38 Autoinflammation and Autoimmunity

Dennis McGonagle and Abdulla Watad

Abstract

The elucidation of the genetic basis for hereditary recurrent fever syndromes validated the role of innate immune dysregulation in diseases formerly viewed as autoimmune. Recognizing the non-autoimmune nature of tumor necrosis factor receptor-associated periodic syndrome (TRAPS), one such syndrome, and the lack of evidence for autoantibodies or B- or T-cell involvement in the context of the emergent genetics, led to the proposal of the term autoinflammation in 1999. While formally coining a new term for this type of inflammation against self, the definition was essentially stating what inflammation was not, rather than what it was. Based on the lack of an association with humoral or cellular mediated immunity and the propensity for recurrent seemingly unprovoked attacks of inflammation, fevers, elevation of inflammatory markers, without high-titer autoantibodies or antigen-specific T lymphocytes, the new designation of autoinflammatory disorders also included some conditions that would have previously been considered autoimmune, e.g. Behçet disease (BD). BD is a prime example of the two-tiered classification of inflammation against self since BD has a strong population level human leukocyte antigen (HLA)-B51 association. Given the classically defined role of major histocompatibility complex (MHC)-I molecules in peptide presentation to T cells, this incriminates adaptive immunity in BD immunopathology, which was supported by clinical therapeutics, where immunosuppressant agents like azathioprine had a proven role in disease management. The purpose of this chapter is to summarize the overlap and differences between autoinflammatory and autoimmune disorders.

Keywords

Autoimmunity · Autoinflammation Periodic fever · Immunological diseases continuum · TNF-alpha · IL-1

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Abbreviations

AAV	ANCA-associated vasculitis
ACPA	Anti-citrullinated protein antibodies
ALPS	Autoimmune lymphoproliferative syndrome
AOSD	Adult-onset Still disease
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
ATD	Autoimmune thyroid disorder
BD	Behçet disease
CAPS	Cryopyrin-associated periodic syndromes
CARD	Caspase activation and recruitment domains
CMML	Chronic myelomonocytic leukaemia
DITRA	Deficiency of IL-36 receptor antagonist
DM	Dermatomyositis
DMARD	Disease modifying anti-rheumatic drugs
ERAP-1	Endoplasmic reticulum aminopeptidase 1
FMF	Familial Mediterranean fever
GCA	Giant cell arteritis
GWAS	Genome-wide association studies
HIDS	Hyperimmunoglobulinemia D syndrome
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
IPEX	Immune dysregulation polyendocrinopathy enteropathy x-linked syndrome
MAS	Macrophage activation syndrome
MDS	Myelodysplastic syndrome (MDS)
MHC	Major histocompatibility complex
MKD	Mevalonate kinase deficiency
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor kappa B
NLR	Nucleotide-binding oligomerization domain-like receptors
NOD	Nucleotide-binding oligomerization domain
PAAND	Pyrin-associated autoinflammation with neutrophilic dermatosis
PAPA	Pyogenic arthritis pyoderma gangrenosum and acne syndrome
PBS	Primary biliary cirrhosis
PM	Polymyositis
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RAEB	Refractory anemia with excess blasts
RCMD	Refractory cytopenia with multilineage dysplasia
SJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SNS	Self/non-self
SpA	Spondyloarthropathies
SSc	Systemic sclerosis
STAT	Signal transducer and activator of transcription
T1DM	Type 1 diabetes mellitus
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome

Key Points

- **Mutations in genes implicated in innate immunity spawned the autoinflammation concept and has allowed "inflammation against self" to be viewed in a new light**
- **There is occasional ambiguity concerning the diagnosis of autoimmune diseases and autoinflammatory disorders due to genetic, clinical and therapeutic aspects that are shared by both diseases**
- **The immunological diseases continuum is a useful tool for better understanding of the link between autoimmunity and autoinflammatory disorders and overlaps between the two**

38.1 Introduction

Given the close functional integration and interdependence of innate and adaptive immune system function at multiple levels it was evident that

autoinflammation, as defined in the relatively rare monogenic disorders, likely had a much more general relevance to medicine and immunology. Autoinflammation was defined as a disorder of innate immunity (in clear contradistinction to autoimmunity), where self-directed inflammation, induced by local factors at sites that lead to activation of innate immune cells, results in target tissue damage (Box 38.1). For example, disturbed homeostasis of canonical cytokine cascades (as in the recurrent fever syndromes), aberrant bacterial sensing (as in Crohn disease), and tissue microdamage predispose to site-specific inflammation that is independent of adaptive immune responses [1]. This resulted in the emergence of the immunological disease continuum classification of inflammation against self (Fig. 38.1). Consequently, for the classical autoimmune diseases this implied tolerance failure in the primary and secondary lymphoid organs with normal tissue being later subject to an immunological attack. Some diseases considered as classical autoimmune were then recognized to have a primary autoinflammatory initiation with

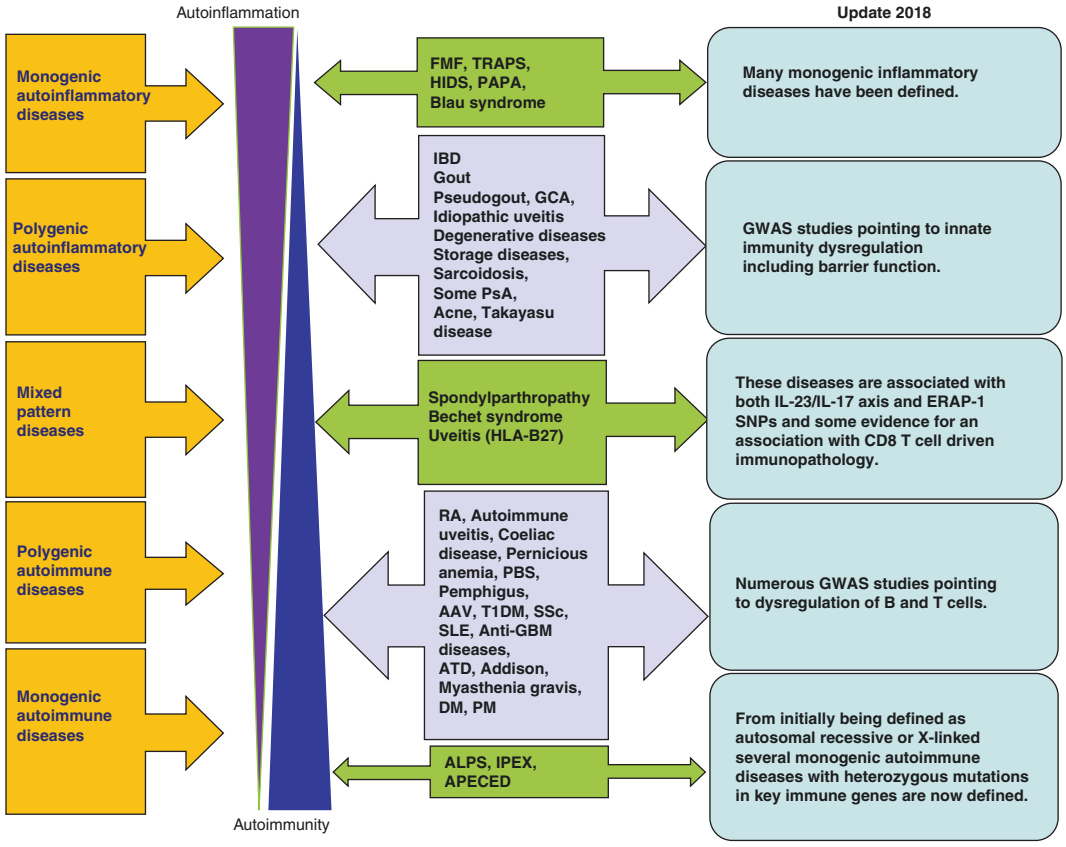

Fig. 38.1 The immunological disease continuum with pure autoimmunity and pure autoinflammation or innate immunopathology at opposites. *FMF* familial Mediterranean fever; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome; *HIDS* hyperimmunoglobulinemia D syndrome; *PAPA* pyogenic arthritis pyoderma gangrenosum and acne syndrome; *IBD* inflammatory bowel disease; *GCA* giant cell arteritis; *PsA* psoriatic arthritis; *PBS* primary biliary cirrhosis; *AAV* ANCA-associated vasculitis; *T1DM* type 1 diabetes mellitus; *SSc* systemic sclerosis; *SLE* systemic lupus erythematosus; *ATD* autoimmune thyroid disorder; *DM* dermatomyositis; *PM* polymyositis; *ALPS* autoimmune lymphoproliferative syndrome; *IPEX* immune dysregulation polyendocrinopathy enteropathy x-linked syndrome; *APECED* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *GWAS* genome-wide association studies; *ERAP-1* endoplasmic reticulum aminopeptidase 1; *SNP* single nucleotide polymorphism

secondary T-cell mediated target tissue autoimmune reactions that resulted in the emergence of intermediate diseases between autoimmunity and autoinflammation (Fig. 38.1).

The innate immune basis for autoinflammation was reaffirmed and refined in later viewpoints that autoinflammation simply represented non-infectious diseases involving innate immunity [2]. The underlying cardinal innate immune mechanisms underpinning these disorders were later proposed to include interleukin (IL)-1β activation disorders, nuclear factor kappa B (NF-κB) activation syndromes, protein misfolding disorders, complement regulatory diseases, disturbances in cytokine signaling, and macrophage activation syndromes (MAS) [3] (see Chap. 10), but it is clearly much broader than this. Thus, after the late nineteenth century work on humoral and cellular immunity and late twentieth century research on rare monogenic inflammatory disorders, a unified theory of non-infectious inflammation against self emerged, whereby innate immune mediated immunopathology and autoimmunity were closely integrated, just as the physiological immune response often encompasses and integrates innate and adaptive immunity.

38.2 The Immunological Disease Continuum

From this platform of an immunological disease continuum of inflammation against self, with pure autoinflammation (innate immunity) and autoimmunity at opposite boundaries, some important subgroups have emerged. Kastner et al. [4] proposed the term "horror autoinflammaticus" that highlighted the innate immune system dysregulation in these conditions. Then, the recognition of gain- or loss-of-function in the immune system along the continuum helped to conceptualize the complexity of autoimmunity and autoinflammation in relationship to immunodeficiency states [4] (Figs. 38.2 and 38.3). It also emerged that two key cytokines linked to innate immunity, namely type 1 interferon (IFN) and IL-1β are polarized too, with the former being more strongly

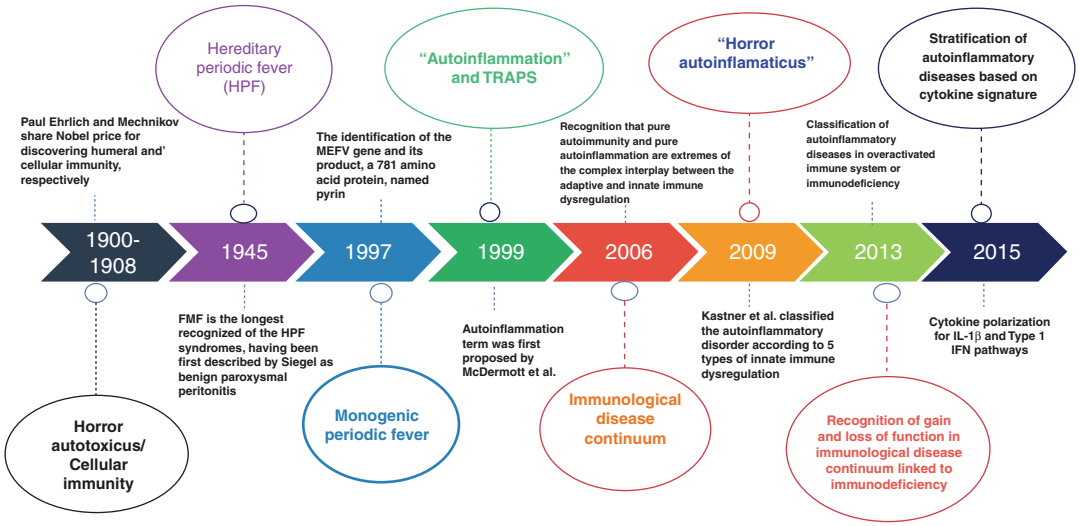

Fig. 38.2 This figure illustrates some important milestones in the evolution of the classification of autoinflammatory and autoimmune disease inter-relationships during the last decades. *FMF* familial Mediterranean fever; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome; *IL* interleukin; *IFN* interferon; *HPF* hereditary periodic fever; *MEFV* Mediterranean fever

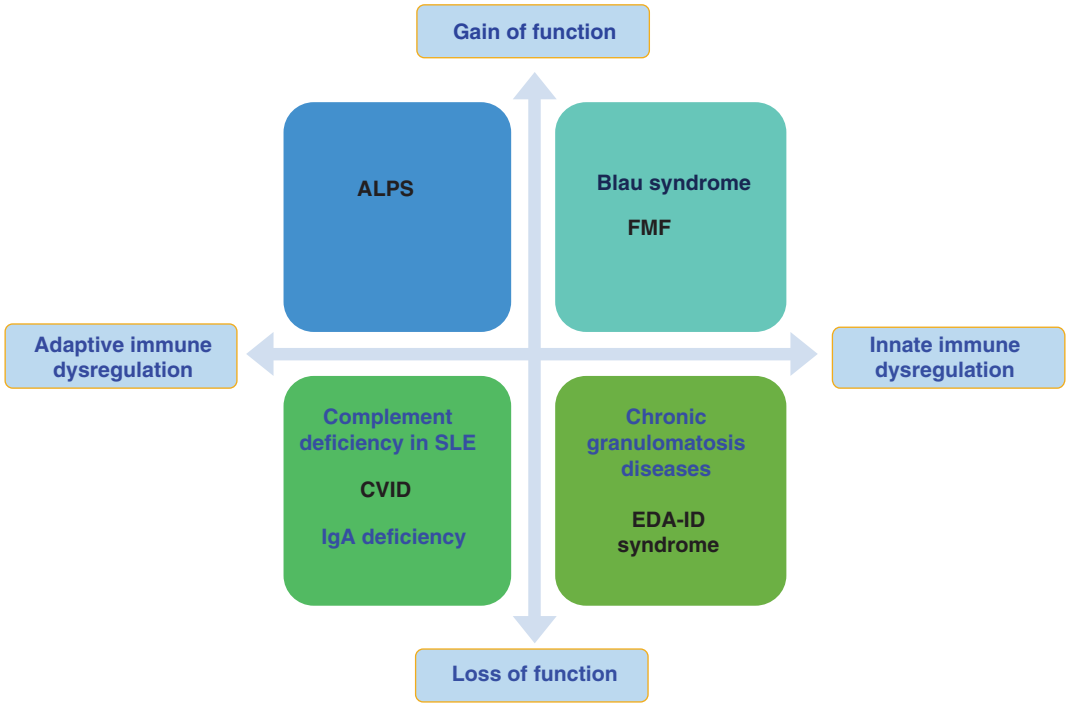

Fig. 38.3 Immunological disease continuum viewed in terms of gain- and loss-of-function mutations in innate and adaptive immunity. Based on references [2, 6]. *ALPS* autoimmune lymphoproliferative syndrome; *FMF* familial Mediterranean fever; *SLE* systemic lupus erythematosus; *CVID* common variable immunodeficiency; *EDA-ID* anhidrotic ectodermal dysplasia with immunodeficiency; *IFN* interferon; *CTLA4* cytotoxic T-lymphocyte–associated antigen 4

associated with autoimmune disease, namely monogenic forms of systemic lupus erythematosus (SLE), and the latter linked to pure innate immune driven pathology. The recognition of Type I IFN dysregulation driving autoimmunity whilst nucleotide-binding oligomerization domain-like receptors (NLR) perturbation driving classical autoinflammatory diseases that do not exhibit autoantibody formation led to the realization that these pivotal cytokines polarize immune disease classification (Figs. 38.2 and 38.4) [5]. From the original recognition of autoinflammatory diseases being linked to NLR cytoplasmic resident innate immune receptors (NLRP3 in particular) [6], other inflammasomes including NLRC4 have been implicated in innate immune mediated pathology [7] (see Chap. 5). Remarkably, NLR family members are consistently linked to both monogenic and polygenic autoinflammatory disease whereas toll-like receptors (TLR) are not, possibly indicating functional redundancy in the latter receptors.

38.2.1 Inflammation against Self: Self/Non–Self Discrimination *Versus* Danger Signals

The historical understanding of non-infectious inflammation was based on self/non-self (SNS) discrimination and immune tolerance failure which dominated immunological thinking until the mid 1990s. The importance of SNS discrimination in the organ transplant rejection setting powerfully validated the concept in the clinical arena. However, this model is largely based on

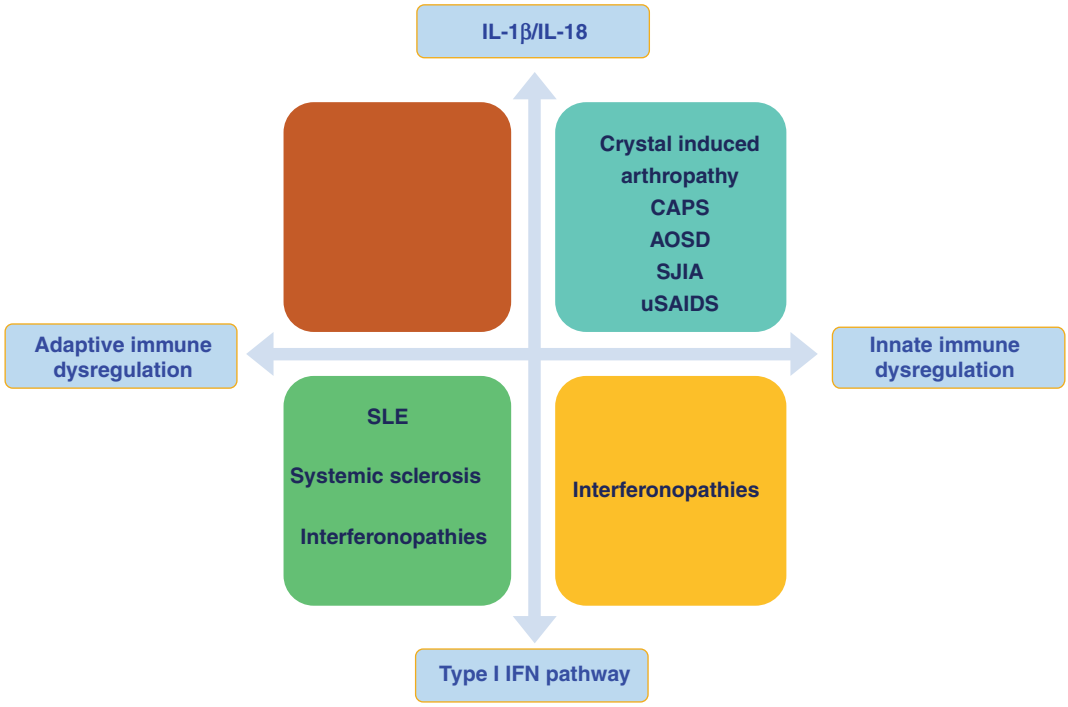

Fig. 38.4 Immunological disease continuum viewed in terms of cytokines pathways mutations in innate and adaptive immunity. Based on references [2, 5]. *IL* interleukin; *CAPS* cryopyrin-associated periodic syndromes; *AOSD* adult-onset Still disease; *SJIA* systemic juvenile idiopathic arthritis; *uSAIDS* undifferentiated systemic autoinflammatory disorder

the autoimmunity concept of dysregulated T- and B-cell function. In the 1990s, Matzinger advocated the danger theory of inflammation against self, whereby the immune system was not so much concerned with SNS discrimination but with responding to danger signals [8]. This theory was proposed as an alternative to the classical SNS model and was enthusiastically embraced by some, but not all immunologists. The discovery of pattern recognition receptors, most notably TLR, provided a biochemistry basis for how local danger signals could activate immunity [9]. Even more relevant was the recognition that damaged self-tissues, including degraded proteins and nucleic acids in the wrong cellular compartments, cytoplasmic and extra-cellular and rather than nuclear, were capable of triggering immune activation [10]. Collectively, these observations provided strong support for the role of danger signals in disease initiation.

In 2002, Matzinger developed the danger signal hypothesis postulating that the target tissues actually controlled the immune response by sending alarm signals [11]. This is especially noteworthy given that the originally described autoinflammatory disorders have a tissue tropism that cannot be explained by autoimmune mechanisms. Broadly, these disorders have a strong, but not exclusive, predilection for the "moving parts" of the body including skin, joints, peritoneal cavity, pleural cavity and pericardium but not for example the non-mechanically stressed endocrine organs. Other diseases that were subsequently shown to have an autoinflammatory genesis, including pyogenic arthritis pyoderma gangrenosum acne (PAPA) syndrome, showed a tissue tropism that was linked to injury in the target tissues. Also, according to the Matzinger viewpoint cytokines were also danger signals and around the turn of the millennium two such cytokines were

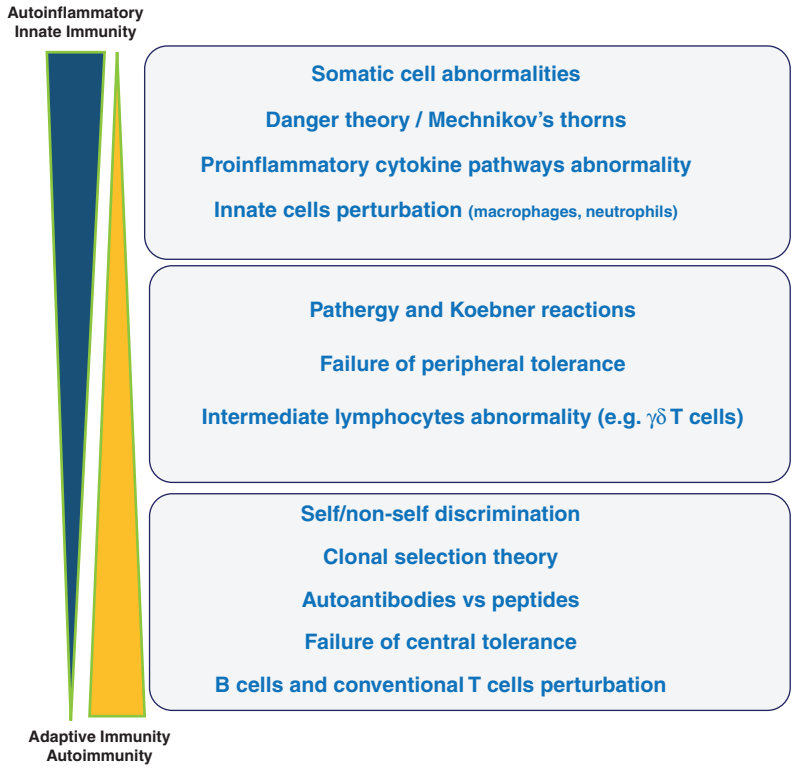

Fig. 38.5 The theoretical concepts that underpin autoinflammation and autoimmunity are best viewed along the immunological disease continuum model

pre-eminent in the autoinflammation field: IL-1β and tumor necrosis factor (TNF) [11].

The implications of these clinical and theoretical considerations were the reconciliation of seemingly contradictory immunological terminology along the immunological disease continuum of innate and adaptive mediated inflammation. Hence, SNS discrimination underlines peripheral and central tolerance failure and B- and T-cell dysfunction and autoimmunity, while tissue specific danger signals are involved in innate immunopathology or autoinflammation (Fig. 38.5). The intrinsic dysregulation of TNF receptor (TNFR) and NLRP3 inflammasomes in the monogenic autoinflammatory diseases with increased levels of danger cytokine signals nicely fits into the non-autoimmune model for inflammation that essentially captured hyperinflammatory responses within the innate immune system. Thus, hitherto confusing immunological lexicon could be more comfortably accommodated along the immunological disease continuum [2, 12].

38.2.2 Autoinflammation: Proof of Concept of the Pivotal IL-1β Connection *Via* Therapy

The "classically described" monogenic autoinflammatory disorders are clinically and genetically heterogeneous [2, 12] but despite this there has been a remarkable therapeutic convergence. The original definition of the cryopyrin-associated periodic syndromes (CAPS) group of disorders led to the recognition that *NLRP3* mutations resulted in dysregulated and constitutive overproduction of IL-1β [13]. Subsequently, the demonstration of a rapid onset and potent action of anakinra, an IL-1 receptor antagonist therapy, a strategy that was suboptimal in the management of autoimmune disorders such as rheumatoid arthritis (RA), confirmed the role of the IL-Iβ pathway in the autoinflammatory setting [14]. Given the genetics of TRAPS and its link to the TNF pathway, it was somewhat surprising that IL-1 antagonism was effective for

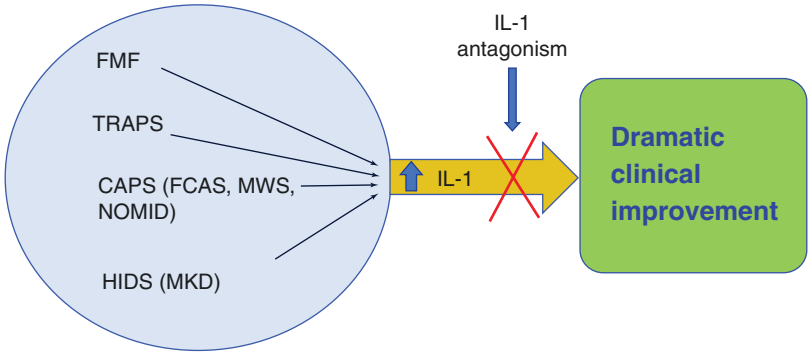

Fig. 38.6 The original defined monogenic autoinflammatory disorders all show clinical responses to interleukin (IL-1) antagonists. The classical autoimmune diseases do not generally show such remarkable responses. *FMF* familial mediterranean fever; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome; *CAPS* cryopyrin-associated periodic syndromes; *FCAS* familial cold autoinflammatory syndrome; *MWS* Muckle-Wells syndrome; *NOMID* neonatal-onset multisystem inflammatory disease; *HIDS* hyperimmunoglobulinemia D syndrome; *MKD* mevalonate kinase deficiency

TRAPS [15]. Patients with TRAPS had prompt response to anakinra and disease relapse after treatment withdrawal, with therapy re-introduction leading to a dramatic response. Likewise, IL-1 blocking strategies have proven to be beneficial in hyperimmunoglobulinemia D syndrome/mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF) [16, 17]. Indeed, IL-1 blocking therapy has proven to be highly effective in patients with non-monogenic hyperinflammatory disorders as well, including crystal arthropathy, systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still disease (AOSD) [18]. In fact, the concept of the intertwined nature of autoinflammation and IL-1 has contributed to the "real world" clinical practice of using IL-1 blocking strategies in adult and pediatric cases with inflammatory phenotypes that exhibit autoinflammatory features (Fig. 38.6) [19]. Indeed, just as corticosteroids might be used as a therapeutic trial to help diagnose and simultaneously treat polymyalgia rheumatica, so is the case with poorly defined suspected autoinflammatory disorders, where rapid responses to IL-1 antagonism supports the diagnosis of an autoinflammatory disease [19].

38.2.3 Autoinflammation Underpinning Autoimmunity

The immunological disease continuum placed SLE towards the boundary of autoimmunity but even in 2006 it was recognized that soluble innate immunity, or the complement system, was associated with various SLE features with C2, 3 and 4 deficiencies leading to an SLE phenotype [20] (Fig. 38.7). Hence, it was posited that at the population level, SLE sat closer to the adaptive boundary or self-directed inflammation, but innate immunity might also be involved. However, beyond complement, Mendelian disorders collectively termed "the interferonopathies", due to dysregulated metabolism of self-nucleic acids, with associated elevated levels of type-I IFN also resulted in autoantibody associated SLE [21]. This realization emerged from a series of elegant papers in Aicardi-Goutières syndrome by Crow and colleagues [22] (see Chap. 24). Indeed, several monogenic diseases leading to an SLE phenotype were reported recently such as DNase II deficiency, leading to SLE consequent to impaired nucleic acid metabolism [23]. For SLE in particular, there is a strong immunological basis for aberrant handling of self-nucleic acids consequent to dysregulation of DNA and RNA metabolizing

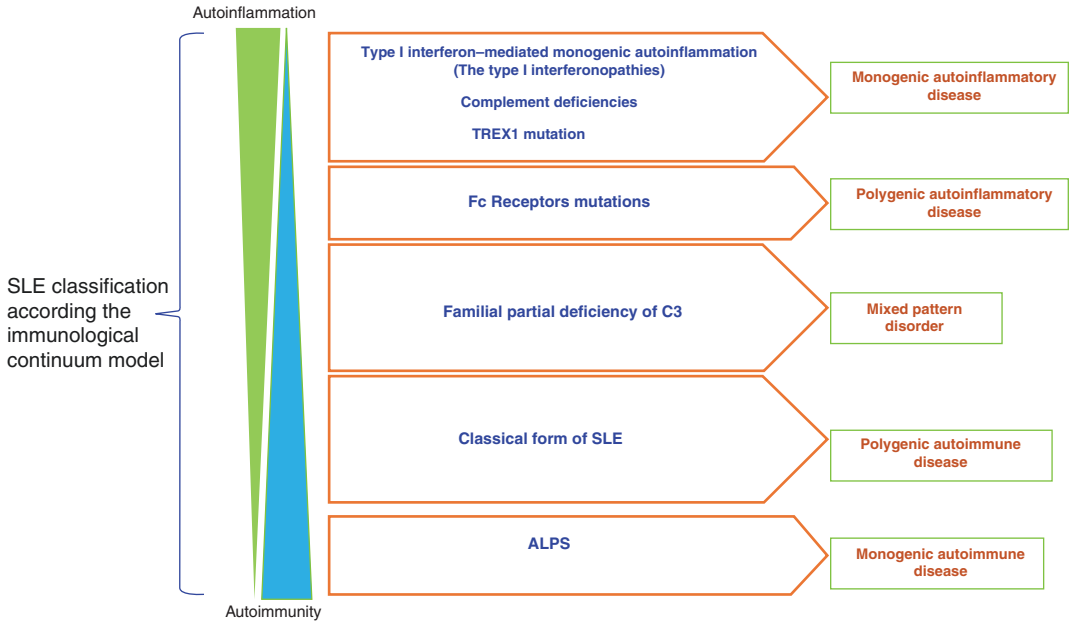

Fig. 38.7 SLE is a one of the best examples in which the immunological continuum model can be applied showing the diversity of clinical manifestation according the involvement of different genetic and immune system components. The figure is based on references [2, 6]. *SLE* systemic lupus erythematosus; *ALPS* autoimmune lymphoproliferative syndrome; *TREX1* three prime repair exonuclease 1

enzymes that leads to nucleoprotein-nucleic acid interactions with TLR7 and TLR9 related pathways and autoimmunity development [24]. Thus the IFN and IL-1β axis have defined a major cytokine split within the immunological disease continuum (Fig. 38.4), with pure autoinflammatory disease at one end and innate dysregulation of IFN leading to classical autoantibody mediated disease or an SLE-like pattern of disease at the other [6]. This has major implications for the proper stratification of SLE (Fig. 38.7).

38.2.4 Intermediate Diseases Between Autoinflammation and Autoimmunity: Major Histocompatability Complex (MHC)-I Associated Disorders

The group of clinically overlapping disorders, collectively termed the spondyloarthropathies (SpA), are generally autoantibody negative, and include psoriasis, psoriatic arthritis, BD, ankylosing spondylitis, Crohn disease, ulcerative colitis and uveitis and other related disorders. Historically these have been difficult to conceptualize in relationship to autoinflammation and autoimmunity. There are several monogenic autoinflammatory syndromes that seem to be closely related to these conditions, including deficiency of IL-36 receptor antagonist (DITRA), Majeed syndrome and PAPA syndrome [25].

Focusing on BD as an example, the lack of autoantibodies, periodicity of attacks and neutrophil related inflammation originally lead to calls for BD to be designated as autoinflammatory (see Sect. 38.2) Genetically, BD has been linked to heterozygous mutations in the *MEFV* gene [26], rather than homozygous or compound heterozygous mutations that usually characterize FMF. The *MEFV* gene encodes for pyrin and is predominantly expressed by innate immune cells [3]. The BD phenotype also exhibits a site-specific injury known as pathergy phenomenon

(see Chap. 35). Moreover, sometimes and especially in early phases of the disease course there is ambiguity concerning the diagnosis of BD and FMF due to genetic, clinical and therapeutic aspects that are shared by both diseases, thus strengthening the association of BD to autoinflammation [27].

Within this group of disorders, psoriasis also exhibits a link between site specific physical injury and disease development- a phenomenon termed the Koebner response. The primary pathogenic process begins in the tissues where an abnormal response to stress or injury at the entheses, adjacent bone or disturbance of the bowel barrier function triggers activation of the innate immune system. Hence, the SpA concept is strongly linked to clinical features including site specific injury leading to local innate immune activation. Furthermore, several monogenic autoinflammatory disorders including DITRA, DIRA and CARD14-associated psoriatic disease clinically resemble the SpA group of disorders [28].

However, at the population level, the genetic architecture of the SpA group diseases is very distinct from autoimmunity, with the SpA related-disorders converging on the IL-23/17 cytokine axis and cell mediated immunity dysregulation. The SpA related disorders also converge on common MHC-I associations of HLA-Cw06 (psoriasis), HLA-B51 (BD) and HLA-B27 (AS and uveitis) [29]. Furthermore, epistatic endoplasmic reticulum aminopeptidase 1 (ERAP)-1 polymorphisms are associated with these disorders, which incriminates peptide loading for presentation to CD8 T-cells. Consequently, these disorders have been designated as intermediate disorders between innate and adaptive immunity or MHC-I-opathies [29–31]. It is thought that the MHC-I association of BD, namely the HLA-B51 link, through local factors can trigger secondary adaptive immune CD8 T-cell responses with prominent neutrophilic inflammation that culminate in exacerbation and recurrence of disease manifestations [29]. Accordingly, BD and allied disorders that were broadly classified under the seronegative SpA concept were designated as being primary autoinflammatory or initiated by site specific innate immune dysregulation with subsequent adaptive CD8 T-cell driven immunopathology. While this concept appears increasingly robust in the case of HLA-Cw06 associated psoriasis and HLA-B27 associated uveitis, it certainly needs much more research in the case of ankylosing spondylitis [29], where a role of CD8 T-cells or response to T-cell blocking therapies needs to be defined.

The IL-17 cytokine axis is remarkable in that deficiency of IL-17A, IL-17F and related pathways is strongly associated with a propensity for immunodeficiency and specifically fungal infections [32]. The targets for these fungal infections include the nail, scalp and genital regions, which is especially noteworthy since the involvement of these sites in subjects with psoriasis leads towards an increased propensity for PsA. Indeed, patients with PsA treated with IL-17A blockers had a higher prevalence of candida infection in comparison to those treated with placebo [32]. Moreover, single nucleotide polymorphisms (SNPs) in the IL-23 pathway such as IL23A and IL23R confer susceptibility to PsA, implying a central role of the IL-23/IL-17 axis in PsA disease pathogenesis [33, 34]. Thus, the original use of "pure autoinflammation" and "pure autoimmunity" with the placement of the MHC-I associated disorders as intermediate diseases with site specific autoinflammation and adaptive CD8 T-cells responses has been strengthened in recent years with the emergence of SNPs in ERAP-1, which trims peptides for MHC-I presentation. Thus, IL-1β, type I IFN and IL23/17 genetic associations define distinct immunological diseases. The fundamental differences between these disorders and classical autoimmunity are summarized in Table 38.1.

38.2.5 Autoimmunity–Autoinflammatory Overlap

The phenotype of both SJIA in children and AOSD are viewed as part of the autoinflammatory spectrum (see Chap. 32). This is supported

Table 38.1 The main differences between autoimmune and monogenic autoinflammatory disorders

Variable	Autoimmune disease	Monogenic autoinflammatory diseases	MHC-I-opathy
Epidemiology	Common	Rare	Rare
Gender	Female predominance	None	Disease dependent
Age of onset	Disease dependent	Generally young	Generally young
Primary site of disease	Lymphoid organ	Tissue target	Tissue target
Immunopathogenesis	Predominantly adaptive system dysregulation	Predominantly innate system dysregulation	Innate system dysregulation with secondary MHC-I/ERAP-1 related IL-23/17 cytokine axis dysregulation
Main cellular involvement	B and T cells	Neutrophils, macrophages	Myeloid cells Innate lymphocytes CD8 T cells
Genetic predisposition	MHC II associations	Cytokine and bacterial sensing pathways	MHC-I, ERAP-1/2, IL-23/IL-17 axis
Therapy	DMARDs, B-cell depletion	Anti-cytokines (e.g. anti-IL-1)	Anti-cytokines (IL-23/17 pathway) but not B-cell depletion
Natural history	Progressive	Recurrent episodes	Waxing and waning

MHC major histocompatibility complex; *DMARD* disease modifying anti-rheumatic drug; *IL* interleukin; *MHC* major histocompatibility complex; *ERAP-1* endoplasmic reticulum aminopeptidase 1

by evidence for an IL-1 transcriptional signature and responses to anti IL-1 therapy [35, 36]. Poorly defined, or what was historically termed "atypical AOSD", is now designated as autoinflammatory or undefined systemic autoinflammatory disease [19]. While SJIA has a rare monogenic variant reported in Arab populations, the typical cases of AOSD have an MHC-II association that points towards an overlap between autoinflammation and autoimmunity [37, 38]. The reported IL-1 signature in the context of the clinical phenotypes and response to IL-1 blockade is perhaps the strongest confirmatory evidence that AOSD and SJIA are part of the autoinflammatory phenotypes [35, 36]. At any rate, the recognition of the immunological disease continuum provides a platform for future studies to more accurately classify such disorders.

Rare instances have been described of the co-occurrence of complex phenotypes where patients have classical RA with MHC-II associated anti-citrullinated protein antibodies (ACPA) but simultaneously exhibit an associated autoinflammatory phenotype with sudden onset of severe attacks that are self-limiting with joint erythema. These attacks have a variable response to colchicine and in some cases anakinra but poor response to traditional treatment strategies using disease modifying anti-rheumatic drugs (DMARDs) and anti-TNF biologics [39]. We envisage that this is due to the complex interaction of both innate and adaptive immune mechanisms that are both independently capable of driving inflammatory arthritis. The recognition that autoinflammatory aspects that occur in common autoimmune diseases explain a variable response to therapy needs assessment in longitudinal studies [40].

As an example of the complexity between autoimmunity and autoinflammation, SNPs in the *TNFAIP3* gene, encoding the NF-kB regulatory protein A20, are associated with an array of classical autoimmune disorders but also disorders that are closer to the autoinflammation end of the spectrum [41]. In murine models, conditional knockout of *TNFAIP3* in keratinocytes, enterocytes, B cells or dendritic cells can create completely different inflammatory phenotypes including colitis, rash, RA-like arthropathy, SLE and Sjogren syndrome [42]. In humans, heterozygous loss-of-function mutations in the

TNFAIP3 gene are associated with a BD-like phenotype characterised by mucosal ulceration, uveitis and arthritis [43, 44]. The emerging lesson would appear to be that genes with widespread expression in both innate and adaptive immune cells may lead to very complex or overlapping phenotypes.

38.3 Other Immunological Aspects of Autoinflammatory Disorders

38.3.1 Autoinflammation and Cancer

Sporadic adult autoinflammatory disorders can be linked to an underlying lymphoproliferative disease. This is best defined for Schnitzler syndrome where cases typically present in adulthood with urticaria, fever and bone pain [45] (see Chap. 37). Although no genetic abnormalities have been defined in the NLRP3 inflammasome or other molecules, Schnitzler syndrome responds well to therapy with IL-1 inhibition [46, 47]. The vast majority of cases have a monoclonal IgM gammopathy and a significant number of patients go on to develop a lymphoproliferative disorder [48]. Beyond the well-recognised association between Schnitzler syndrome and autoinflammation there is a more poorly defined link with malignancy.

Beyond Schnitzler syndrome, which is a classical disease to illustrate the link between autoinflammation and cancer, a national French survey found an association between myelodysplastic syndrome (MDS) and hyper-inflammation [49]. Amongst 123 cases defined with MDS, the main clinical manifestations consisted of non-infectious fever with constitutional symptoms, skin involvement and arthritis. While many of these cases had bona fide autoimmune diseases, over 10% had innate immunopathology including Sweet syndrome and pyoderma gangrenosum [49]. Within the MDS group, chronic myelomonocytic leukemia (CMML), refractory anemia with excess blasts (RAEB), refractory cytopenia with multilineage dysplasia (RCMD), and refractory cytopenia with unilineage dysplasia were the most commonly defined entities that were linked to systemic inflammation. From a therapeutic perspective, most of these cases showed corticosteroid responsiveness. However, many patients required DMARD therapy and eventually went on to biological therapy. To emphasise, some of these cases had autoimmune diseases but for various biological therapies the responses rates were under 50%. While the association between classical autoimmune diseases and lymphoproliferative disease is well established with diffuse large B-cell lymphoma in RA, marginal zone lymphoma in Sjogren syndrome and T-cell lymphoma in celiac disease the link between autoinflammation and hematological malignancy is less well understood [50] (see Chap. 39). Given that the MDS group of disorders are essentially linked to the progenitor cells that are linked to myeloid lineage development, it is no surprise that a parallel situation of innate immune system related hematological disorders overlaps with malignancy [51].

The opposite is also true, autoinflammation tendencies might even protect against cancer (see also Chap. 39). The constitutive gain of function in the *MEFV* gene in FMF has recently been associated with a lower rate of cancers raising the possibility that innate immunity or aberrant immune activation propensities may be protective against cancer [52]. However, the link between malignancy and autoinflammation and cytokine pathways seems to be very complicated, indeed, in a study aimed to evaluate the effect of canakinumab on the atherosclerosis process, it was found that blocking IL-1β reduced the incidence and mortality of lung cancer [53]. This shows that the innate immune system plays an important role in malignancies and tumorigenesis and could be equally important to the adaptive immune system.

38.3.2 Autoimmunity, Autoinflammation and Immunodeficiency

A historical misconception was that gain-of-function in the immune system resulted in autoimmunity and loss-of-function resulted in

immunodeficiency. Recognition of the immunological disease continuum with innate and adaptive immune responses defining distinct disease boundaries led to the realization that complex phenotypes with either loss- or gain of immune function could occur within the disease spectrum, as pointed out by Grateau et al. [5] (Fig. 38.3) (see Chap. 28). A wide range of mechanisms is emerging to explain these features. For autoimmune disorders, high titre autoantibodies that neutralize IL-17 family members account for immunodeficiency in the monogenic autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) disease that is associated with multi-organ failure in the endocrine system. In the setting of signal transducer and activator of transcription (STAT)-1 gain-of-function the phenotype is associated with several autoimmune diseases, the counter-regulatory effects of the STAT-1 pathway suppresses IL-17 driven response and makes subjects susceptible to secondary infection. Furthermore, loss-of-function of immunity related to reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is associated with infections but also a Crohn-like disease phenotype that can be treated successfully with anti-TNF therapy [54]. The complex functional integration and a myriad of redundant and counter-regulatory pathways in the immune system underscores this complex immunological triumvirate (Fig. 38.3).

38.4 Clinical Approach to Distinguish Autoinflammation and Autoimmunity

38.4.1 Clinical Investigations

The approach to distinguish between autoinflammation and autoimmunity begins with a careful medical and family history, general physical examination, laboratory tests including complete blood count, general biochemistry, serum complement and immunoglobulin levels, inflammatory biomarkers and relevant autoantibodies. The detailed evaluation for autoinflammatory diseases is described in Chap. 11.

By the time autoinflammation is considered as a diagnosis most patients will already have had an extensive work up including a detailed infectious disease assessment with blood cultures and viral and bacteriological serologic studies. In our experience, underlying chronic disease, including bronchiectasis, may be difficult to recognize, especially if patients do not have significant purulent sputum expectoration. The second major differential diagnosis is underlying malignancy and lymphoproliferative diseases in particular, since myeloid or lymphoid dysregulation can lead to inflammation before malignancy manifests itself. In our experience, some cases of unexplained inflammatory conditions with therapy-resistant disease do have bone marrow findings indicative of probable, but not definite, underlying lymphoproliferative disease at post-mortem examination, although earlier bone marrow examinations had remained inconclusive.

By the time adult subjects with suspected autoinflammatory disease are formally referred for assessment it is likely they will already have had CT imaging of the neck, chest, abdomen and pelvis to search for lymphoproliferative disease, infectious source or large vessel vasculitis. Both upper and lower gastrointestinal tract endoscopy may also have been performed especially if weight loss is prominent. Echocardiography including transesophageal examination is often ordered to exclude bacterial endocarditis. The role of fludeoxyglucose positron emission tomography (FDG PET) has been recently clarified in subjects with inflammation of unknown origin and is informative in subjects over 50 years of age where it is useful in the evaluation of giant cell arteritis which may present with a prominent inflammatory phenotype with fever and constitutional symptoms [55].

Occasionally patients may present with prominent fevers and serositis and constitutional symptoms that appear autoinflammatory in nature. On detailed immunoblot assessment for autoantigens, one autoantibody may be found, not fitting the clinical pattern, only to evolve a classical connective tissue disease pattern at a later stage including autoimmune myositis. Therefore, a high degree of clinical vigilance is needed in the assessment of poorly defined autoinflammatory disease.

38.4.2 Molecular Investigations

The foremost test for the assessment of the autoinflammatory disorders is an initial screen of genes known to be associated with monogenic autoinflammatory disorders (see Chap. 12). In adult autoinflammatory disease clinics, cases tend to be sporadic rather than familial. The complexity of the genetic analysis is increasing, for example the recognition that heterozygous mutations in the *MEFV* gene may be associated with FMF or other inflammatory phenotypes [56]. Whilst homozygous mutations are needed for autoimmune or autoinflammatory phenotypes in animal models, e.g. for CTLA4 or TNFAIP3, heterozygous mutations in the latter are associated with the emergence of a BD-like phenotype [57]. Uncommon variants of NOD2 or TNFR1 are not infrequently found in patients in autoinflammatory disease clinics and their full meaning awaits to be elucidated.

An informatics approach has been used to evaluate whether it is possible to decipher between autoimmune and autoinflammatory disorders by choosing entities from both ends of the spectrum and performing a meta-analysis of publicly available gene expression datasets generated from peripheral blood mononuclear cells [58]. The most striking feature of this dichotomous autoimmune and autoinflammatory disease analysis was that common pathway dysregulation occurred in both settings including TLR, P13k-AKT and NF-κB signalling [58]. The common denominator between autoimmunity and autoinflammation was the integration of signals in both innate and adaptive cell signalling, including immune cell polarization, migration, growth, survival and differentiation.

38.4.3 Clinical Recognition of Sporadic Hyper–Inflammatory States

The monogenic autoinflammatory disorders have provided a strong platform in pediatric medicine for genetic testing and the number of genes is expanding all the time. However, rheumatology, infectious disease and hematology and other specialties consistently see sporadic hyper-inflammatory ill-defined states. The immunological disease continuum provides a platform for a systematic assessment of such cases and whether they are autoinflammatory or autoimmune. The recognition of the sporadic autoinflammatory states that are termed undefined systemic autoinflammatory disease represent an example of this [19]. These cases may present with fever, prominent cutaneous and musculoskeletal manifestations and are resistant to conventional DMARDs that are used for RA and other diseases. Such patients typically undergo repeated hospital admissions under different specialties and repeated investigations that fail to turn up a specific diagnosis. They typically show a good response to high dose corticosteroids, but are unable to wean and develop corticosteroid-related toxicity. The slow onset of action of DMARDs results in several months of inefficacious treatment trials in these cases. However, based on the remarkable efficacy of IL-1 antagonism in the well-defined monogenic autoinflammatory disorders, as shown in Fig. 38.3, IL-1β blocking strategies also often work in many, but not all of these cases [19].

38.5 Severe Complications of Autoinflammatory Disorders *Versus* Autoimmune Disorders

The severity spectrum of autoinflammatory disorders spans from very mild disease to extreme forms leading to high rates of mortality. Patients can present with poorly defined autoinflammatory-driven shock and circulatory collapse resembling sepsis. This actually may be part of the autoinflammatory disease spectrum under the guise of MAS (see Chap. 33). Indeed, MAS and severe sepsis share many clinical, laboratory, and pathologic features, including ferritin elevations, various cytopenias, hepatic dysfunction with transaminitis in particular, coagulopathy with a disseminated intravascular coagulation and tissue hemo-

phagocytosis [59]. In MAS, these features are associated with hyperferritinemia and it is likely that IL-1 is the apical cytokine that may drive a cytokine storm since its blockade was associated with a dramatic improvement in survival [60]. Further studies are needed to formally examine whether early therapy with IL-1 blockade will be effective in this extreme form of autoinflammation. Recently, IL-18, an IL-1 family member that is also regulated by inflammasomes, has emerged as potentially one of the most pivotal cytokines in these poorly designated life-threatening autoinflammatory disorders [61]. In contrast, severe life-threatening autoimmune diseases have a tendency to exhibit a predominant attack of a single organ system and lack the severe constitutional features with some exceptions including catastrophic antiphospholipid syndrome, severe pulmonary involvement in anti-GBM syndrome or severe autoimmune nephritis.

38.6 Therapeutic Implications of Autoinflammation and Autoimmunity

Not only are the autoimmunity and autoinflammation concepts underscored by common anatomical and genetic factors but their successful therapeutic manipulation further dichotomizes immunopathogenesis and appropriate disease classification (Fig. 38.8). The emerging therapeutic responses represent an overarching concept but there are

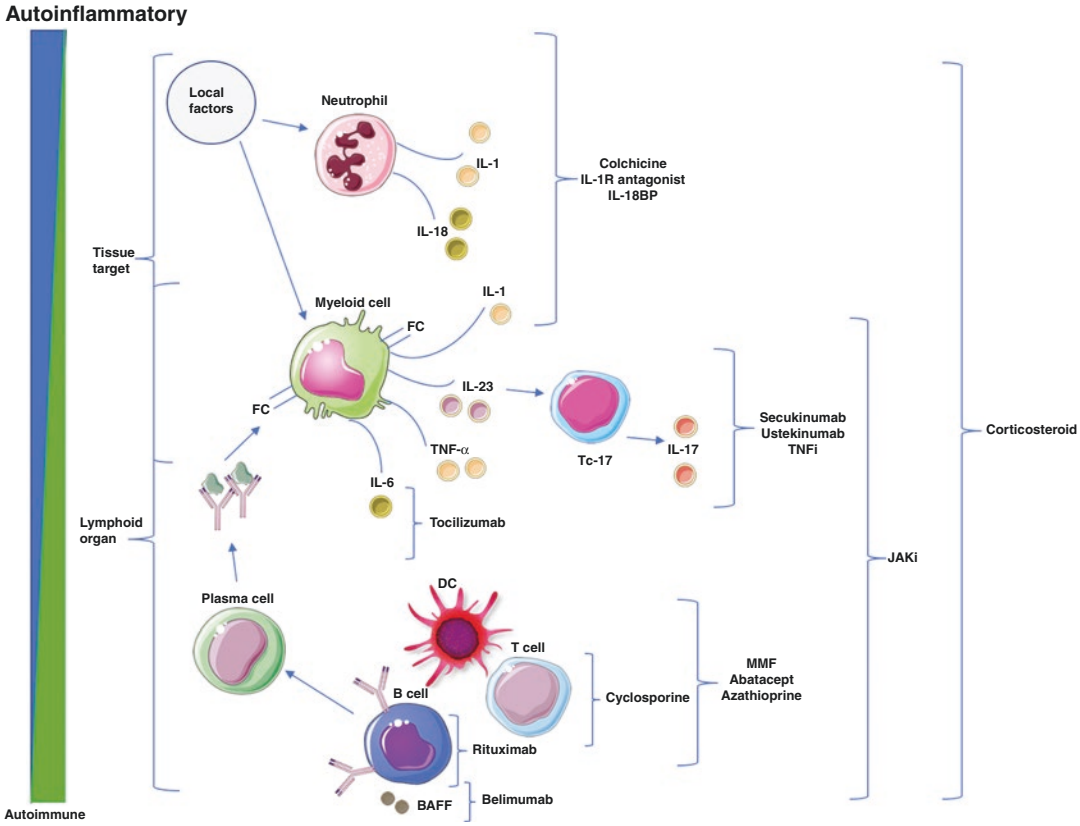

Fig. 38.8 Autoimmunity and autoinflammation classification is reflected in differential therapeutic targeting. Features of this figure are reproduced from https://smart.servier.com (Servier medical art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License), and were changed in terms of shape and size. *MMF* mycophenolate mofetil; *BAFF* B-cell activating factor; *IL* interleukin; *IL-1R* IL-1 receptor; *IL-18BP* IL-18 binding protein; *TNF* tumour necrosis factor; *TNFI* TNF inhibitor; *JAKI* Janus kinase inhibitor

some therapeutic exceptions in these groups. For example, molecules that selectively target B cells (primarily anti-CD20 therapy with rituximab) are effective for many of the classical autoantibody associated diseases. At the other extreme, the predominantly autoinflammatory diseases often show responses to anti-IL-1 strategies (Fig. 38.6). The non-autoantibody mediated SpA related diseases generally show good responses to cytokine blockers and historically the anti-TNFs. The "intermediate diseases" or "MHC-I-opathy" disorders show good responses to therapies that antagonize the IL-23/17 axis likely reflecting how local tissue resident factors ultimately orchestrate the so-called type 17 innate and adaptive lymphocytes to drive IL-17 related pathology. Small molecules that antagonize conventional T cells work over a wide range of inflammatory disorders, but generally less well than cytokine blockers. Corticosteroids work across the entire spectrum of inflammatory diseases likely reflecting their myriad of effects on the immune system. Finally, the heterogeneity and complexity of the immune system needs to be noted, reflecting the fact that some cytokine blockers, especially IL-6 antagonism, is effective for several adaptive immune disorders as well as innate/autoinflammatory disorders like for TRAPS and others (see Chap. 42).

Box 38.1 Definitions of Autoimmunity and Autoinflammation

Generic definition of autoimmunity

Self-directed inflammation, whereby aberrant dendritic cell, B- and T cell, responses in primary and secondary lymphoid organs lead to breaking of tolerance, with development of immune reactivity towards native antigens. The adaptive immune response plays the predominant role in the eventual clinical expression of disease. Organ-specific autoantibodies may predate clinical disease expression by years and manifest before target organ damage is discernible.

Proposal for a definition of autoinflammation

Self-directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage. For example, disturbed homeostasis of canonical cytokine cascades (as in the recurrent fever syndromes), aberrant bacterial sensing (as in Crohn disease), and tissue microdamage predispose one to site-specific inflammation that is independent of adaptive immune responses.

38.7 Conclusion

The ongoing identification of new genetic variants in both autoinflammatory and autoimmune diseases highlights the complexity of these disorders including complex overlapping phenotypes. A careful scrutiny of self-directed inflammation indicates that innate immune driven or autoinflammatory disease is conceptually, clinically and therapeutically very different from the autoimmune disorders. The emergent knowledge has facilitated clinical translational strategies for recognising and treating sporadic inflammatory disorders. The application of the continuum model for classification of immunological disease seems to be a practical and useful tool to approach the diagnosis and treatment of such diseases.

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