



From autoinflammation to autoimmunity: old and recent findings

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Abstract

Autoimmune diseases and autoinflammatory diseases have a number of similar etiopathogenetic and clinical characteristics, including genetic predisposition and recurrent systemic inflammatory flares. The first phase of ADs involves innate immunity: by means of TLRs, autoantigen presentation, B and T cell recruitment and autoantibody synthesis. The second phase involves adaptive immunity, a self-sustaining process in which immune complexes containing nucleic acids and autoantibodies activate self-directed inflammation. The link between autoimmunity and autoinflammation is IL-1 β , which is crucial in connecting the innate immune response due to NLR activation and the adaptive immune responses of T and B cells. In conclusion, although ADs are still considered adaptive immunity-mediated disorders, there is increasing evidence that innate immunity and inflammasomes are also involved. The aim of this review is to highlight the link between the innate and adaptive immune mechanisms involved in autoimmune diseases.

Keywords Adaptive and innate immunity · Autoimmune diseases · Autoinflammatory diseases · T and B cells

Introduction

The term “autoimmunity” used to be referred to a condition associated with the dysregulation of adaptive immunity alone (Table 1), whereas “autoinflammatory” was initially defined solely as a consequence of dysregulated innate immunity (Table 2) [1–5]. Consequently, the pathogenetic mechanisms

of autoimmune diseases (ADs) were considered to be exclusively mediated by B and T lymphocytes whose B and T cell receptors (BCRs and TCRs) recognised specific antigens, started the inflammatory response against autoantigens, and activated B cell-mediated autoantibody production whereas the autoinflammatory diseases were defined as unprovoked episodes of inflammation, without high titre of autoantibodies or antigen-specific T cells [6–10]. This view clearly separated autoinflammation and autoimmunity as distinct immunological diseases. It was believed that in autoinflammation, no pathogenetic role was played by adaptive immunity, autoantibodies or autoreactive lymphocytes [1–5]. More than 10 years ago, McGonagle and McDermott first theorised the existence of a “continuum model” of immunology, in which diseases lie on a spectrum from autoimmune to autoinflammatory, with variable contributions of both the innate and the adaptive immune responses to particular diseases [3].

Autoinflammatory diseases are a group of monogenic and polygenic disorders characterised by recurrent inflammatory episodes whose heterogeneous symptoms are frequently associated with fever (Table 2) [1–5]. The key pathogenetic moment in autoinflammatory diseases is the direct and indirect dysregulation of inflammasomes, the multiprotein cytoplasmic complexes characteristic of innate immunity and inflammatory responses [11]. The main components of inflam-

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masomes are members of the nucleotide-binding oligomerisation domain(NOD)-like receptor (NLR) family, a class of pattern recognition receptors (PRR) [11]. When induced to do so by pro-inflammatory triggers such as the stimuli transmitted by pathogens or damaged cells, NLRs respectively detect pathogen-associated or damage-associated molecular patterns ((PAMPs or DAMPs) and begin inflammasome assembly, which generates the proteolytic activation of caspases and the conversion of pro-interleukin(IL)-1 β into active IL-1 β , a key molecule of inflammation and innate immunity [11].

Although ADs are still considered adaptive immunity-mediated disorders, there is increasing evidence that innate immunity and inflammasomes are also involved [1–5]. It seems clear that despite the differences in the system primarily involved, autoinflammatory and autoimmune disease share common characteristics as the activation against self, with subsequent systemic inflammation, and the absence of an external causal trigger clearly identified. The main difference between the two pathogenetic mechanisms is that in autoinflammatory diseases, the innate immune system is the one directly causing inflammation, while in ADs, it subsequently activates the adaptive system that is the one to activate the inflammatory process.

The link between autoinflammation and autoimmunity: an overview

It is known that innate and adaptive immunity are strictly interconnected. In the case of innate immunity, macrophages, antigen-presenting cells (APCs) and dendritic cells (DCs) act as the first line of host defence [12]. PAMPs and DAMPs are neutralised by NLRs and other classes of PRRs such as Toll-like receptors (TLRs), which recognise various microbial ligands [13], activate inflammasomes, thus increasing the synthesis of pro-inflammatory cytokines including IL1 β , IL-18, tumour necrosis factor- α (TNF- α) and interferon(IFN)- α and IFN- β . These cytokines subsequently activate adaptive immunity [4, 10, 14]. There is increasing evidence that the protracted or increased activation of PRRs plays a key role in autoimmune mechanisms: Leadbetter et al. have shown that the activation of rheumatoid factor-positive B cells mediated by IgG2a/chromatin immune complexes is associated with the synergistic action of the antigen receptor and a protein belonging to the TLR family [15].

This link between TLRs and B cells suggests that TLRs could play a potentially key role in autoantibody responses in various ADs [16–20]. For examples, TLR4 promotes B cell differentiation and leads to the production of antibodies by upregulating the expression of B cell-activating factor (BAFF) [20], a crucial factor that regulates B cell maturation,

survival and function, and is upregulated in systemic lupus erythematosus (SLE) [21–23].

An important link between autoimmunity and autoinflammation is represented by IL-1 β , which is crucial in connecting the innate immune response due to NLR activation and the adaptive immune responses of T and B cells [24–30]. It has been demonstrated by Chung et al. that the increased levels of IL-1 following inflammasome activation can induce T cell polarisation (Th17 differentiation) and, synergized with IL-6 and IL-23, is crucial in maintaining cytokine expression in effector Th17 cells [25].

IL-1 has also been implicated in the activation of IFN- γ in memory T cells [26, 27], T cell proliferation (which is also mediated by IL-2 and its receptor) [28], increased B cell proliferation [29], and increased antibody synthesis [30], thus connecting the inflammasome-driven responses to the adaptive immune system in response to exogenous and endogenous signals.

The role of IL-1 has always been considered of crucial importance in autoinflammatory diseases, as demonstrated by the rapid and sustained improvement in disease severity after treatment with IL-1 β drug. Other than in monogenic autoinflammatory diseases, IL-1 β has a pivotal role in rheumatoid arthritis (RA): it has been shown that IL-1 β induces the expression of different proteolytic enzymes, such as metalloproteinases, collagenases and elastases, thus leading to bone erosions and cartilage destruction [11, 31]. However, treatment with IL-1 drug in RA is not as effective as in autoinflammatory diseases, having a modest effect in comparison with other biologic agents blocking TNF pathways [11, 31].

Other evidence of a link between autoimmunity and autoinflammation regard nucleotide-binding oligomerization domain-containing protein 2 (NOD2) [32], a member of a family of pattern recognition molecules with N-terminal Caspase activation and recruitment domains (CARDs) that is also called the nucleotide binding domain and leucine-rich repeat(LRR)-containing family [33, 34]. NOD2 mutations in NACHT domains are responsible for the autoinflammatory granulomatous diseases Blau Syndrome (BS) and early onset sarcoidosis (EOS). At the same time, polymorphisms in LRRs are also susceptibility regions for Crohn's disease (CD) [33, 34], a disease that is long believed to be on the cross-road between autoinflammation and autoimmunity. In addition, NOD2 is a key molecule recognising bacterial muramyl dipeptide (MDP) [35, 36], the neutralisation of which is abolished in NOD2-deficient mice, thus suggesting that NOD2 may act as an adjuvant receptor for antibody production and play a key role in activating adaptive immunity [32].

Another emblematic example of the link between autoimmunity and autoinflammation is represented by the role of inflammasomes, crucial components of the innate system, in a paradigmatic autoimmune disease such as systemic lupus erythematosus (SLE). Several autoinflammatory disorders, such

Table 1 Main autoimmune diseases

Monogenic autoimmune diseases		Polygenic autoimmune diseases	
Autoimmunity, polyendocrinopathy, candidiasis, ectodermal dysplasia (APECED)	AR disease caused by mutations in the AIRE gene	Arthropathies	Rheumatoid arthritis
Immune dysregulation, polyendocrinopathy, X-linked syndrome (IPEX)	X-linked syndrome due to mutations in FOXP3, a key regulator of TRegs	Connective tissue diseases	Systemic lupus erythematosus (SLE); systemic sclerosis poly-myositis; dermatomyositis; Sjögren’s syndrome; undifferentiated connective tissue disease (UCTD); mixed connective tissue disease (MCTD); overlap syndromes
Autoimmune lymphoproliferative syndrome (ALPS)	Lymphoproliferative disease with autoantibody positivity and SLE-like characteristics caused by mutations in the genes involved in the Fas-mediated apoptosis pathway	Vasculitis	ANCA-associated vasculitis
Complement fraction 1q (C1q) deficiency	SLE associated with mutations in the C1q gene	Autoimmune diseases with a prevalently autoimmune pathogenesis Autoimmune diseases with a prevalently inflammatory pathogenesis	Celiac disease; primary biliary cirrhosis; auto-immune hepatitis; auto-immune haemolytic anaemia; autoimmune thrombocyto-penia; pemphigus; vitiligo Spondyloarthritis; Crohn’s disease (CD) ulcerative colitis (UC); multiple sclerosis (MS)

AIRE, autoimmune-regulator; AR, autosomal recessive; FOXP3, forkhead box P3; TRegs, T-regulator cells

Table 2 Main pathogenetic aspects of monogenic autoinflammatory syndromes

Group	Disease	Gene	Inheritance	Mutated protein
Hereditary periodic fevers	FMF	MEFV	AR	Pyrin
	TRAPS	TNFRSF1A	AD	TNFRSF1A
	MKD	MVK	AR	Mevalonate kinase
Cryopyrinopathies	FCAS	NLRP3/CIAS1	AD	Cryopyrin
	MWS		AD	
	CINCA		Sporadic or AD	
Granulomatous diseases	NLRP12AD	NLRP12	AD	Monarch 1
	BS	NOD2/CARD15	AD	NOD2
Pyogenic diseases	EOS		Sporadic	
	PAPAs	PSTPIP1/CD2BP1	AD	PSTPIP1
	MS	LPIN2	AR or sporadic	Lipin-2
Vasculitis	DIRA	IL1RN	AR	IL-1 receptor antagonist
	DADA2	CECR1	AR	ADA2
IFN-mediated diseases	AGS	TREX1, RNASEH2A, RNASEH2B, RNASEH2C and SAMHD1	AR	TREX1 and subunits of the RNASEH2 endonuclease complex
	CANDLE	PSMB8	AR	PSMB8

AD, autosomal dominant; ADA2, adenosine deaminase 2; AGS, Aicardi-Goutieres syndrome; AR, autosomal recessive; BS, Blau syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CINCA, chronic infantile neurological cutaneous articular syndrome; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of interleukin-1 receptor antagonist; EOS, early-onset sarcoidosis; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; MS, Majeed syndrome; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NLRP12AD, NLRP12-autoinflammatory-associated disorder; NOD2, nucleotide-binding oligomerisation domain containing protein 2; PAPAs, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PSMB8, proteasome subunit β 8; PSTPIP1, proline-serine-threonine phosphatase-interacting protein 1; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; TREX1, 3’ repair exonuclease 1; TNFRSF1A, TNF receptor superfamily, member 1A

as CAPS, FCAS, MWS and NOMID, have been linked with mutations in inflammasomes, particularly involving NLRP3 inflammasome, thus leading to increase in release of IL-1 [37]. These mutations have also been linked with polygenic inflammatory disorders, such as gout and pseudogout. In comparison the understanding of the role of inflammasomes in autoimmunity is less clear. In recent years there have been increasing evidence that inflammasomes, particularly NLRP3, could play a potentially key role in SLE, with various mechanisms. Immune complexes formed secondarily to antibody recognition have been shown to stimulate inflammasome activation through upregulation of TLR-dependent activation of NF κ B and subsequent activation of the NLRP3 inflammasome [38]. Kidney biopsy findings from SLE patients have shown increased expression of inflammasome components, including NLRP3 and caspase-1 [39]. C3a, which is released during complement activation in tissues in SLE, regulates ATP secretion in inflammasome thus causing their activation and subsequent production of IL-1 [40]. Anti-dsDNA antibodies (Abs) play critical roles in the development and progression of SLE. The activity of caspase-1 was significantly increased in active SLE patients and was correlated with serum levels of anti-dsDNA antibodies and with disease activity. It was observed that anti-dsDNA Abs activated NLRP3 inflammasome in monocytes/macrophages from SLE patients by binding to TLR4 and inducing the production of mitochondrial ROS [41]. Moreover, activation of NLRP3 is involved in the pathogenesis of podocyte injuries and the development of proteinuria in lupus nephritis [42].

Autoinflammatory diseases

Autoinflammatory diseases are a group of monogenic and polygenic disorders characterised by dysregulation in the innate immune system, particularly in key cytokine pathways such as the ones involving TNF and interleukin 1, including the complex of adaptor molecules known as inflammasome, as well as mutations in proteins associated with bacterial sensing. They share as clinical manifestations recurrent episodes of unprovoked inflammation, often accompanied by fever and a wide range of systemic manifestations involving cutaneous, vascular and musculoskeletal systems in the absence of auto-antibodies or antigen specific T-lymphocytes. The first autoinflammatory disease described, and also the most common, was the mediterranean familial fever, followed by TNF receptor-associated periodic syndrome (TRAPS) in 1999, when the autoinflammatory disease term for these diseases was proposed by McDermott and colleagues. Since then an increasing number of diseases were classified, with a wide range of monogenic and polygenic mutations identified in the innate immune pathways [3].

The hereditary periodic fevers are familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), and TNF receptor-associated periodic syndrome (TRAPS) [43–45]. FMF and MKD are respectively due to Mediterranean fever (MEFV) and mevalonate kinase (MVK) gene mutations codifying pyrin protein and mevalonate kinase (MK) enzyme (MK), and associated with enhanced procaspase-1 activation and increased IL-1 β processing and secretion, whereas TRAPS is due to mutations in TNFRSF1A, whose intracellular accumulation in the endoplasmic reticulum (ER) leads to the activation of ER-stress responses and the mitochondrial release of reactive oxygen species (ROS), with the upregulation of pro-inflammatory cytokines such as IL-1 β , TNF- α and IL-6 [43, 44]. As seen before, the autoinflammatory granulomatous diseases Blau syndrome (BS) and early-onset sarcoidosis (EOS), are caused by NOD2 mutations in NACHTdomains. NOD2 polymorphisms in LRRs are also susceptibility regions for Crohn's disease (CD) [33, 34].

The adaptive immune response is also potentially linked to innate immunity through the Th1 and Th17 cell responses mediated by the nucleotide oligomerisation domain-like receptor family, pyrin domain-containing 3/caspase-1 (NLRP3) inflammasome, mutations of which are responsible for the autoinflammatory diseases known as cryopyrinopathies (CAPS) [43, 44].

In addition to hereditary periodic fevers, granulomatous diseases and CAPS, an autoinflammatory group includes pyogenic diseases, adenosine deaminase 2 (ADA2) protein deficiency, and NLRC4-mediated diseases [43–63]. The pyogenic MAIDs include pyogenic arthritis pyoderma gangrenosum and cystic acne syndrome (PAPAS), Majeed syndrome, and interleukin-1 receptor antagonist (DIRA) deficiency, which are respectively due to mutations in PSTPIP1, LPIN2, and IL1RN genes [45–48]. MAIDs also include diseases mediated by adenosine deaminase 2 (ADA2) protein deficiency, an increased synthesis of type I IFN, proteasome dysfunction, and IL-18 dysregulation [50]. The more recent identification of autosomal-recessive mutations in the CECR1 gene leading to ADA2 protein deficiency has been found to be responsible for the early-onset febrile vasculitis associated with stroke [51, 52]. Other recently described monogenic autoinflammatory diseases are the IFN-mediated autoinflammatory diseases (IMADs) due to genetic mutations leading to an increased synthesis of type I IFN, which include Aicardi–Goutières syndromes (AGS) and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome) [53–59]. Another recently identified, rare monogenic autoinflammatory disease directly involving the inflammasome complex and caused by mutations in NLRC4 gene is an autoinflammatory syndrome with enterocolitis that is associated with susceptibility to macrophage activation syndrome (MAS) [60, 61]. Physiologically, NLRC4 is an adapter protein for caspase-1 activation that cooperates with cytosolic

receptors for various bacterial proteins (NAIPs). NLRC4/NAIP oligomerisation leads to the recruitment of the adaptor protein apoptosis-associated speck-like protein enclosing a CARD (ASC) [61–64], which allows the NLRC4 inflammasome to activate pro-caspase-1, thus increasing IL1 β synthesis and cell inflammation [61–64].

The main pathogenetic aspects of monogenic autoinflammatory diseases are shown in Table 2.

Greater understanding of the main pathogenetic mechanisms underlying a number of polygenic disorders has led to them being considered autoinflammatory disorders [1]: these include periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPAS), systemic-onset juvenile idiopathic arthritis (So-JIA), adult-onset Still's disease (AOSD), macrophage activation syndrome (MAS), Schnitzler syndrome, chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, pyoderma gangrenosum, Sweet's syndrome, and CD [1, 64]. However, more than 10 years ago, McDermott and McGonagle suggested that a number of these diseases, classically considered to be exclusively autoimmune, were on the borderline between autoimmune and autoinflammatory diseases with a prevalent inflammatory component [3].

From autoimmune to autoinflammatory genetics

Genetic variants of the major histocompatibility complex (MHC) or the human leukocyte antigen (HLA) region located on the short arm of chromosome 6 are associated with autoimmune and inflammatory diseases [65, 66]. Fernando et al. made a pooled analysis of different studies investigating the causal links between MHC variants and various autoimmune and inflammatory diseases, and found that HLA-DR2 and HLA-DR3 were alleles inducing susceptibility to SLE and multiple sclerosis (MS) among Europeans, and that several HLA-DR4 haplotypes may predispose to SLE (HLADRB1*0401) and MS (multiple HLA-DRB1*04 alleles) [65]. HLA-DRB1*0401 and *0405 are associated with RA, whereas haplotypes DR3, DR4 and DR9 are associated with type 1 diabetes (T1D), class I MICA5.1 and HLA-A19 and class II HLA-DR5, -6, -8, and -10 are associated with inflammatory bowel disease (IBD) [65]. Various HLA-DR1 haplotypes have been associated with a predisposition to CD, ulcerative colitis (UC) and RA, and various DR2 haplotypes have been observed in SLE, MS, and UC [65]. HLA-DR3 haplotypes predispose for SLE, MS and T1D, and HLA-DR9 haplotypes predispose for RA and T1D [65]. HLA-DR4 is a shared disease susceptibility allele in RA, SLE, CD, MS, and T1D [65].

Autoimmune diseases with distinctive autoantibody profiles and diseases seronegative for autoantibodies are

respectively associated with MHC class II and class I alleles [67–70], and HLA-DR3-DQ2, HLA-B8 and HLA-A1 alleles are associated with diseases such as celiac disease, T1D and autoimmune thyroid diseases (also due to linkage within the MHC locus) [67–71].

In the case of autoimmunity both mechanisms involved in the binding between self-peptide and the MHC complex and post-translational modifications in self-peptide can be involved in the pathogenesis of autoimmune disease in subjects with an HLA risk allele [45, 67]. For example, a change from arginine to citrulline and the synthesis of autoantibodies against citrullinated peptides and proteins (anti-citrullinated protein antibodies [ACPAs]) can be detected years before the clinical onset of RA, and their identification may be predictive of RA in subjects with HLADRB1*04:01 and *04:04 [67, 72–76]. Post-translational modification can also be involved in the pathogenesis of autoimmune diseases by affecting the uptake of antigen by APCs [67, 76].

In patients with Behçet's disease, ankylosing spondylitis (AS) and psoriasis, there is an association between polymorphisms in the aminopeptidase gene endoplasmic reticulum aminopeptidase 1 (ERAP1) and disease-associated MHC class I alleles [77, 78].

In RA patients, the P4 and P6 pockets of HLA-DR proteins have been identified as the most important polymorphisms associated with susceptibility [79, 80]. Autoimmune diseases with autoantibodies show associations between MHC class II and various adaptive immune genes; in the case of RA, there is an association with cytotoxic T lymphocyte antigen-4 (CTLA4) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) [81, 82].

There are genetic overlaps between innate immunity-mediated diseases such as CD and some MHCs [83]. For example, an association has been reported between CD and MHC class I-associated diseases that represents a disease at the crossroads between autoinflammation and autoimmunity. Furthermore, despite the association with MHC (mainly MHC class I), it has been found on the basis of recurrent systemic clinical findings and the response to IL-1 inhibition that other polygenic diseases such as So-JIA, and AOSD are linked to predominant innate immunity involvement [81, 84, 85].

The phases linking innate and adaptive immunity provide that peptide/MHC (pMHC) class II tetramers play a predominant role in the interactions between T cells and APCs [79–82]. Self-peptide/MHC complexes on thymic APCs are essential for developing T cells [83], and MHC class II tetramers are important for characterising CD4 T cell specificity. Selection against high-affinity self-Ag recognition influences the avidity of the interactions between a TCR and its pMHC [86–88]. Specific APCs located in the thymic cortex and medulla can be key factors in coordinating the selection of a functional and self-tolerant T cell repertoire, and allowing the activities of mature T cells in the periphery [89].

A number of autoinflammatory mechanisms related to monogenic mutations can be found during the course of various autoimmune diseases [90] including autoimmune lymphoproliferative syndrome (ALPS), which is characterised by adenomegaly, splenomegaly, cytopenia, autoantibodies, and SLE-like characteristics, and caused by mutations in the genes involved in the Fas-mediated apoptosis pathway [90, 91].

Various innate immunity-related genes may help in clarifying the phenotype and pharmacogenomics of autoimmune conditions; for example, the IL-1 α 889T allele can be associated with the a lack of response to cyclophosphamide in systemic sclerosis (SSc) [90, 92].

It has been reported that numerous genetic polymorphisms of inflammasomes are associated with susceptibility, disease activity and therapeutic response of a number of autoimmune diseases [86]. These include single nucleotide polymorphisms (SNPs) affecting the priming of inflammasomes, and the TLR7 and TLR9 polymorphisms associated with SLE [93–97]. Furthermore, polymorphisms of the purinergic P2X7 receptor (P2X7R), a key molecule for ATP release from damaged cells that can cause the potassium efflux activating the NLRP3 inflammasome have been associated with susceptibility to RA, MS, SLE and lupus nephritis in different populations. [93, 98]. The increased priming of inflammasomes in autoimmune diseases has also been reported to be associated with pro-inflammatory stimuli, including apoptotic cell debris [24, 39, 93, 99, 100].

NLRP1 and NLRP3 play a key role in tissue damage, and NLRP1 SNPs are associated with SLE, RA, SSc and vitiligo in various populations, and NLRP3 SNPs are associated with So-JIA and increased inflammation in autoimmune diseases [93, 101–104].

Another link between the innate and adaptive sides of immunity can be found in the occurrence of autoimmune manifestations during the course of primary immune deficiency disorders, which have an early onset and are associated with a family history of severe and atypical autoimmune diseases [105, 106]. A deficiency in complement factors (mainly C1, C4 and C2) leading to alterations in the mechanisms of central tolerance and the clearance of apoptotic cell debris are closely associated with SLE [105]. Impaired central and peripheral tolerance leads to two primary immune deficiency disorders: autoimmunity, polyendocrinopathy, candidiasis, ectodermal dysplasia (APECED) and immune dysregulation, polyendocrinopathy, X-linked syndrome (IPEX) [105, 107–109]. APECED is an autosomal recessive disease caused by mutations in the autoimmune-regulator (AIRE) gene, and IPEX is an X-linked syndrome due to mutations in forkhead box P3 (FOXP3), a key regulator of T regulator cells (TRegs) [105, 107–109].

Defects in B cell tolerance with a lack of mature B cells and immunoglobulins gives rise to congenital agammag

lobulinemia and possible autoimmunity. Autoimmunity can also occur during the course of common variable immune deficiency (CVID), in which there are autoreactive B cells despite the reduction of isotype-switched memory B cells [105, 110–112].

Various mechanisms also contribute to autoimmunity in Wiskott–Aldrich syndrome (WAS), which is caused by mutations in the gene encoding WAS protein (WASP), which is essential for cytoskeletal structure: impaired tolerance causes alterations in the negative selection of autoreactive B cells [105, 113, 114].

T cell impairment involving central tolerance may also be closely associated with autoimmunity and, in the case Tregs, both central and peripheral tolerance may be involved [105, 115].

Components of innate and adaptive immunity during the course of autoimmune diseases

DCs are APCs capable of stimulating the clonal expansion of naïve T cells, impairing tolerance of self-reactive lymphocytes, and inducing autoimmune mechanisms in ADs [116–120]. DCs play a significant role in breaking tolerance of self-reactive lymphocytes and in supporting autoimmune responses. Low- molecular-weight chemoattractant proteins recognised as chemokines contribute to recruiting DCs and immune cells (including T and B cells), thus leading to the formation of lymphoid tissue structures within target tissue [116–120]. DCs can also guide naïve T cells to become Th1, Th2 or Treg cells by means of cytokine IFN- γ , IL-4 or IL-10 stimulation [116–120].

As part of the innate immune system, DCs have been identified within cellular infiltrates presents in salivary glands of patients with Sjögren's syndrome, in the synovium of RA patients and in the lymphoid tissue present in autoimmune thyroid disease, also in the skin lesions identifiable in patients with psoriasis [116].

T and B cell clonal selection is essential for the adaptive immune system and, as T and B cell repertoires are extremely different, cell clones can be divided into naïve and memory subsets [121]. The naïve T cell repertoire contains distinct T cell clones (effector and memory T cells), memory B cells and plasma cells [121]. Memory T cell subsets expand in response to *in vivo* antigen stimulation. They are functionally widely heterogeneous, and can also differentiate into pathogen-specific memory cells when guided by specific microbial patterns [121–124]. During immune responses, antigen-specific naïve B cells clonally expand and are selected by means of germinal centre reactions to differentiate into memory B cells [121–124]. B cells also differentiate into plasma cells, which are capable of synthesising and secreting antibodies, and their

persistence in bone marrow leads to steady serum antibody levels [121–124]. B cells produce immunoglobulins, secrete cytokines, and act as APCs [119]. They also express clonally rearranged, antigen-specific BCRs and TLRs, thus combining both adaptive and innate immunity [119, 120]. By the expression of both BCR and TLR B cells integrate antigen specific and danger associated signals. It was proposed that, based on functional responses and their BCR repertoire, naïve B cells can be divided as innate like or adaptive like cells [125], the first ones able to generate rapid antibody responses independent of T cell stimulation, whether the latter participants in T dependant responses that lead to high affinity antibodies production. Activation of different TLRs on these cells is important to differentiate their immune responses.

Dual BCR and TLR signals can markedly promote the activation of self-reactive B cells by uptaking antibody/DNA complexes via a rheumatoid factor-specific BCR [125, 126]. Variations in TLR expression and signalling can modify B cell responses, and so individual TLR expression profiles allow various effector B cell populations to manifest specific forms of antibody production, cytokine secretion and antigen presentation [125, 127, 128]. Cooperation between TLR, BCR and B cell-intrinsic MYD88 signals plays a key role in B cell responses to different pathogens (mainly viruses), through these characteristics B cells are crucial in linking innate and adaptive immune mechanisms [125, 129].

Impaired tolerance of self-antigens or modified self-antigens due to the non-clearance of apoptotic debris, inflammation-mediated modification of self-antigen, or cross-reactivity between non-self and self-antigens are responsible for the synthesis of autoantibodies. Some autoantibodies can cross-react between an extra- or intracellular ligand TLR and the cell surface, thus leading to the perpetuation of B cell activation and autoantibody-mediated responses [130–134]. The synthesis of (mainly IgG) autoantibodies can lead to inflammation with the release of intracellular or modified self-antigens, thus determining antibody effector function and the proliferation of the autoreactive B cell clones [130]. Given their ability to recognise various self-antigens, TLRs also play a key role in starting autoantibody responses and acting synergistically with Fc-mediated effector functions [130–135].

Non-haematopoietic stromal cells, resident leukocytes and infiltrating immune cells control inflammation by supporting immunological defences against infection, trauma, injury and cancer [136]. Their good communication and function lead to host defence, antigen removal, and adequate control of tissue damage, but autoimmunity and chronic and severe disease can occur in the case of the perpetuation or inappropriate regulation of these mechanisms [136].

Ectopic lymphoid-like structures (ELS) are lymphoid aggregates containing lymphocytes, monocytes, macrophages and DCs, and may be simple B and T cell aggregates or well-organised, functional germinal centres [136]. They often

develop at inflammatory sites and act as an essential part of the immune response by affecting both protection and progress during the course of transplant rejection, autoimmune infections and malignancies [136]. In ADs, the accumulation of autoreactive B cells in ELS maintain autoimmunity against specific antigens and self-antigens [136]. It has been suggested that EBV infection may remain latent and promote B cell survival and proliferation [136]. Ectopic follicles in the organs of subjects with autoimmune diseases such as RA and Sjögren's syndrome frequently show latent EBV infection, leading to the belief that Epstein–Barr virus (EBV) may also play a role in the development of autoimmunity [136].

Other cells involved in the pathogenesis of autoimmunity are T cells [137]. TCRs are heterodimers consisting of two disulphide-linked chains: one α and one β chain, or one γ and one δ chain [138, 139]. All TCR chains have a constant and a variable domain with six hypervariable loops recognised as complementarity-determining regions (CDRs), a membrane-spanning region, and a cytosolic tract [138, 140]. The TCRs located on T cells are the primary units recognising pMHC [138]. In the thymus, the binding of TCRs and pMHC leads to cell differentiation, and some thymocytes differentiate into mature T cells [138, 141]. In secondary lymphoid organs, the binding provides a complex differentiation programme associated with effector action [138, 142].

In SLE, serum and organ clonal T cell expansion may be reactive to antigens, autoantigens such as nucleosomal histones and U1 small nuclear ribonucleoprotein A, and drive tissue inflammation and damage [137, 143–149]. Thapa et al. made a longitudinal analysis of peripheral blood T cell receptor diversity in patients with SLE using next-generation sequencing and, in comparison with healthy controls, found a significant decrease in T cell diversity in peripheral blood [137].

Glycolysis, lipid oxidation and mitochondrial processes are also essential in regulating the activation, proliferation, and differentiation of CD4+ T and memory cells [150, 151]. In a recent study, Yin et al. found that impaired T cell metabolism was a key factor in the pathogenesis of SLE and suggested that it might be an appropriate therapeutic target [150]. They also reported that CD4+ T cells from a B6.Sle1.Sle2.Sle3 lupus-prone mouse model showed increased *ex vivo* and *in vitro* glycolysis and mitochondrial oxidative metabolism in comparison with non-autoimmune controls [150].

Another T cell population involved in the pathogenesis of autoimmunity is that of Th17 cell, which can express transcription factor ROR γ τ and synthesise a number of chemokines. The IL17 axis cytokines include IL-17A-IL-17F, IL-22, TNF- α and IL-6, which have pro-inflammatory activity in autoimmune and autoinflammatory diseases [152–159]. Th17 differentiation is due to the cooperative action of TGF- β and other pro-inflammatory cytokines such as IL-6 and IL-23, that is involved in the immune action of Th17

cells at the level of various tissues including skin, lung, and mucosal tissue. The dysregulation of Th17 cells is crucial for autoimmunity and inflammation. Two types of Th17 cells have been identified *in vivo*, differing from one another for the property to express IL-10 or IFN- γ . IL-1 stimulation during the polarisation phase, strongly suppresses IL-10 and promotes IFN- γ induction, thus these two kind of Th17 cells, that posses either proinflammatory or anti-inflammatory functions, can be modulated by IL-1 β [160]. As seen before, autoinflammatory syndromes are characterised by overproduction of IL-1 β caused by dysregulation of inflammasomes. Noster and colleagues have demonstrated that in the autoinflammatory disease Schnitzler syndrome, a loss of anti-inflammatory T_H17 cells is present, and that physiological levels could be restored after therapeutic IL-1 β inhibition. This could have implications for disease pathogenesis and future therapeutic strategies [161].

IL-27 downregulates Th17 as a result of IL-10 synthesis and release [152, 153], whereas the absence of TGF- β , IL-10 and Th-17 cell dysregulation leads to inflammatory responses during host defence inflammation and autoimmune processes [152, 162]. TGF- β and IL-6 can induce a population of IL-17 and IL-10 double-producing cells that are not capable of inducing experimental autoimmune diseases; IL-23 stimulation of TGF- β /IL-6-dependent T cells is necessary for T cells to play a pathogenetic role [163]. IL-6 and IL-23 are regulatory cytokines that promote defensive responses in the phase of interaction between the host and the environment [152, 162].

Tregs are critical in ADs because of their effect on immune homeostasis and the maintenance of peripheral self-tolerance. Their development and function are controlled by the Foxp3 transcription factor [155, 156]. Altered Treg development, function and balance are associated with the development of inflammation and autoimmune mechanisms, whereas the homeostasis of Tregs and effector T cells (Teffs) balance tolerance and effector immune responses [164, 165]. In a study of murine autoimmune arthritis, Chevalier et al. found that Tregs had a stable phenotype and were fully functional *in vitro* suppression assays. However, their expansion was late compared with Teffs (T follicular helper cells and Th17 cells) during the early autoimmune phases, and this imbalance is likely to have induced autoimmunity as a result of insufficient Treg control of Teffs [164]. The dysregulation of thymic and peripheral Treg and Teff homeostasis drives the induction and progression of autoimmunity, and even a short period of insufficient Treg control of autoreactive Teffs may allow the onset of subsequently uncontrolled autoimmunity [164]. The inflammatory milieu generated by disease onset may then further deregulate Treg/Teff homeostasis, and exacerbate the course of the disease course. The authors identified IL-2 and IL-21 as key players in disturbed peripheral Treg and Teff homeostasis as inflammation and lymphopenia triggered autoimmunity by suppressing the expansion of IL-2-controlled

regulatory T cells and increasing the expansion of IL-21-mediated effector T cells [164].

Discriminating self and non-self is key element in responding to microbial antigens and inhibiting autoimmunity [166, 167]. Immunological self-tolerance is the absence of responsiveness to self-antigens and is supported by various mechanisms: central tolerance eliminates potentially self-reactive T cells in the thymus, and peripheral tolerance control the T cells that by-pass thymic selection and move to the periphery [166, 168–170]. CD4+CD25+ Tregs have an immunosuppressive function and mediate immunological self-tolerance by suppressing the potential suppression of autoreactive T cells [166, 168–170], and an altered number and/or function of CD4+CD25+ Tregs has been associated with severe autoimmune diseases, including RA and SLE [166, 171, 172].

The complement system, a key component of the innate immune system, represents another link between innate and adaptive immunity. Its main function is to recognise and eliminate pathogens by means of direct killing or to stimulate phagocytosis in modulating adaptive immunity, thus bridging innate and adaptive responses [173, 174]. When complement mechanisms are unbalanced, the complement system may cause damage by mediating tissue inflammation [173, 175]. Dysregulation of the complement system has been implicated in the pathogenesis and clinical manifestations of a number of autoimmune diseases, including RA, SLE, Sjögren's syndrome, the vasculitides, dermatomyositis, SSc, and antiphospholipid syndrome [173, 175]. Complement deficiencies have also been associated with an increased risk of developing autoimmune disorders. [173, 175, 176], and various SLE phenotypes may be associated with a congenital deficiency in the early components of the complement system (C1q, C2, and C4) [90, 91]. This makes the complement system a potential therapeutic target by inhibiting complement activation components, complement receptors, and the membrane attack complex [173].

Autoimmune diseases are a direct effect of tissue and organ damage mediated by autoreactive immune mechanisms [177, 178] and, in this context, a key role is played by autoantibodies, such as rheumatoid factor or antinuclear antibodies, which are totally absent in autoinflammatory diseases [1, 177, 178].

Innate and adaptive immunity as the main therapeutic target

The relationship between innate and adaptive immunity is the main target of immunosuppression, and the relationships between different cell types mediated by soluble molecules such as cytokines, or by cell-to-cell interactions, or by ligand/

receptor binding, are therapeutic targets in both ADs and autoinflammatory diseases [179, 180].

Agents interfering with the activation, differentiation or survival of immune cells or indirectly blocking cell interactions or neutralising soluble molecules are all means of suppressing immune responses [179, 180]. Immunosuppression induced by corticosteroids, cytotoxic agents or target-specific monoclonal antibodies has become the mainstay of AD treatment, and has also been reported to be efficacious in autoinflammatory diseases [1, 179–181]. In addition to inhibiting the synthesis of prostaglandins, steroids regulate the adaptive and innate immune systems mainly by inhibiting the synthesis of pro-inflammatory cytokines such as IL-2, IL-6 and IFN- γ [179, 181], and other targets of immunosuppression are components of innate immunity (macrophages, DCs and NK cells) and adaptive immunity (T and B cells) [179, 180].

Anticytokine therapies are particularly successful in the case of ADs with a strong inflammatory component [179]. Blocking TNF- α leads to favourable outcomes in RA, AS, psoriatic arthritis, psoriasis, and inflammatory bowel diseases, and a number of biological agents are available that neutralise TNF- α or block its receptor [179, 182, 183]. They have also been reported to be efficacious in refractory autoinflammatory disorders, such as FMF and TRAPS, particularly in the case of articular involvement [184–186].

On the other hand, immunity can be directed against anti-cytokine therapy. In particular, the anti-TNF- α immunogenicity (mainly against the chimeric mouse/human anti-TNF- α IgG1 antibody infliximab [IFX]) due to anti-chimeric antibody (HACA) formation can occur after monotherapy, leading to a loss of efficacy and side effects such as infusion-associated reactions [187, 188]. In order to avoid IFX immunogenicity, it is suggested to use concomitant methotrexate-induced immune suppression [187]; concomitant immunosuppressive therapy also decreases the formation of HACAs [188].

In relation to other anti-cytokine treatments, IL-1 inhibition is useful in various ADs. Anakinra, a recombinant human IL-1 receptor antagonist that competes with IL-1 α and IL-1 β and thus inhibits the pro-inflammatory effects of both is approved for use in RA at a recommended subcutaneous dose of 100 mg/day. It has been widely used to treat monogenic and polygenic autoinflammatory conditions, and leads to sustained disease remission [189, 190].

Given the effects of IL-6 on the immune system and inflammatory processes, IL-6 antagonism is a potential therapeutic strategy in both autoinflammatory and autoimmune disorders [191–195]. IL-6 is a pleiotropic cytokine secreted by various cell types (T and B cells, macrophages, osteoblasts, fibroblasts, keratinocytes and endothelial cells). is involved in numerous immune pathways, and plays a pivotal role in regulating immune response [193]. Tocilizumab is a humanised

monoclonal antibody that specifically inhibits IL-6 by competitively blocking the binding site on the IL-6 receptor, and is approved for the treatment of RA [194].

In addition to TNF, the TNF superfamily (TNFSF) includes a number of the ligand/receptor mechanisms involved in the pathogenesis of autoinflammatory and autoimmune diseases. Its members can initiate immune activation, tissue inflammatory responses, and cell death or suppression, and have been evaluated as possible therapeutic targets in order to control cell responses or restore tolerance [196, 197]. Among these, BAFF is a crucial factor that regulates B cell maturation, survival and function, and is upregulated in SLE [21–23]. The BAFF inhibitor belimumab can improve musculoskeletal and mucocutaneous SLE disease activity [198].

Rituximab is a chimeric monoclonal antibody against CD20, a specific B cell differentiation membrane antigen that participates in B cell activation and proliferation [199]. It is administered intravenously and has been approved for use in lymphomas (375 mg/m² a week for four cycles) [199] and RA (two 1 g infusions separated by an interval of 2 weeks, with repeated courses decided on the basis of an individual clinical evaluation) [200]. The off-label use of rituximab to deplete peripheral CD20-expressing B cells in patients with other immune-mediated diseases has been increasing [201–203], but there are no data concerning its use in autoinflammatory diseases.

Other agents targeting IL-17 (sekukinumab) [204] or the p40 chain of IL-12 and IL-23 (ustekinumab) [205], or inhibiting T-cell co-stimulation and activation (abatacept) [206], have been reported to be efficacious in inflammatory arthritides such as RA and PsA [207] but, once again, there are no data concerning its use in autoinflammatory diseases.

Recent studies of therapeutic tolerance in the setting of human transplantation have suggested tolerogenic mechanisms as potential targets [180]. Therapeutic tolerance is the resetting of immune tolerance to autoantigens or the use of tolerance towards alloantigens without the need for immunosuppression [180]. The main cell therapies that have shown promise in human tolerogenesis are haematopoietic chimerism, multipotent mesenchymal stromal cells, the *in vivo* tolerogenic manipulation of T cells, and the use of exogenous Tregs and DCs [180].

Conclusions

ADs and autoinflammatory diseases have a number of similar etiopathogenetic and clinical characteristics, including genetic predisposition and recurrent systemic inflammatory flares [6–8].

The first phase of ADs involves innate immunity: by means of TLRs, DCs recognise and internalise autoantigens arising from the process of apoptosis, which leads to IFN- α

production, DC maturation, autoantigen presentation, B and T cell recruitment, and autoantibody synthesis [6–9, 17]. The second phase involves adaptive immunity, a self-sustaining process in which immune complexes containing nucleic acids and autoantibodies are internalised by DC by means of Fc γ -receptors (Fc γ Rs), thus leading to IFN- α synthesis, additional DC and T cell activation, and autoantibody production [6–9, 126].

Various data indicate that innate and adaptive immunity represent two strictly interconnected phases in the development of ADs [1–5]. The protracted or increased activation of PRRs plays a key role in autoimmune mechanisms [15], and the strict link between TLRs and B cells suggests that innate immunity may play a key role in inducing autoantibody responses [16–20]. Another important link between autoimmunity and autoinflammation is IL-1 β [25–32, 208], which is crucial in connecting the innate immune response due to NLR activation and the adaptive immune responses of T and B cells [25–32, 208–210]. It has been reported that the increase in IL-1 levels following inflammasome activation induces T cell polarisation (Th17 differentiation) [25]. Adaptive immune responses are potentially linked to innate immunity through the Th1 and Th17 cell responses mediated by the NLRP3 inflammasome, mutations in which are responsible for CAPS [44–46].

The study of the connections between autoimmunity and autoinflammation represents an exciting challenge for further studies [211–214]. Recently a study by Arakelyan and colleagues, using a comparative gene expression analysis of a large set of transcriptome data, focused on finding existing similarities and common inflammatory components in ADs and autoinflammatory diseases [215]. The results revealed that some pathways were similarly perturbed in both diseases such as PI3K-Akt, Toll-like receptor, and NF-kappa β signalling, all important signals involved in immune cell polarisation, migration, growth, survival and differentiation [215]. They identified two clusters of diseases basing on specific dysregulated pathways: one prevalently composed by autoimmune and the other by autoinflammatory disease [215]. Interestingly, some diseases did not seem to belong to the cluster they classically were believed to belong to. PAPA, one of the autoinflammatory diseases discussed above, was closer to the cluster of autoimmune diseases [215], confirming some differences found between this disease and the others autoinflammatory syndromes, such as the poor response to IL-1 blockade [209, 215]. Furthermore, SLE, a typical autoimmune disease, seemed to belong to the cluster of autoinflammatory syndromes [215], thus apparently remarking the systemic inflammatory nature of SLE and, as discussed above, a possible role for inflammasomes in its pathogenesis. This study identified disease specific variations in activation of common pathways, thus highlighting not only the similarities but also the basic differences between the two

types of diseases. The inflammatory aspects and the role of innate immunity in ADs should be further studied in order to identify their underlying autoinflammatory pathogenesis, thus opening up new perspectives on the link between innate and adaptive immune mechanisms. This would be a useful step towards developing the best tailored treatment strategy.

Compliance with ethical standards

Disclosures None.

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