

Comparison of autoinflammation and autoimmunity using TRAPS and rheumatoid arthritis as prototypes of these conditions

Classical autoimmune diseases are associated with the presence of autoantibodies and autoantigen-specific T cells. However, in addition to the classical major histocompatibility complex class II-associated diseases, such as systemic lupus erythematosus and rheumatoid arthritis, the autoimmunity paradigm has also been the dominant conceptual framework when considering the pathogenesis of a range of other chronic inflammatory conditions, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease) and systemic juvenile idiopathic arthritis. Several difficulties arise when the autoimmunity concept is invoked to describe the self-directed tissue inflammation encountered in many diseases, such as ankylosing spondylitis, inflammatory bowel disease and psoriasis; these include an absence of autoantibody associations, which is seen in all these conditions, and a lack of major histocompatibility complex allelic associations. These autoinflammatory diseases are not associated with the presence of autoantibodies and autoantigen-specific T cells, and appear to be mainly cytokine driven. For the purpose of this review, we have chosen to describe the autosomal dominant, TNF receptor-associated periodic syndrome as a prototype of this category of disorders. We compare the genetic basis, pathophysiology and treatment of TNF receptor-associated periodic syndrome with rheumatoid arthritis, which we present as an example of an autoimmune disease.

KEYWORDS: autoimmune ■ autoinflammatory ■ cytokines ■ rheumatoid arthritis ■ TNF receptor-associated periodic syndrome ■ TRAPS

Concept of autoinflammation

Immune-mediated diseases tended to be viewed from an autoimmune perspective until the term 'autoinflammatory diseases' was introduced just over 10 years ago [1]. It was proposed that this category of disorders is quite distinct from the classical autoimmune diseases, which are associated with the presence of autoantibodies and autoantigen-specific T cells, as found in conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Type 1 diabetes (T1D). The autoimmune diseases usually have strong major histocompatibility complex (MHC) class II associations, and recent genome-wide association studies have emphasized the polygenic nature of many of these conditions [2,3].

This fundamental shift was ushered in by an improved understanding of a range of monogenic inflammatory disorders termed the 'hereditary periodic fevers' (HPFs). The HPFs encompass a range of monogenic innate immune-mediated diseases, such as familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS) and mevalonate kinase deficiency. Specifically, mutations in proteins associated with innate immune cells, such as monocytes/macrophages and neutrophils, have

firmly implicated innate immune dysregulation in the pathogenesis of many of these disorders, which have been collectively termed the autoinflammatory diseases [3,4]. The term 'autoinflammation' is now used interchangeably with the term 'innate immune-mediated inflammation', and has become an accepted way of describing innate immune-mediated disease [5]. In the past decade, polygenic disorders, such as Crohn's disease, ulcerative colitis and Behçet's syndrome, have been reclassified as autoinflammatory disorders [3,4,6,7].

We have proposed an immunological disease continuum to describe the spectrum of immune-mediated disease and there are some clear overlaps between the two types of inflammation – autoinflammation and autoimmunity – especially concerning MHC class I-associated disorders (FIGURE 1) [8]. The concept of the immunological disease continuum hinges on the notion that tissue perturbations at the target sites of inflammation, rather than the immune system *per se*, is key to disease expression, whereby diseases could be classified as being driven by adaptive or innate immune responses, with the majority of conditions involving variable degrees of interaction between these two systems [9].

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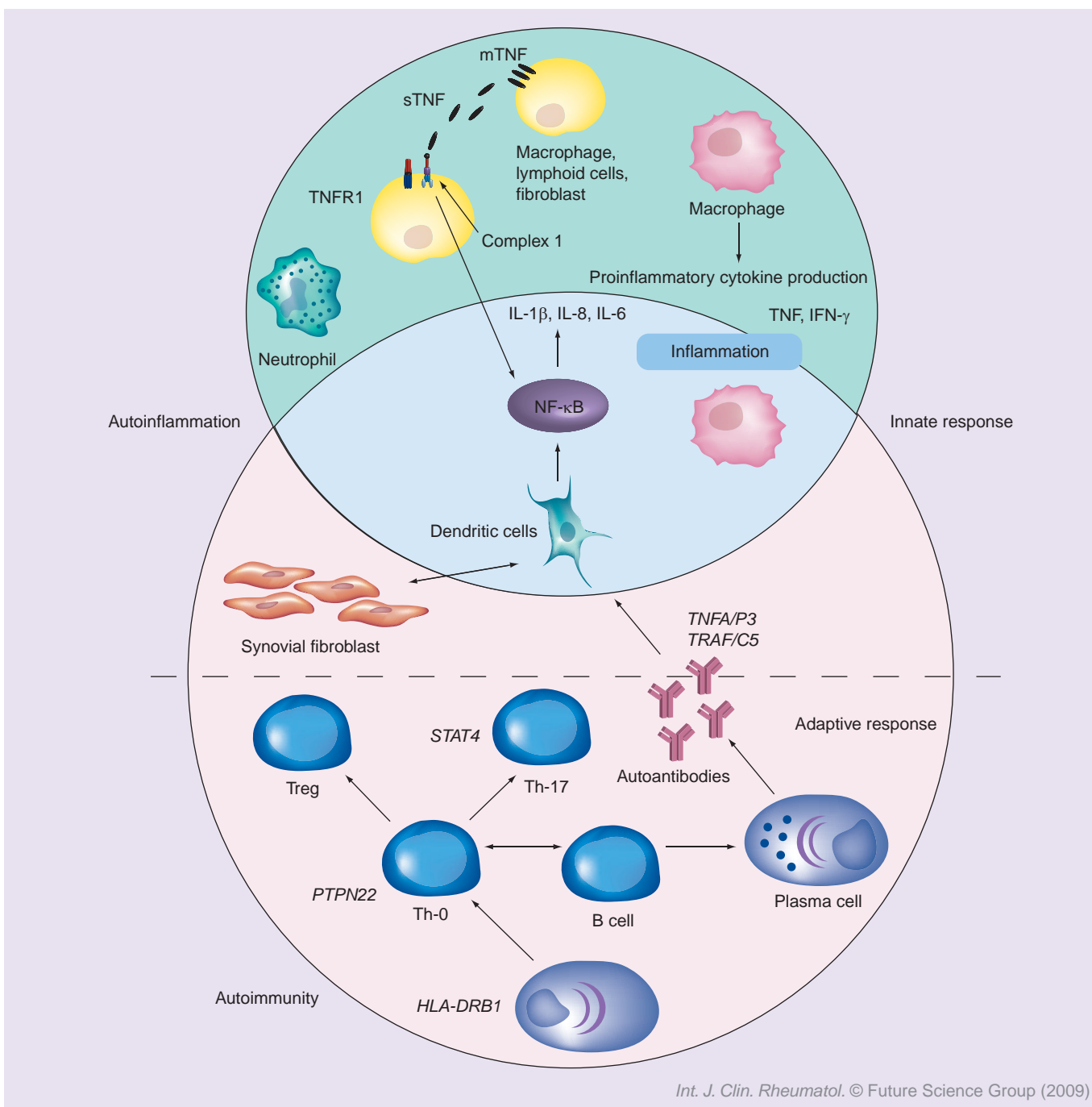


Figure 1. An overview of autoinflammation and autoimmune response with a common inflammatory response.

In autoinflammation (green circle), the release of membrane-bound TNF and the binding of soluble TNF to TNFR1 initiate the ligation of the receptor. This ligation induces the formation of complex I at the cell membrane, and this complex induces NF-κB activation, which results in proinflammatory cytokine production that leads to inflammation. In autoimmune diseases (the autoimmune response is shown by the pink circle), a number of immune cells are believed to be involved, as well as genes and environmental factors. Autoantibodies produced by B cells (adaptive response) are recognized by macrophages/dendritic cells (innate immune system), which initiate the proinflammatory cytokine production leading to inflammation (blue intersection).
 mTNF: Membrane TNF; sTNF: Soluble TNF; Th: T helper.

Genetic analysis of autoinflammatory conditions has led to the discovery of new molecules involved in recognizing exogenous and endogenous signals. As a specific example, mutations in the Nod-like receptor (NLR) *NLRP3* (*NALP3*, *CIAS1*) gene, which encodes

the NLRP3 protein, have been associated with a range of autoinflammatory conditions that are encompassed by the term CAPS. These rare monogenic conditions are caused by gain-of-function mutations [10] and share a common mechanism, whereby the closed inactive

NLRP3 protein is disrupted by the various mutations, leading to activation of the NLRP3 inflammasome complex and IL-1 β release [11].

The innate immune system is the first line of defense and plays a critical role in host homeostasis by responding to external signals in the form of molecular motifs that are expressed by a range of pathogens (pathogen-associated molecular patterns) and intracellularly-derived molecules, such as nucleic acid variants (DNA and dsRNA) and monosodium urate crystals. These monosodium urate crystals have been demonstrated to act as danger signals that activate the NLRP3 inflammasome in gout; likewise, calcium pyrophosphate dihydrate crystals, the causative agent in pseudogout, lead to the maturation of IL-1 β and IL-18 via the same mechanism [12]. Unravelling these responses has led to advances in understanding the pathophysiological foundations of the innate immunity, which is not a nonspecific first line of defense, but a sophisticated pathogen recognition system for activation of an appropriate response and is essential for restoration of health. Pathogen-associated molecular patterns are recognized through an array of receptor molecules, including Toll-like receptors, NLRs, retinoic acid-inducible gene-like receptors and C-type lectin receptors, which are collectively known as pattern recognition receptors and serve to alert the immune system [13,14].

■ Autoimmune disorders

Autoimmune disorders affect a wide spectrum of individuals around the globe; currently, there are more than 100 recognized autoimmune illnesses, including multiple sclerosis, SLE, RA, T1D, Sjögren's syndrome, inflammatory myopathy, vasculitic syndromes and autoimmune hematological disorders, such as autoimmune hemolytic anemia and thrombotic thrombocytopenic purpura. These diseases are usually defined either in terms of defects in B- or T-cell selection or self-directed inflammation, involving aberrant dendritic cell, B- and T-cell responses in primary and secondary lymphoid organs that lead to the breaking of tolerance with the development of immune reactivity towards native antigens. The adaptive immune response plays the predominant role in the eventual clinical presentation of disease, and immunological changes may be manifest before target organ damage is discernable [8].

■ Autoinflammatory disorders

'Hereditary periodic fevers' is a collective term that describes a rare group of Mendelian autoinflammatory disorders (autosomal dominant

or recessive) characterized by recurrent episodes of fever with multisystem inflammation. For the purpose of this review, we have chosen to describe the autosomal dominant TRAPS as a prototype of this category of disorders.

TRAPS as a prototype for the autoinflammatory disorders

TNF receptor-associated periodic syndrome (Mendelian Inheritance in Man [MIM] 142680) was initially described in a Scottish-Irish kindred in 1982 [15]. In 1998, a candidate interval was identified on chromosome 12p13 for this condition [16], and a year later, six missense mutations were identified in *TNFRSF1A*, the gene encoding the 55-kDa receptor for TNFR1 [1]. More than 80 sequence variants of *TNFRSF1A* have been recorded so far and more than 50 of these were associated with the TRAPS phenotype, with the rest probably being polymorphisms. The majority are single nucleotide missense mutations in exons 2–6, affecting the cysteine-rich domains (CRD; CRD1–CRD3) of the ectodomain of the mature TNFR1 protein with the following exceptions – an exon-intron junction mutation that prevents correct transcript splicing, resulting in a 15 amino acid insertion [17], a single amino acid deletion in exon 3 (Δ D42) [18] and one deletion insertion (H69fs) [19]. The CRDs are involved in disulfide bond formation, which is important for the correct folding of receptors on the cell surface [20]. Mutations involving cysteine residues of TNFR1 may result in abnormal disulfide-linked oligomers that fail to interact with the wild-type receptor through the preligand assembly domain and therefore, are retained intracellularly [21]. Cysteine mutations may result in a higher penetrance of the clinical phenotype and also in an increased probability of developing life-threatening amyloidosis [22–24]. By contrast, the R92Q variant has been reported in 1% of healthy individuals [25], a finding that suggests incomplete penetrance [26,27]. Moreover, it has been demonstrated that most TRAPS patients carrying the R92Q variant display a more heterogeneous clinical presentation, with a milder disease course and a lower prevalence of amyloidosis [25,27]. A percentage of patients have been found not to possess a *TNFRSF1A* mutation but are identified as having the TRAPS phenotype, and consequently, the term 'TRAPS-like phenotype' is used for this group of patients [18].

Validated clinical criteria for TRAPS do not currently exist, and differential diagnosis with other recurrent fevers is challenging when solely

based on clinical grounds. As with all HPFs, TRAPS often presents as a pediatric disease, with a median age of onset of 10 years [28]. However, owing to a lack of information regarding this condition and the absence of a specific phenotype marker, many patients experience a delay of up to 20 years before the correct diagnosis is made. TRAPS is the second most common HPF worldwide behind FMF, with a prevalence of approximately one individual per million in the UK [29].

TNF receptor-associated periodic syndrome is characterized by recurrent attacks of fever (with a temperature of 38–41°C) lasting 1–3 weeks and occasionally it may persist for a number of months. Recurrent inflammatory episodes may occur over a period of 6 months or more. Several symptoms may occur simultaneously, such as abdominal pains and myalgias, which are believed to be due to monocytic fasciitis [30]. Fasciitis is often accompanied by a migratory erythematous macular rash that may overlie the affected muscles. Histological examination of skin lesions has revealed monocytic and lymphocytic (CD3⁺, CD4⁺, CD8⁺, CD68⁺, CD79a⁻ and CD20⁻) infiltration [31]. Conjunctivitis/periorbital edema, chest pain, arthralgias or monoarticular synovitis are among other clinical manifestations of TRAPS. A positive family history may not always be present, and *de novo* mutations have been described [32,33]. Systemic amyloidosis (AA fibril type) represents the most serious long-term complication, with a prevalence ranging from 14 to 25% [33]. Risk factors associated with amyloidosis include prolonged high levels of serum amyloid A (SAA), a positive family history and the presence of cysteine mutations [22]; however, the percentage of amyloidosis patients with cysteine mutations has dropped from an initial estimation of 93 to 64%, based on reports in the current literature [33]. Laboratory findings include raised acute-phase response proteins and reduced soluble TNFR1 (sTNFR1) levels in the serum [1]. Genetic screening is routinely performed for mutations in exons 2–5 of *TNFRSF1A*, but advances in rapid sequencing techniques will allow screening of the complete locus in selected cases in the near future.

Pathophysiology of TRAPS

■ Defective TNFR1 shedding

TNFR1 is expressed as a homotrimer on many cell surfaces and, upon activation by TNF, undergoes cleavage of the extracellular part by metalloproteinase action [34]. *In vitro* studies of leukocytes from patients bearing the C52F

mutation indicated impairment in this normal cleavage process of cell-surface p55 receptors [1]. Several TRAPS mutations were reported to have reduced cleavage following stimulation, with a subsequent increase in TNFR1 expression on the cell membrane [26]. Dysregulated inflammation may result owing to a lack of appropriate TNF inhibition by antagonistic sTNFR1, with subsequent amplification of the TNF-induced signaling cascade. Heterogeneity exists in the degree of shedding defects between different cell types, and dermal fibroblasts, rather than leukocytes, from C33Y patients exhibited reduced shedding in transfected cell lines expressing wild-type or mutant TNFR1 [35]. Receptor clearance is thought to have a negative homeostatic effect, both by preventing repeated stimulation through membrane TNFR1 and by creating a pool of antagonistic soluble receptors, and thus, a cleavage defect could, at least partially, account for the hyperinflammatory phenotype in TRAPS. Low levels of sTNFR1 in plasma have been associated with defective TNFR1 shedding and a high circulating TNF level has been implicated in symptoms of TRAPS [28]. However, some mutations are not associated with defective TNFR1 shedding [18,35], suggesting that additional mechanisms could be related to disease pathogenesis.

■ Impaired TNF-induced apoptotic signaling

TNF is able to induce cell apoptosis via TNFR1 binding and activation of the extrinsic caspase cascade [36,37]. There is an 80 amino acid-long death domain at the C-terminus of TNFR1, which is critical for inducing apoptosis [38]. The TNFR1 homotrimer complex is internalized into the cytoplasm upon activation by TNF and recruits the proapoptotic proteins, Fas-associated protein death domain (FADD) and caspase-8 [39]. During cell activation, this intracellular signaling pathway is inhibited by the continuous expression of anti-apoptotic factors, such as the caspase-8 inhibitor protein – Flice-like inhibitory protein long – which is produced through the activation of the NF-κB pathway [36]. When the NF-κB activity subsides, the proapoptotic signals induced by the intracellular TNFR1 complex lead to cell death. Thus, TNFR1 plays a unique role in the control of TNF-induced apoptosis of activated cells and represents a second strategy for downregulation of TNF activity during acute inflammation. Skin fibroblasts and circulating neutrophils from TRAPS patients display defective TNF-induced

apoptosis [28]. This defect may represent an additional mechanism to explain the sustained activation of inflammatory cells observed during fever episodes in TRAPS, but the underlying intracellular mechanisms for apoptosis resistance have not yet been identified.

■ Impaired intracellular TNFR1 trafficking and TNF binding

Normal TNFR1 proteins are transported from the endoplasmic reticulum (ER) to the Golgi, where they are pooled before being transported to the surface [40]. Mutations in TNFR1, and particularly those involving cysteine residues, may result in the accumulation of misfolded proteins in the Golgi apparatus [41] and ER [21,42], with subsequent failure of intracellular trafficking, owing to oligomerization and abnormal disulfide bond formation, which may contribute to low levels of expression on the cell surface. This intracellular sequestration of the mutated unfolded TNFR1 in the ER may lead to the so-called ER overload response that can lead to constitutive NF- κ B activation, which may result in the unopposed action of TNF and excessive cytokine release [43].

There is also evidence of a significant increase in cell surface TNFR1 expression in peripheral blood mononuclear cells of TRAPS patients (C73R) [44]; however, at present, it is not possible to distinguish between mutant and wild-type TNF receptors due to a lack of specific antibodies.

■ TNF-independent NF- κ B activation

A recent study demonstrated that the wild-type TNFR1 and the mutant (T50K) variant were able to associate in the absence of TNF and were able to activate the p65 (RelA) subunit of NF- κ B, which did not occur with the wild-type alone [45]. A mutation at the splice site in intron 4 of *TNFRSF1A* has also been identified and is associated with increased NF- κ B signaling in TRAPS patients [17]. Thus, part of the inflammatory process in this condition may be induced by a TNF-independent upregulation of TNFR1 expression, with subsequent NF- κ B activation.

■ Serological profile of TRAPS

In general, the levels of proinflammatory cytokines, such as IL-6, IL-12p70 and TNF, are found to be high in TRAPS patients and correlate well with the severity of symptoms and serological markers of inflammation (erythrocyte sedimentation rate and C-reactive protein [CRP]). Prolonged high levels of SAA are associated with the development of amyloidosis and

serial measurements of SAA levels should be included, if possible, in all therapeutic regimes for TRAPS. CRP is a marker of systemic inflammation that is produced in the liver and is modulated by IL-6, which has a negative feedback effect by inducing IL-1 receptor antagonist (IL-1RA) and soluble TNF receptors. IL-1 induces itself and CRP induces TNF, IL-6, IL-8 and IL-12 [46]. Churchman *et al.* demonstrated increased levels of cytokines (IL-1 β , IL-2, IL-6, IL-10 and IL-12) [17] in the serum of TRAPS patients with a splice site mutation, as well as in T50K and C88R patients. The level of CRP in different TRAPS patients may not reflect the level of cytokines. For example, high levels of CRP in C33Y TRAPS patients were associated with high serum levels of IL-6 and IL-8; this is unlike the cytokine profile in the serum of RA patients, which shows elevated levels of IL-6, IL-8, IL-10 and IL-1 β . Treatment with etanercept may reduce certain cytokine levels, such as IL-6 and IL-8, but the level of IL-12 may remain high [47]; the level of TNF was also found to increase during treatment with etanercept in a report on a C33Y patient [48], but this was mostly due to binding of TNF by etanercept, which may produce a spuriously high TNF level. Other periodic fever syndromes, such as FMF and hyperimmunoglobulin D syndrome, are characterized by elevated IL-6, TNF [49], IL-8 [50] and IFN- γ [51] levels.

■ Treatment of TRAPS

TNF receptor-associated periodic syndrome is usually responsive to glucocorticoids whereas colchicine therapy is generally ineffective [52]. Infliximab, an anti-TNF monoclonal antibody, has been reported as being either ineffective or, indeed, as aggravating the symptoms of TRAPS [53]. *In vitro* studies of infliximab on peripheral blood mononuclear cells of T50M TRAPS patients have demonstrated an inhibition of apoptosis owing to failure of shedding infliximab-bound TNF/TNFR1 from the cell surface, and the induction of c-Rel activation, which leads to the release of proinflammatory cytokines, namely IL-6, IL-8, IL-12 and IL-1 receptor [54]. Etanercept, an anti-TNF fusion protein, has been used during the attacks and usually abolished the symptoms by day 3 at doses of 0.4 mg/kg taken subcutaneously twice weekly for 6 months, and no further symptoms occurred during treatment [55,56]. However, whereas etanercept treatment was successful in clearing the symptoms, prophylactic administration of etanercept failed to prevent future attacks [57].

Treatment with etanercept may also improve renal function with reduction in the incidence of amyloidosis in some TRAPS patients [19]. Recently, the IL-1RA drug, anakinra, has been used to treat TRAPS patients [58], and an improvement in symptoms and a reduction in serum levels of SAA and acute-phase reactants was observed [59]. Anakinra has also been used successfully when patients failed to respond to etanercept [60].

Indeed, the success of IL-1 β blockade using anakinra in a number of diseases with wide-ranging phenotypes, such as gout [61], pyoderma gangrenosum in pyogenic arthritis, pyoderma gangrenosum and acne syndrome [62], in addition to Schnitzler's syndrome [63], as well as the reported efficacy of long-acting IL-1 antagonism using rilonacept in systemic-onset juvenile idiopathic arthritis, points to a pathogenic state in all of these conditions, as well as CAPS and TRAPS, whereby the NLRP3 complex generates excessive IL-1 β secretion through activation of caspase 1, which then cleaves the inactive pro-IL-1 β to its active form.

RA as a prototype of autoimmune disease

Rheumatoid arthritis is a complex polygenic autoimmune disorder of unknown etiology that occurs in up to 1% of Caucasian populations; the prevalence varies across racial and ethnic groups, reflecting the prevalence of predisposing genes that are described later. The synovial joints are the main target organs in RA and are characterized by thickening of the synovial membrane, with proliferation of macrophage-like synoviocytes and fibroblast-like synoviocytes, as well as extensive synovial infiltration with inflammatory cells, including macrophages, B and T lymphocytes, and dendritic cells (FIGURE 1). In early RA, disease localization is to the synovium, which is in keeping with the concept of the synovium being the primary target organ. However, in an autoinflammatory disease such as early psoriatic arthritis, the inflammatory changes have a widespread distribution and relate to local tissue factors, including patterns of joint stressing around ligaments, adjacent bone and soft tissues, rather than a specific antigen territory [64].

Analysis of synovial tissue architecture confirms heterogeneity in its organization with three main forms – diffuse infiltration, aggregates and ectopic germinal center – suggesting differences in the main drivers of pathogenesis [65]. The traditional paradigm interprets RA as an aberrant response of the adaptive immune system, with

T lymphocytes that are specific to an unspecified arthritogenic antigen inducing a memory response and tissue destruction as the sequelae of persistent antigen-driven T- and B-cell responses. However, the initiating events and sustained inflammation of RA are also dependent on cytokine production by macrophage-like synoviocytes and fibroblast-like synoviocytes, which may act on each other in an autocrine or paracrine manner. Although adaptive immunity plays a prominent role in RA, an antigen-independent induction phase involving innate immune responses [66] precedes the adaptive response in RA, and both the IL-1 β and TNF proinflammatory cytokines induced through NF- κ B activation are pivotal regulators in the pathogenesis. IL-1 β may have a more potent effect on joint destruction than TNF [67]. The NLRP3 (NALP3) inflammasome is a large intracellular protein complex that generates IL-1 β cytokine production, which is then secreted and leads to cartilage damage owing to rheumatoid synovial T-helper (Th)-1 activation [68].

The systemic effects of RA, which may be the cause of significant morbidity and mortality, involve the connective tissues and cardiovascular system. In RA, there is a complex interplay between a number of susceptibility genes and environmental factors that lead to the development of this potentially crippling condition (see TABLE 1). Among the local manifestations of the disease is a massive cellular infiltration of the synovial joints, which may result in destructive erosive disease and associated morbidity. Currently, the European League of Rheumatology and the American College of Rheumatology are collaborating to define a new standard set of criteria for the classification of RA [69].

■ Presence of autoantibodies

Clinically, RA is a heterogeneous disease and there is a developing consensus that this condition is composed of at least two separate clinical subgroups that were initially characterized by the presence or absence of rheumatoid factor (RF) [70] and, more recently, by seropositivity for anti-cyclic citrullinated peptide antibodies (ACPA) [69]. ACPA is a family of IgG antibodies that recognize structural changes brought about by the post-translational modification of arginine to citrulline [71]. The importance of these antibodies has been recognized since the early 1990s when it became evident that their presence was the highest specificity for the presence of RA (between 87.8 and 96.4%) [72]. ACPA have

Table 1. Comparison of autoinflammation and autoimmunity as exemplified by TRAPS and RA as prototypes of these conditions.

Categories	TRAPS (autoinflammatory)	RA (autoimmune)
Factors determining disease manifestations	Innate immune activation Local tissue factors at disease-prone sites, including tissue trauma, necrosis, mechanical factors, bacteria or their constituent molecules	Adaptive immune activation Clinical disease expression determined by events taking place in primary lymphoid tissues, including bone marrow, the thymus, lymph nodes and spleen
Key theory relating to disease expression	Various danger signals with tissue-specific factors determining disease localization	Breakdown of immunological tolerance and aberrant self–nonself discrimination
Immunological basis	Genetically related to perturbations of innate immune function, including proinflammatory cytokine signalling/bacterial sensing/local tissue abnormalities	Acquired immune perturbation is key to disease expression: infiltration of RA synovium, proliferation of macrophage-like synoviocytes and fibroblast-like synoviocytes, and infiltration of inflammatory cells, including B and T lymphocytes, and dendritic cells
Cellular basis	Expression determined by cells of the innate immune system, including neutrophils and macrophages or nonimmune cells	An antigen-independent induction phase – expression is mainly determined by factors affecting B- and T-cell activity.
Genetic basis	Mutations in <i>TNFRSF1A</i> encoding TNFR1	Polygenic – susceptibility loci include <i>HLA-DRB1</i> and <i>PTPN22</i>
Disease heterogeneity	Mutation-positive TRAPS and mutation-negative TRAPS-like phenotype	ACPA+ – SE and <i>HLA-DRB1</i> ; ACPA- – <i>HLA-DRB1*03</i>
<p><i>Some of the key features that allow differentiation of a 'pure autoinflammatory disease' (TRAPS) from a 'pure autoimmune disease' (RA). The rare monogenic hereditary periodic fevers are the prototypic autoinflammatory diseases, whereas the prototypes for autoimmune diseases include the polygenic MHC- and autoantibody-related diseases, including RA, as well as some rare monogenic diseases.</i></p> <p>ACPA: Anti-cyclic citrullinated peptide antibodies; RA: Rheumatoid arthritis; SE: Shared epitope; TRAPS: TNF receptor-associated periodic syndrome. Adapted from [8].</p>		

a similar sensitivity to RF (69.6 and 77.5%) [72] and may be present in the blood for many years before the first manifestation of RA, with a risk of over 93% for individuals that present with swelling and articular pain of shortly developing RA [73,74]. The fact that the presence of ACPA can be detected years before the symptoms begin is a major advancement for the diagnosis of this condition. Several studies in early RA have demonstrated that radiological changes are more severe in the ACPA-positive group, suggesting an associated risk [75]. Autoantibody profiling showed an increase in ACPA-positive patients and a drop in RF-positive patients at follow-up compared with patients with early RA. The presence of RF and ACPA were associated with erosive disease [76].

However, the course of ACPA development is still relatively unclear. IgM ACPA is produced in the blood of both healthy controls and RA patients. By contrast, IgG ACPA is only found in RA patients, which may be indicative of an active immune reaction requiring T-cell help for the generation of highly specific IgG. An association between the presence of ACPA and smoking has also been established [77]. Conventional DMARDs and biologics used in rheumatological practice only induce a marginal reduction in ACPA titres.

■ Genetic susceptibility to RA

Studies of monozygotic twins in RA patients and multiplex family studies have produced evidence for inheritability of this disease, which has been calculated to be approximately 60% in British and Finnish populations [78]. RA has long been linked to the HLA chromosomal region located in the MHC on the short arm of chromosome 6 (6p21.3) (FIGURE 1) [79]. Genetic susceptibility has been mapped to the shared epitope (SE), located in the third hypervariable region of a set of alleles of the class II (*HLA-DRB1*) locus [80,81]. The *HLA-DRB1* genes encode the MHC class IIβ chain molecules that present antigen to CD4⁺ Th cells. The SE is a conserved sequence of amino acids found within the peptide binding pocket and is formed by MHC class II heterodimers, and alleles encoding the SE are specific for diseases characterized by antibodies to citrullinated peptides (ACPA-positive RA) [82]. Apart from the MHC susceptibility to ACPA-positive RA, RA has been linked to several other regions on different chromosomes and ACPA-negative RA has been associated with one–two genes [83].

PTPN22

PTPN22 encodes the protein tyrosine phosphatase nonreceptor 22 (PTPN22) and is the second susceptibility gene for RA, identified in

2004 [84]; the *PTPN22* 620W allele is also associated with a number of other autoimmune disorders such as T1D and SLE [85,86]. The *PTPN22* gene is not associated with RA susceptibility in Japanese or Korean populations [87].

Remarkable progress has been made in the genetics of RA through genome-wide association and candidate gene approaches. In 2007, the Wellcome Trust Case-Control Consortium study confirmed association of RA with *HLA-DRB1* and *PTPN22* as well as with nine other loci that demonstrated evidence of linkage [88].

TRAF1-C5

The *TRAF1-C5* locus encodes TNF receptor-associated factor 1 and complement component 5 (chromosome 9) and is associated with an increased risk of anti-cyclic citrullinated peptide (CCP)-positive RA; a genome-wide association study in US and Swedish populations reported the initial association with this locus and this was subsequently corroborated by a separate study [89,90].

STAT4

STAT4 encodes a transcription factor in the signaling pathway of several cytokines, including IL-12, IL-23 and type I interferons, and is involved in the production of IL-17 by Th-17 cells in response to IL-23. *STAT4*-dependent signaling may be involved in regulating the balance of Th-1 versus Th-17 responses. *STAT4* has been associated with both RA and SLE in American as well as Swedish case-control studies [91], and this has been subsequently confirmed in a Korean RA population [92]. There are some unique and revealing aspects of the *STAT4* association with RA. This is the first genetic variant, apart from the SE, that is clearly associated with RA susceptibility in both Caucasian and Asian populations, suggesting that this risk haplotype may be ancient and predate the divergence of the major racial groups. This is in marked contrast with the other risk genes for RA, such as *PTPN22* (associated with multiple autoimmune diseases in Caucasians only) and peptidylarginine deiminase 4 (*PADI4*; associated with RA in Asians but much less strongly, if at all, in Caucasians). There is also evidence for a gene-dosage effect, since homozygosity of the risk allele of *STAT4* was associated with a more than doubled risk for SLE and a 60% increased risk of RA.

Among the burgeoning numbers of other loci associated with RA are *OLIG3-AIP3* [89], the MHC class III region encoding for, amongst other genes, TNF and lymphotoxin [93], and

PADI4, which is associated with RA in Japanese and Korean populations [94,95] but is generally not replicated in Caucasians.

Genetic predisposition to ACPA-negative RA

ACPA-negative RA has been associated with the *HLA-DR3* allele, *HLA-DRB1*03*, in two independent studies [96,97]. Interferon regulatory factor 5 (*IRF5*), which was previously associated with susceptibility to SLE, was found to be a second risk factor for ACPA-negative RA in a Swedish and a Dutch cohort of patients [98], but this has not been confirmed in French and Spanish studies [99,100].

Role of B cells and T cells in the pathophysiology of RA

■ B cells

There is increasing evidence to support the involvement of B cells in autoimmunity and in RA. The inability to control self-reactive B cells is one of the mechanisms involved in the pathogenesis of RA [101]. Much of the supporting evidence comes from the observed improvement in patients treated with B-cell depletion therapy in clinical trials [101–105]. However, the underlying mechanisms are not currently clear, but it is believed that there may be one or more breaches in the ‘check-points’ of B-cell tolerance [105]. The rituximab studies provide strong evidence to suggest that the mechanisms involved in removing self-reactive B cells are defective before these cells enter the mature cell pool [106,107].

■ T cells

The role of T cells has been demonstrated in animal models of arthritis, such as adjuvant-induced arthritis, which is T-cell dependent, and collagen-induced arthritis, which does not develop in mice lacking T cells [108]. In addition, targeted deletion of lymphotoxin- α -positive Th-1 and Th-17 cells suppressed collagen-induced arthritis in mice [109]. Lymphotoxin- α (along with *DRB1*03*) is encoded within the region of MHC class III which is part of the ancestral haplotype that has been associated with RA susceptibility [84]. However, there are marked differences between RA and animal models and evidence of a central role for T cells in RA is more circumstantial. T-cell depletion from synovial tissues is a recognized feature of therapeutic response [110]; however, RA synovial T cells are more quiescent than activated T cells and do not produce cytokines in abundance. The synovial infiltrate is composed of approximately 30%

T cells, which are predominantly of the Th-1 population and are found in a perivascular location. It is thought that the main effect of T cells in RA is to potentiate the autoimmune response and activate B cells (thereby promoting autoantibody production) in cooperation with macrophages, dendritic cells, synovial cells and fibroblasts. In addition, T cells interact with osteoclasts, ultimately promoting the development of angiogenesis, and they ultimately the destruction of bone and cartilage. RA synovitis is characterized by the activation of deleterious T cells, predominantly Th-1 and Th-17 cells, and an increased production of proinflammatory cytokines [111]. These recently identified Th-17 cells may have a role in driving disease chronicity and there is a reduced suppressive capacity of 'natural' regulatory T cells (Tregs) in patients with active RA [112]. However, suppressive function may be restored by anti-TNF therapy and the Th-17/Treg balance was demonstrated to shift in favor of Tregs, thereby re-establishing immune tolerance [113]. There is also emerging evidence that conversion of Tregs into Th-17 cells may be induced by IL-1 β [114].

■ Environmental associations

Studies on identical twins demonstrated that only 60% of both twins develop RA [79]. These studies clearly indicate that some environmental or other nongenetic factors must be at play in the susceptibility of RA. Caffeine, cigarettes, obesity and high birth weight have been associated with increased risk, whilst tea, a 'Mediterranean diet', breast feeding and alcohol are linked with decreased risk [115]. However, only cigarette smoking has now been established as one of those environmental factors that has a clear relationship with ACPA-positive RA onset [116–118].

■ Undifferentiated arthritis

It is crucial to understand the biological differences between the different stages of RA, including the preclinical stage, in order to develop novel strategies and use them effectively. Undifferentiated arthritis (UA) has been defined as any arthritis that has the potential to progress to a persistent course without fulfilling the classification criteria for specific rheumatic disorders [119]. The prognosis of patients with UA may vary from self-limited to severe destructive RA. Emerging evidence suggests that intervention can halt the progression of UA to RA. Recent evidence suggests that UA is a disease in evolution, the outcome of which can be influenced by early identification and treatment [120–122].

Furthermore, RA is, in many cases, the end result of an evolving process, and strong evidence exists for a therapeutic 'window of opportunity' in ACPA-positive UA patients, which may postpone the development of RA [123]; and finally, remission is achievable at early stages for all disease subtypes [124,125]. Various studies have reported that 6–55% of patients with recent onset arthritis who presented with UA progressed to RA, according to the American College of Rheumatology classification criteria, or according to the rheumatologist [119]. The presence of ACPA antibodies, polyarthritis, symmetric arthritis and erosions on radiographs were demonstrated to predict the development of RA; anti-CCP has the highest specificity and predictive value for RA [126].

■ Treatment of RA

NSAIDs and simple analgesics are used to relieve pain and stiffness in the early stages of RA. DMARDs, which reduce erosive damage, are also initiated as early as possible. Some commonly used DMARDs include methotrexate, which is the most widely used, sulfasalazine, hydroxychloroquine (Plaquenil, Winthrop Pharmaceuticals, Division of Sterling Drug, Inc. [New York, USA]) and cyclosporine (Sandimmune[®], Novartis [Basel, Switzerland]). Combinations of two or more DMARDs are often used in severe RA [127] and steroids (intra-articular, intramuscular or oral) may be used to manage disease flares.

The ultimate goal in treating RA is to produce remission or, at least, very low disease activity. The introduction of targeted treatments using biologics response modifiers (biologics or biologicals) has radically changed the management of RA patients and new insights into joint immunopathology have emerged from use of these therapies. TNF inhibitors are usually given to patients with active RA in whom the response to one or more conventional DMARDs, such as methotrexate, has been unsatisfactory [128]. The remarkable, and somewhat unexpected, success of TNF inhibition in RA [129] points to perturbations of innate immune function, even in established RA, since TNF is mostly secreted by macrophages.

Although much progress has been made in managing this condition, particularly with the introduction of biologics over the past 15 years or so, the incidence of true remission in RA is still less than approximately 40% in most patients, especially in those reported from large registries [130]. Of the other 60%, approximately a third are defined as nonresponders (European League

Against Rheumatism criteria), and the remaining two thirds are moderate or partial responders [130]. Furthermore, patients lose response over time (secondary failure or acquired therapeutic resistance) or experience adverse events owing to treatment.

Among the proposed mechanisms of action of TNF inhibitors, such as infliximab and etanercept, are the neutralization of soluble TNF and reverse signaling through membrane TNF, where membrane TNF acts as a receptor to reverse the signal, with additional effects on cytokine regulation, cell recruitment and reduction of angiogenesis [131]. A new generation of biologics with novel targets has been developed and these include rituximab (Mabthera®, Roche [Basel, Switzerland]), a chimeric monoclonal antibody to CD20 on the surface of B cells, tocilizumab, an IL-6 receptor inhibitor, and abatacept, an immunoglobulin fused to the extracellular domain of CTLA-4.

B-cell-targeted therapy using rituximab has been demonstrated to significantly inhibit the progression of structural joint damage in RA patients with long-standing, active and treatment-resistant disease [101]. Abatacept (anti-CTLA-4) blocks the interaction between antigen-presenting cells and T cells, thereby diminishing T-cell activation and possibly improving overall cell regulation. Abatacept is effective in decreasing the pain, disability and radiological joint damage and provides lasting remission or low levels of disease activity in selected patients [132].

IL-6 receptor inhibition therapy using tocilizumab has also been successful in anti-TNF biological failures, suggesting that a different disease mechanism may be operative in these patients [133]. The mechanism(s) of response and nonresponse to biologics remains unclear, indicating that there is a major unmet need. Understanding the basis of nonresponse in RA is necessary for the development of an effective treatment algorithm. These challenges are coupled with the changing place of biologics. It is apparent that a window of opportunity exists in the early stages of RA, during which intensive treatment may produce remission [134]. Furthermore, in UA and early inflammatory arthritis, spontaneous remission occurs in 40–50% patients while approximately 30% go on to develop RA [135]. The new biologics constitute a valuable addition to the current therapeutic armamentarium for RA, and it is hoped that full remission will be an attainable goal for the overall population of RA patients in the foreseeable future.

There are a number of on-going clinical trials on anti-IL-17 biologics (e.g., LY2439821 from Eli Lilly [IN, USA] and AIN457 from Novartis) in RA patients. Preliminary data showed promising results with reported symptomatic improvement [136,137]. However, until clinical studies involving large numbers of RA patients are carried out, the position of anti-IL-17 therapy remains to be defined. In addition, these treatments only focus on Th-17-controlled inflammatory pathways, which may produce rather modest clinical effects owing to the limited numbers of IL-17-secreting cells in tissues and the reported overlap with the effects of TNF [138].

It is important to treat a specific target in RA patients, just as glycosylated hemoglobin (hemoglobin A1c) has been used to assess control of blood sugars in T1D. The disease activity score is a combined index that has been developed to measure the disease activity in patients with RA; among other objective measurements of response to therapy are the multidimensional health assessment questionnaire, the simplified disease activity index and the clinical disease activity index.

Future perspective

In the next 10 years, whole-genome screening will continue to unravel the complex genetics of RA, and genome sequencing of newborns may become established. Increased understanding of the mechanistic basis of the genetics of RA and the function of synovium, bone and cartilage in the pathogenesis of RA will enable safer therapies. Improved molecular imaging will allow visualization of intracellular functions with improved understanding of the pathophysiology of both TRAPS and RA. Pharmacogenomics will assist in the diagnosis and management of early undifferentiated arthritis. We anticipate that modulation of the immune system through network regulation (e.g., by microRNA) and gene therapy, rather than biologics, will lead to disease control in the majority of cases.

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Executive summary

- TNF receptor-associated periodic syndrome (TRAPS) is an autoinflammatory disease owing to mutations in the *TNFRSF1A* gene.
- Rheumatoid arthritis (RA) is a complex polygenic autoimmune disorder that is composed of at least two separate clinical subgroups.

Pathophysiology

- The inflammation of TRAPS is mostly innate immune-mediated.
- RA is a disorder of both innate and adaptive immunity.
- The main clinical subgroups of RA are characterized by the presence or absence of autoantibodies, such as rheumatoid factors and anti-cyclic citrullinated peptide antibodies.
- Cigarette smoking has now been established as one of the environmental factors that has a clear relationship with RA onset.

Therapy

- Anti-TNF therapy may be effective in both TRAPS and RA.
- Etanercept treatment may be successful in alleviating the symptoms of TRAPS, but prophylactic administration of etanercept is less successful. More recently, the anti-IL-1R antagonist drug, anakinra, has also been used for TRAPS.
- The new biologicals constitute a valuable addition to the current therapeutic armamentarium for RA, and it is hoped that full remission will be an attainable goal for the overall population of RA patients in the foreseeable future.

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