobial peptide that forms complexes with extracellular nucleic acids thus allowing their internalization and presentation to intracellular TLR7, 8, and 9. Recently, increased expression of LL37 in the skin of patients with psoriasis has been suggested as pathophysiological mechanism in psoriasis, since LL37 i) contributes to the maturation and activation of DC subsets, and ii) serves as an autoantigen to circulating T cells, contributing to their activation and induction of Th17 cytokine expression [50,51].

Another link between innate and adaptive immune responses are so-called Munro-abscesses, which are located in epidermal layers and mainly consist of neutrophilic granulocytes. Of note, Munro microabscesses periodically develop in stable plaque-type psoriasis, indicating that innate and adaptive immune mechanisms co-exist in psoriasis and influence one another, driving inflammatory responses [38,39]. This hypothesis is further supported by the observation that psoriasis patients i) respond to treatment targeting innate cytokines, including IL-1 and TNF-α, and that ii) this treatment is more efficient in patients with pustulous psoriasis as compared to predominantly Th17, and Th1-mediated papulopustulous or plaque psoriasis who more sufficiently respond to IL-23- or IL-17A-directed treatment.

4. "Classical" autoimmune disorders: systemic lupus erythematosus

Systemic lupus erythematosus [16] is a prototypical autoimmune disorder, characterized by the presence of autoantibodies, the formation of immune complexes, and self-reactive B- and T lymphocytes [52,53]. As a result of severe immune dysregulation, affected individuals present with systemic inflammation and variable organ damage. The molecular pathology of SLE is highly complex and only incompletely understood. It is known to involve both genetic and environmental factors. While most genetic associations are not strong enough to confer disease, in some rare cases, mutations in single genes cause SLE or related diseases [14,54]. The identification and study of such rare disorders contributed to a better understanding of common pathophysiological mechanisms in autoimmunity, also indicating that innate immune mechanisms may initiate or sustain autoimmunity in SLE.

4.1. Complement deficiencies

The complement system comprises a number of soluble proteins that resemble a rather underappreciated group of innate immune mechanisms. Main complement functions are binding immune complexes, apoptotic material, or foreign cell surfaces (e.g. bacteria), thus contributing to their clearance through phagocytes. Deficiencies of early factors of the classical complement activation pathway have been linked to mutations in the corresponding genes *C1q*, *C2*, and *C4*, which cause lupus-like disorders in a large percentage of individuals (C1q: 90%, C2: 30%, *C4*: 60%) [52,55]. The genes encoding for complement factors C2 and C4 are located in the MHC II region on chromosome 1, while *C1Q* is located in the MHC III locus, a well-accepted SLE susceptibility region on chromosome 6. Complement factor C1 is responsible for the activation of the complement cascade on the classical pathway in response to immune complexes, and apoptotic material. Subsequently, complement factors C2 and C4 become activated, forming the so-called C3 convertase. As a result, C3 is activated and induces the cleavage and activation of down-stream complement factors and the formation of the lytic complex, which induces the aforementioned lysis of foreign cells. The complete or partial deficiency of early components of the classical complement pathway, namely C1, C2, or C4, contributes to SLE or related disorders. The generally accepted pathophysiological model is based on the assumption that an accumulation of apoptotic material, cellular debris, and immune complexes in peripheral vessels prompts the release of vasoactive mediators, chemokines, and cytokines, altogether resulting in leukocytoclastic vasculitis and organ damage. Furthermore, in animal models, C4 deficiency has been linked to defective negative selection of B cells and subsequently increased numbers of autoreactive B lymphocytes in the periphery. The role of self-reactive B cells not only in C4 deficiency but also in other early complement factor defects is supported by the observation that patients with C1 or C2 deficiency and autoimmune phenomena respond to B lymphocyte depletion. Since immune complexes include immunoglobulins, B cell depletion also most likely has an impact on immune complex formation and deposition, and may therefore influence leukocytoclastic vasculitis in such patients [52,55–58].

Of note, complete complement deficiencies are rare disorders, accounting for a maximum of 1–4% of SLE patients. However, patients with classical SLE tend to exhibit lower gene copy numbers of C4, and some express autoantibodies against C1q, both potentially contributing to impaired clearance of immune complexes and accumulation of autoreactive B lymphocytes. Thus, defective activation and function of the innate complement system contributes to the induction of autoimmune processes in SLE [53].

4.2. Type I interferonopathies

Next to complement deficiencies, additional single-gene mutations have been implicated with the development of lupus-like disorders [52,53]. The majority of defects result in chronically increased and uncontrolled expression of type I interferons (interferon (IFN-)α, and IFN-β). Thus, such disorders are summarized in the group of type I interferonopathies. Clinically, interferonopathies are characterized by lupus-like disease phenotypes, or the presence of symptoms that also occur in classical SLE [14,52,59].

Chilblain lupus erythematosus [60] is a rare form of chronic cutaneous lupus. It usually affects middle-aged women, and up to 20% of patients with CHLE develop SLE later during the course of disease. Main clinical features of CHLE include blue-reddish inflammatory skin lesions at exposed body parts, such as fingers and toes, ears, nose and cheeks in response to exposure to cold and/or damp air [61]. Rare familial cases are caused by mutations in molecules involved in the sensing and processing of nucleic acids: *TREX1*, encoding for the 3′-5′ DNA exonuclease TREX1, and *SAMDH1*, encoding for SAM domain and HD domain-containing protein 1, an enzyme that exhibits phosphohydrolase activity, converting nucleotide triphosphates (NTPs) to triphosphate and a nucleoside, thus depleting the pool of NTPs subsequently preventing virus replication. Furthermore, SAMHD1 has been demonstrated to have ribonuclease activity [14].

In familial CHLE, both genders can be affected and symptoms occur earlier in life, sometimes during childhood. All reported disease-causing *TREX1* mutations in CHLE are located in the exonuclease domain

of the gene. Thus, the current pathophysiological hypothesis claims the accumulation of cytosolic DNA results in an activation of type I interferon genes through the STING:TBK1:IRF3 pathway (Fig. 2). A central pathophysiological role for defective DNA clearance in autoimmune-inflammatory disorders is further underscored by recently reported loss-of-function mutations in *DNASE1L3*, encoding for the endonuclease DNAse I. Homozygous mutations segregate with rare familial cases of pediatric-onset SLE, and likely feed into the same pathophysiological mechanisms as *TREX1* mutations. The authors furthermore claimed that release of intracellularly accumulated DNA into the extracellular space after cell death may also contribute to autoantibody production [62]. Rare *TREX1* variants, however, have also been detected in 0.5–3% of individuals with "classical" SLE. Polymorphisms were mostly located in genomic regions that are not crucial for the exonuclease activity of TREX1, suggesting an additional pathomechanism: TREX1 associates with the SET protein complex, centrally contributing to granzyme A-mediated and caspase-independent cell death. It has been postulated that individuals with SLE and such *TREX1* mutations may exhibit increased survival of autoreactive immune cells [52]. Of note, TREX1 polymorphisms in "classical" SLE increase the risk for neurological symptoms and complications, which links TREX1 mutations to another group of disorders, referred to as Aicardi Goutières syndrome [63,64]. Patients with AGS present with signs of intrauterine or congenital infections, including pleocytosis in the cerebrospinal fluid, calcifications in the basal ganglia, and resulting symptoms, such as muscle weakness or spasticism, neurological or cognitive impairment. Some patients exhibit additional symptoms, including chilblains, and livid discolorations at prominent body parts, livedo reticularis, thus showing clinical overlap with the aforementioned condition CHLE and SLE. As CHLE, AGS is caused by defective removal of intracellular DNA (mutations in *TREX1*) or RNA (mutations in *RNASEH2B*, *RNASEH2C*, *RNASEH2A*, or *IFIH1*) metabolism, resulting in cytoplasmic accumulation of nucleotides which trigger type I IFN release [14,59,65,66]. Most AGS-associated mutations result in altered RNA processing through loss-of-function mutations in genes encoding for RNAses. Mutations in *IFIH1*, encoding for the protein MDA5, however, result in a gain of function and increased RNA sensing and subsequent type I interferon responses [14].

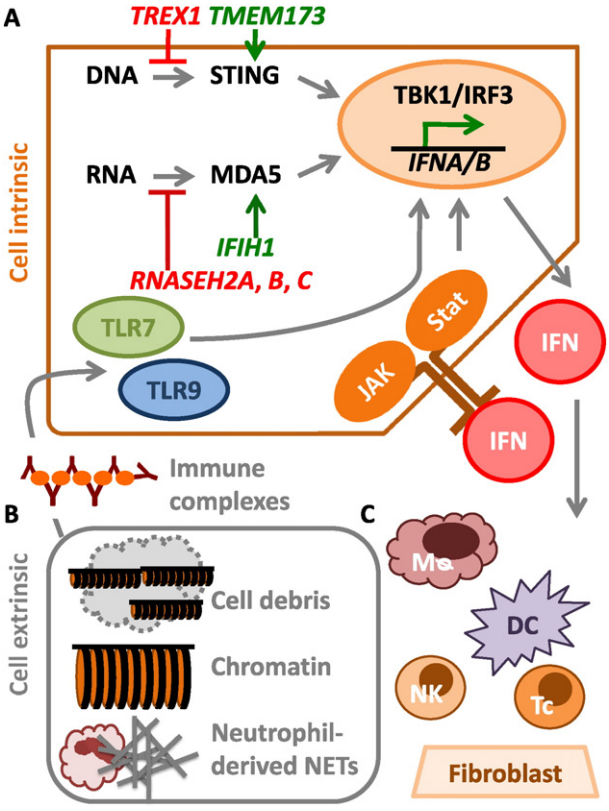

Fig. 2. The role of type I interferons in the pathophysiology of SLE. A) Rare mutations in *TREX1* cause familial chilblain lupus or Aicardi Goutières syndrome. Loss of function mutations in *TREX1*, encoding for the exonuclease TREX1, result in increased amounts of cytoplasmic DNA, activating the STING-dependent intracellular nucleotide sensing machinery and increased type I interferon expression through the and TBK1/IRF3 signaling pathway. Gain of function mutations in *TMEM173*, encoding for STING cause STING-associated vasculitis with infantile onset (SAVI). Continuous activation of STING results in chronic type I interferon expression. Loss of function mutations in RNAses (*RNASEH2A*, *B*, *C*) cause Aicardi Goutières syndrome. Mutations result in increased MDA5-dependent nuclease sensing and subsequent type I interferon expression. Gain of function mutations in *IFIH1*, encoding for the RNA sensing molecule MDA5, cause Aicardi Goutières syndrome through activation of the same pathways. B) Several extracellular (or extrinsic) mechanisms increase type I interferon expression in SLE. Increased apoptosis and neutrophilic NET formation in SLE cause increased levels of cellular components in tissues and the blood stream, including extracellular chromatin. Physiologically intracellular components in the extracellular space induce the formation of immune complexes, which are internalized and sensed by TLR7 or TLR9, feeding into type I interferon pathways. C) Type I interferon receptors can be found on cells of the innate and adaptive immune system, and non-immune cells (Mø: macrophage/monocyte; NK: natural killer cell; IFN: type I interferon, TLR: Toll like receptor).

Recently, a new intereferonopathy named STING-associated vasculopathy with onset in infancy (SAVI), has been reported and linked to gain-of-function mutations in the *TMEM173* gene, encoding for STING. STING is an adapter molecule in the intracellular nucleotide sensing machinery (Fig. 2) [67,68]. Its activation mediates IRF3-dependent expression of IFN-beta, resulting in a chronically increased type I interferon signature in the blood. Patients develop symptoms of dermal vasculitis, and microangiopathic thromboses during the first weeks of live. Later during the course of disease, additional symptoms develop, including interstitial pulmonary disease, and myositis. During the course of SAVI, the activation of adaptive immunity can be assumed, given variable and sometimes high-titer autoantibody production. Autoantibody production, however, varies widely between patients and (provided limited data from small patient numbers) does not appear to be associated with specific organ involvement or disease activity or severity [14,67,68].

Additional interferonopathies have already been reported, but extend beyond the scope of this manuscript, or are to be discovered. Regardless of their rarity, the discovery of type I interferonopathies aided in gaining a better understanding of shared pathomechanisms with classical multietiological SLE, particularly since cell intrinsic (DNA, RNA) and cell extrinsic (immune complexes from extracellular chromatin, neutrophil-derived NETs, etc. are recognized by endosomal TLR7/9) stimuli contribute to the expression of type I interferons in classical multifactorial SLE (Fig. 2) [69]. Since IFN receptors are expressed on various cells of the innate (monocytes, macrophages, etc.) and the adaptive (T lymphocytes) immune system, and non-immune cells (fibroblasts), the induction of a persistently strong type I interferon signature results in the activation of pro-inflammatory pathways and a strong integral inflammatory response that is not limited to the innate immune system [68,70].

4.3. Risk alleles for the development of SLE

Most SLE patients, however, do not carry aforementioned rare mutations in single genes, but rather common single nucleotide polymorphisms (SNPs) in genes that are more likely to be found in SLE patients when compared to healthy controls, but not strong enough to confer disease. The presence of SNPs, in some cases their combination, or copy number variations of single genes results in so-called risk alleles that increase the personal risk for developing autoimmune phenomena, usually to a rather minor extent (usually not above 2–4-fold) [52]. A considerable proportion of such lupus-associated mutations or copy number variations can be found in and/or around genes that encode for proteins that are involved in innate immune mechanisms. Aforementioned reduced copy-numbers of C4 can frequently be found in SLE patients [52,56,58]. Polymorphisms in *TLR7* and/or *TLR9* have been associated with increased risk to develop SLE [71–73]. As described

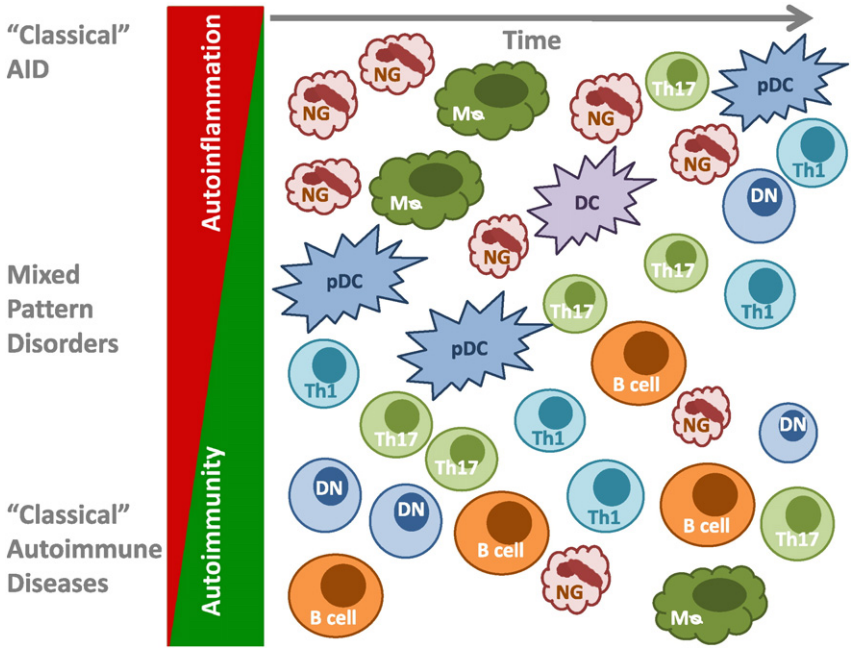

Fig. 3. The immunological continuum hypothesis. As proposed almost a decade ago by McGonagle and McDermott [13], autoimmune-inflammatory disorders can be placed in an immunological continuum with "classical" autoinflammatory disorders at the one end, and prototypical autoimmune disorders at the other end of the spectrum. Recent scientific observations indicate that various innate immune mechanisms are centrally involved in the activation of the adaptive immune system and vice versa. In agreement with the initial immunological spectrum hypothesis, innate and adaptive components of the immune system cannot be seen separately, but promise tailored therapeutic interventions depending on disease phase or stage in individual patients (NG: neutrophilic granulocytes; Mφ: macrophage/monocyte, DC: Dendritic cell, pDC: plasmacytoid dendritic cell; Th1: T helper cell 1; Th17: T helper cell 17).

above, TLR7 and TLR9 play a central role during the processing of immune complexes and cellular debris, and are finally responsible for the induction of type I interferon expression (Fig. 2) [69]. Mutations have been suggested to impair immune complex processing, and clearance of apoptotic material, which may contribute to increased local inflammation and the generation of autoantibodies against endogenous proteins. Alternatively, pathologically increased TLR7 or TLR9 activation may increase the expression of type I interferons [52,71–73]. Another gene locus associated with SLE is the so-called Fc-gamma receptor cluster on chromosome 1. Fc-gamma receptors are low-affinity receptors for immune complexes. Various receptors are expressed on cells of the innate and/or adaptive immune system, providing another interconnection between innate and adaptive immune mechanisms. *FCGR2A* encodes for the IgG receptor Fc-gamma 2C on monocytes and macrophages, and *FCGR3B* encodes for the IgG-specific Fc-gamma receptor 3B on neutrophilic granulocytes. Through the clearance of immune complexes, Fc-gamma receptors 2A and 3B were claimed to exert anti-inflammatory functions. SNPs in *FCGR2A* and low copy numbers of *FCGR3B* are risk alleles for SLE, while high copy numbers of *FCGR3B* protect from glomerulonephritis in SLE, suggesting that high copy numbers protect from SLE or tissue damage [16,60,74–77].

5. Conclusions

Over the past decade, the identification of disease-causing mutations in single genes and the association of polymorphisms in disease-associated gene loci contributed to a deeper understanding of the pathophysiology of various autoimmune-inflammatory disorders. Recent observations underscore the significance and relevance of a previously proposed immunological continuum, ranging from monogenetic autoinflammatory disorders at the one end to autoimmune diseases at the other end [13]. Scientific observations and well-accepted pathopysiological hypotheses in model disorders from either end of the continuum indicate the close interconnection between innate and adaptive immune mechanisms (Fig. 3). A better understanding of molecular pathomechanisms in autoimmune-inflammatory disorder and the relative contribution of innate and adaptive mechanisms will help to introduce individualized, and target-directed treatments with increased efficacy and reduced side-effects.

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