Mechanistic immunological based classification of rheumatoid arthritis

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\textbf{ABSTRACT}

The classical autoimmunity paradigm in rheumatoid arthritis (RA) is strongly supported by immunogenetics suggesting follicular helper T-cell responses driving high titre specific autoantibodies that pre-dates disease onset. Using the immunological disease continuum model of inflammation against self with “pure” adaptive and innate immune disease at opposite boundaries, we propose a novel immune mechanistic classification describing the heterogeneity within RA. Mutations or SNPs in autoinflammatory genes including MEFV and NOD2 are linked to seronegative RA phenotypes including some so called palindromic RA cases. However, just as innate and adaptive immunity are closely functionally integrated, some ACPA+ RA cases have superimposed “auto-inflammatory” features including abrupt onset attacks, severe attacks, self-limiting attacks, relevant autoinflammatory mutations or SNPs and therapeutic responses to autoinflammatory pathway therapies including colchicine and IL-1 pathway blockade. An emergent feature from this classification that non-destructive RA phenotypes, both innate and adaptive, have disease epicentres situated in the extracapsular tissues. This mixed innate and adaptive immunopathogenesis may be the key to understanding severe disease flares, resistant disease subsets that are unresponsive to standard therapy and for therapies that target the autoinflammatory component of disease that are not currently considered by expert therapeutic recommendations.

1. Background

The common clinical phenotype characterised by non-infectious persistent polyarticular swelling, especially of small joints, that leads to bone erosion and progressive joint destruction and deformity is known as rheumatoid arthritis (RA) \cite{1}. However, persistent periarticular synovitis irrespective of the immunopathogenesis is associated with joint erosion and destruction- so irrespective of the immune trigger the same clinical phenotype emerges \cite{2}. A logical extension of this view is that immunologically diverse scenarios may be associated with the clinical RA phenotype. An unmet need exists in the translational setting to develop a robust paradigm for the assessment, diagnosis and prognostication in patients that present with polyarthritides that is suggestive of early RA, especially in the current era where the primary role of innate immunity or autoinflammation is well recognised in other chronic inflammatory diseases \cite{3}. Using the paradigmatic shift that occurred following the description of autoimmunity against citrullinated antigens in many RA cases \cite{4}, we propose a novel classification for the full clinical disease spectrum of RA (Fig. 1). This immunological disease continuum model of inflammation in RA \cite{5}, has implications for therapeutic strategies (Fig. 1).

2. Classical autoimmune RA

The recognition that anti-citrullinated protein antibodies (ACPA) predate clinical RA in the majority of cases permitted disease classification in subjects with limited joint swelling \cite{6,7}. That ACPA+ RA represents a distinct entity that is strongly vindicated by genetic studies demonstrating numerous genetic polymorphisms related to B and T cells including MHC-II associations with such autoantibody positivity \cite{8,9}. Indeed, that ACPA+ disease is strongly associated with multiple genetic abnormalities including PTPN22, CTLA4, CD40 and others that firmly point towards genetic effector mechanism upstream of the joint in the lymphoid organs \cite{10}. The preferential response of ACPA+ RA

\textbf{Abbreviations:} NLRP3, NOD-like receptor 3; RA, rheumatoid arthritis; SJIA, systemic juvenile idiopathic arthritis; AOSD, adult onset stills disease; PMR, polymyalgia rheumatica; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; OA, osteoarthritis; ACPA, antibodies to citrullinated protein antigens; CTLA-4, cytotoxic T-lymphocyte-associated protein 4

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to B cell depletion therapeutically validates the autoimmune model [11,12]. The co-occurrence of RF and ACPA+ status and worse prognosis RA is conceptualised in terms of immune complex activation by RF agglutination of ACPA+ immune complexes that lead to an increase of pro-inflammatory cytokine production including TNF [13,14].

The preclinical phase in this autoimmune category of RA is related to emergent synovitis, the synovium being considered the primary joint target based on ultrasound, MRI and arthroscopic assessment [15,16]. The extra-articular disease features including nodulosis and lung involvement are also understood in terms of protein citrullination, immune complex formation at sites of either macrophage infiltration or residence in the extra-synovial structures [17]. Recently, it has become evident that ACPA are not the only autoimmunity players in RA and emerging evidence for anti-CarP as important autoantibodies in RA but these are usually present simultaneously with ACPA [18]. As in other autoantibody associated diseases, the natural history of RA is characterised by persistent inflammation until the target organ is completely destroyed [19]. Whilst RA may go into spontaneous remission this is much less likely to occur in the ACPA+ or RF+ subgroup [20].

3. Other autoimmune forms of RA

Several other RA associated antibodies against modified protein antigens that predate clinical disease, including the aforementioned anti-carP autoantibodies, have been described thus supporting the idea that early key events in the primary and secondary lymphoid organs that house the adaptive immune system likely drive disease [21–23]. An ANA positive RA group without ACPA/RF is occasional reported [24] (Fig. 1). This is strongly associated with anti-RA 33 antinuclear antibodies with a specificity of for RA of 84.6%, and in the absence of anti-U1-RNP antibodies, can be used as a serological marker for RA [25] (Fig. 1).

Rheumatoid arthritis-like polyarthritis may be a feature of SLE and other connective tissue diseases (CTDs) including dermatomyositis and systemic sclerosis and undifferentiated CTDs (UCTDs) [26]. Sometimes a proportion of such cases fall under the “rhuspus” umbrella [24,27]. This is viewed as an overlap type of disease or a form of UCTDs with predominant RA pattern. In a patient presenting with ANA positive synovitis, it is only with time that it may be possible to definitively diagnose another category of arthritis (Fig. 1). On conventional radiography, ANA positive RA-like polyarthritis may evolve into a severe deforming arthropathy but with minimal erosion termed Jaccound's arthropathy. The basis for the generally less X-ray erosive phenotype of SLE has been poorly understood [28–30], although recent MRI studies also indicate a large burden of erosive disease in SLE [31].

4. Monogenic autoimmune rheumatoid arthritis

The immunological disease continuum model placed monogenic forms of diseases at the two boundaries of pure autoimmune and pure autoinflammatory disease (Fig. 1). At the present time, there is remarkably little evidence for monogenic autoimmune RA. Possibly the best illustrative example of monogenic autoimmune RA is cytotoxic T lymphocyte antigen-4 (CTLA-4) haploinsufficiency. CTLA-4 helps to control the magnitude of T cell activation and is also expressed on Tregs where it is a key functional determinant of functional regulatory activity. Patients with heterozygous autosomal dominant mutations in CTLA-4 develop immune dysregulation and immunodeficiency syndrome due to reduced expression of functional CTLA-4 [32]. Recently, a detailed description of 133 CTLA-4 mutation carriers, of which 90 individuals were thought to be clinically affected has been published [32]. This condition has a variable penetrance and the disease onset varies between early childhood from age of 1 year to age of 59 with the median age of 11. Interestingly, 3% had arthritis at the time of presentation, with one bone fide RA case, and overall arthritis was seen in 14% of patients. These findings are in keeping with a notion that single gene defects affecting T cell tolerance might predispose to development of RA, but this remains contentious given that the background
prevalence of RA is in the same range. Variants of NOD2 have also been associated with a sporadic inflammatory arthritis than can be usually differentiated form typical patterns of RA on clinica grounds [114].

5. Historical lessons showing innate immunity in RA pattern disease

The concept of immunological disease heterogeneity within RA was originally derived from the meticulous clinical observations by Bywaters when he defined Adult onset Still’s Disease (AOSD) [33]. He built a case stating that subjects with ASOD suffered from the paediatric equivalent of Stills Disease (a type of juvenile rheumatoid arthritis). Moreover, amongst other things, ASOD cases were RF negative and the associated polysynovitis sometimes resolved spontaneously and without joint destruction. Demonstrating scholarly foreknowledge, Bywaters even commented that the spectrum of ASOD may merge with a then little known entity called the Muckle-Wells syndrome (MWS) [33]. Nowadays, joint inflammation in MWS is known to result from gain of function mutations in the NLRP3 inflammasome leading to constitutive hypersecretion of activated IL-1β with MWS being classified as monogenic autoinflammatory diseases representing primary innate immune dysregulation [34,35]. These comparative clinical phenotypes between RA and polyarticular ASOD clearly define the previously hidden heterogeneous nature of RA- a heterogeneity that until now has not been exploited in the classification of RA. According to the genetically based mechanistic classification of inflammation against self, we conceptualised the heterogeneity of RA along an immunological disease continuum with some categories of RA were in fact more likely to be driven by innate immunity and sit along a disease continuum of separate clinical entities (Fig. 1) [5].

6. Monogenic autoinflammatory RA

Unlike adaptive immune mediated RA, the evidence for monogenic autoinflammatory arthropathy manifesting as RA is much more compelling. For example, familial Mediterranean fever (FMF) is mainly an autosomal recessive Mendelian condition and an archetypal autoinflammatory related to mutations in the MEFV gene leading to gain of function in the pyrin protein that leads to aberrant activation of multimeric protein complexes called inflammasome which is expressed predominantly in neutrophils where it regulates inflammatory response [36–38]. Moreover, heterozygous mutations in the MEFV gene were strongly associated with seronegative RA in a Spanish cohort [39]. This finding supports that the MEFV gene might participate in the pathogenesis of other undifferentiated relapsing inflammatory rheumatic disorders [40].

Blau’s syndrome is a monogenic autoinflammatory autosomal dominant disease that may lead to a destructive RA like polyarthritis especially in the paediatric population where recognition as a distinct entity is facilitated by granulomatosis uveitis and skin disease [41,42]. The mutation underlying this RA-like phenotype is in NOD2 which is an intracellular NLR family receptor for bacterial cell wall constituent muramyl dipeptide and it is evident that most of this group with RA pattern polyarthritis lack ACPA antibodies [43–46].

7. The wider spectrum of seronegative RA

In the region of 20–40% of RA cases are ACPA negative [47]. Allowing for the fact that some seronegative RA cases may have an undefined relevant autoantibody, there is accumulating evidence suggesting that non-Mendelian seronegative RA diverges from the classical ACPA+ disease at multiple levels including the micro-anatomical basis for disease (Fig. 2), genetic architecture, cellular pathology and even therapeutic responsiveness [48–50]. The immunological disease heterogeneity in seronegative RA is supported by clinical outcomes in patients developing polyarthritis can be extremely variable especially in those with antibody negative disease who may have a better prognosis [51,52].

Likewise, diseases including gout and pseudogout that can be misdiagnosed as RA have been linked at the molecular level to NLRP3 inflammasome activation [53]. Indeed, seronegative RA has a higher burden of tissue urate acid crystal deposition compared to antibody positive disease [54]. Taking cognizance of the fact that uric acid crystals are powerful activators of the NLRP3 inflammasome supports the idea that such IL-1β mechanisms might contribute to RA [55].

A small joint polysynovitis can occur in patients with psoriasis and in patients whose first degree relatives have psoriasis [56]. These are defined as psoriatic arthritis (PsA) and the vast majority of this group are ACPA-negative indicating that they are not merely RA and co-incidental psoriasis, a chance finding in the 1/10000 of the population assuming a prevalence of 1% for RA and 2% for PsA [57]. At the population level this small joint polysynovitis group are associated with clinically unrecognised enthesitis in the swollen joints [58]. However, this is not sufficiently common to be diagnostically useful but points towards an anatomical similarity. That common genetic associations might contribute to these phenotypes is supported by the fact that TNFAP3 encoding for the A20 protein, a NF-kB regulatory protein is associated with both PsA and RA [59]. However, at the present time, the only clearly defined difference is the presence of autoantibodies in RA and the anatomical level differences centered on the enthesis in PsA [58].

Polyarticular rheumatica (PMR) may present with an RA pattern in the elderly and it is characterised by polysynovitis [30,60]. However, it typically has an abrupt onset and an ultimately good prognosis but on occasion can be hard to tell from RA in “polyarticular onset of RA” [61,62]. Like in elderly patients with sudden onset polyarthritides, physicians may suspect a PMR type disease and consequently use low dose steroids without consideration for disease-modifying anti-rheumatic drugs (DMARDs) therapy. A scholarly evaluation of PMR recently suggested that at the population level it sits closer to the innate immune boundary of the immunological disease continuum [63]. Furthermore, a clinicopathological entity termed remitting symmetrical seronegative synovitis with pitting oedema (RSSPE) has features of RA but may ultimately have a good prognosis with an excellent therapeutic response to low dose steroids [64,65].

8. Autoimmune-autoinflammatory overlap RA

In addition to population level differences in predominant autoimmune or predominant innate immune mechanisms in the RA spectrum, a more complex interplay between both facets of the immune system in disease expression, especially for clinically recalcitrant cases is now starting to emerge. Recently we reported 5 cases of seropositive inflammatory arthritis case with the DRB1 shared epitope, who met the EULAR/ACR diagnostic criteria for RA but who simultaneously exhibited unusual clinical phenotypes resembling autoinflammatory disease [66]. They all had abrupt onset of synovitis with associated joint erythema, excellent response to colchicine or IL-1 pathway antagonism but poor response to conventional DMARDs. Mutations or SNPs in the NLRP3, MEFV or NOD2 gene were evident in all but one of these cases. Furthermore, a previous case of concomitant Muckle-Wells syndrome and ACPA+ RA has been reported in the literature [66].

Beyond the genetics, the effect of the autoinflammatory pathway and NLRP3 is quite pervasive in RA [67]. For example, NLRP3 synovial expression correlates with the clinical and radiological arthritis severity in the collagen-induced model of arthritis [68]. In human studies, the genetic variation in NLRP3 inflammasome components as well as NLRP3 inflamasome activity have been shown to influence the susceptibility and severity of RA and response to conventional DMARDs and TNFi therapy [69,70]. Also, in a joint immunology-rheumatology autoinflammatory disease clinic we noted that some subjects previously designated as seronegative RA whom we re-designated as undefined
systemic autoinflammatory disease exhibited good responses to IL-1 pathway antagonism [71].

9. Haploinsufficiency of A20 (HA20)- a unique link between autoinflammatory and autoimmune RA

HA20 is a recently discovered monogenic autoinflammatory disorder resulting from high-penetrance heterozygous mutations in TNFAIP3, which encodes the NF-κB regulatory protein A20 [72]. The resulting haploinsufficiency of A20 is associated with inadequate inhibition of NF-κB pathway and excessive production of several pro-inflammatory cytokines. However, unlike other monogenic autoinflammatory disorders, HA20 seems to be associated with broad clinical phenotypes, ranging from typical autoinflammatory conditions such as JIA to more traditional autoimmune diseases such as SLE [73]. We have recently described a family with a novel splicing mutation in TNFAIP3, which encodes the NF-κB regulatory protein A20 [72]. The resultant haploinsufficiency of A20 is associated with inadequate inhibition of NF-κB pathway and excessive production of several pro-inflammatory cytokines. However, unlike other monogenic autoinflammatory disorders, HA20 seems to be associated with broad clinical phenotypes, ranging from typical autoinflammatory conditions such as JIA to more traditional autoimmune diseases such as SLE [73]. We have recently described a family with a novel splicing mutation in TNFAIP3, which encodes the NF-κB regulatory protein A20 [72].

Fig. 2. Microanatomical basis for the spectrum of RA phenotypes.

Although different anatomical structures and cells are involved in RA pathogenesis, resident macrophages play the key role, maintaining the integrity of joints in healthy subjects whereas in RA patients they exhibit pathological effects. Pathological processes taking place in the juxta-articular tissues, capsule, synovium or within fluid and cartilage may lead to macrophage activation and then predictable periarticular destruction and the RA phenotype. The role of stromal cells as key initiators in RA phenotypes awaits further study. The ACPA+RF+ group have the most severe and persistent inflammation and exhibit the most destructive phenotype.

Note: A- Cartilage, B- Bone, C- Capsule, D- Fascia, E- Dermis and Epidermis.

10. Microanatomy considerations that may help to explain RA phenotypes

The immunological disease continuum model places an emphasis on the microanatomical basis for disease localisation (Fig. 2). Remarkably, there is evidence for anatomical compartmentalisation for both autoinflammatory spectrum and autoimmune RA that are linked to the likelihood of destructive joint phenotypes based on intra-synovial or extracapsular involvement. MRI studies have confirmed prominent capsular based inflammation in some ANA positive polyarthritis cases which is very distinct from ACPA+ disease where disease involvement is typically synovium centric [29,80]. This ANA positive category of RA like disease, therefore, may have a distinct anatomical territory of inflammation focussed on the extracapsular tissues. Indeed, these extra-synovial signs of soft tissue pathology and less bony alterations help explain Jaccoud's arthropathy phenotypes from classical forms of erosive RA disease [80]. This anatomical compartmentalisation is also evident in the RS3PE variant of RA which is also capsular based, but not deforming and thought to be more autoinflammatory in nature since it is a benign self-limiting polyarthritis [81]. Hence an anatomical epicentre of inflammation outside the synovial cavity may give clinical joint swelling but without necessarily the joint destruction typical of the classical ACPA+ RA.

11. Clinical considerations for early RA classification

In the clinical setting, there are many features of RA in addition to the diagnostic criteria that may influence a physician’s approach to disease therapy [82]. For example, patients that are autoantibody negative generally have less destructive disease [83-85]. An acute onset
of disease may be associated ultimately with a good prognosis (Table 1). In a patient with a sudden onset polyarthritis it may not be possible to identify a specific viral trigger hence physicians may adopt a wait and see approach.

12. Interplay between innate and adaptive immunity in the pathogenesis of ACPA+ RA

As stated there is limited evidence for monogenic forms of pure autoimmune RA in the literature. Clinical observations including the non-placental transfer of RA strongly argue against a classical autoimmune disease that is dependent to cardinal events occurring in the primary and secondary lymphoid organs, with a subsequent attack on a completely normal tissue [19]. Although autoimmune in nature, we originally placed RA closer to the innate immune boundary than other classically recognised autoimmune diseases [5]. It is now thought that the initial phases of RA occur outside the primary and secondary lymphoid organs with non specific inflammation, likely prominent innate immune related protein citrullination and other post-translational modifications taking place at sites of tissue inflammation most notably the periodontal tissues [86] and lungs [87] but other sites including the gut and indeed the joint tissues themselves [8], where presumed inflammation related citrullination may occur in OA [88–90]. These initiating events rather than dysregulated central tolerance mechanisms likely culminate in shared epitope positive T-cells driving B-cell responses as indicated by higher titre autoantibodies is shared epitopes (SE) alleles positive disease [91]. After disease localisation to the joints, local amplification of the autoimmunity occurs with higher titre pathogenic antibodies consequent to the B cell and plasma cell protected by synovial niches [89,92]. Finally, this process boomerangs back onto innate immunity with citrullinated immune complexes activating Fc receptor mediated myeloid cell activation and pivotal innate cytokine production (Fig. 3) [92]. Consequently, for the classical autoimmune form of RA there is ample non-specific innate immune activation contributing to the initial events in post-translational protein modifications at the outset and innate immune cell activation in the final effector phase [93]. Beyond the recently recognised autoinflammatory genes that could modify the classical autoimmune RA phenotype [94], a myriad of other environmental, epigenomic and microbial factors may influence disease [95–97]. Translational immunology observations where TNF is effective in autoimmune RA [98] but not in other autoimmune humoral mediated diseases is consistent with this important innate immune component in driving this autoimmune disease.

13. Fibroblast-like synovitis in RA

Stromal cells including synovial intimal fibroblasts, subsynovial fibroblasts and mesenchymal stem cells are abundant in the RA joint and could also constitute local tissue specific auto-inflammatory mechanisms contributing to joint inflammation [99]. A role for stromal cells in chronicity of autoimmunity is strongly suggested [100] but a direct role for a primary fibroblastic autoinflammatory RA phenotype is not sufficiently established for inclusion in the classification scheme at this time (Fig. 1). However, in animal models, a specific role for stroma related joint destruction, ostensibly independent of T and B cells was demonstrated nearly 3 decades ago [101]. There is also evidence that some cases of RA polyarticular synovitis have a fibroblastic tissue composition rather than the classical inflammatory component [102]. Studies are ongoing to determine whether such a phenotype might be linked to therapy responses in RA and whether it supervenes on chronic autoimmune ACPA+ RA or where it might represent a polyarticular autoinflammatory disorder [103].

14. Therapeutic implications

A strong isolated autoinflammatory component or shared with classical autoimmune RA may respond to agents such as colchicine or interleukin-1 pathway blockade (Fig. 4). Indeed, in the clinical trial program with IL-1 blockade, a subgroup of patients had impressive ACR70 responses, which has never been fully understood [104], and in another study the percentage of responders according to ACR50 was significantly higher in those treated with canakinumab than placebo [115]. In the AOSD group the efficacy of anakinra points towards a fundamentally different pathology from autoimmune RA where such therapy does not work to the same degree [105]. Therefore, in cases of RA which conventional therapy is not effective, genotyping is abnormal and clinical features of autoinflammatory disorders it is worthy to consider agents that target the innate immunity such as colchicine, IL-1 antagonists or in the future potentially IL-18 blockers given that such strategies are used in AOSD [106–111]. Therefore, therapeutic studies clearly show that diseases under the historical uniform umbrella of “RA” clinically, genetically and therapeutically fit into the autoinflammatory spectrum, even though the genetics of AOSD remain poorly defined (Fig. 4).

A significant proportion of sporadic MWS patients have somatic NLRP3 mutations with a variable degree of mosaicism [112]. It is therefore possible that somatic mutations in key autoinflammatory genes could also occur in autoantibody positive RA and profoundly influence the disease phenotype. Indeed, genetically NLRP3 and other autoinflammatory related gene SNPs have been reported in RA and therefore might impact the joint involvement in such diseases leading to RA-like disease (Fig. 5) [67]. Beyond NLR and RA, studies have also reported the role of TLR2 and TLR4 function in RA pathogenesis, thus, TLRs may be future potential therapeutic targets for RA [113]. Although autoinflammatory or innate immune mechanisms are clearly operational in classical autoimmune RA, the failure to anti-IL-1 therapy
Fig. 3. Innate immunity in classical ACPA+ RA.
This figure shows how classical autoimmune related RA actually has pivotal tissue-specific innate immune events taking place in extra-articular and articular tissues in the form of non-specific protein citrullination at sites of inflammation including the lungs, mouth, gut and joint. The biology of the adaptive immune system and MHC-II related follicular T cell help for B cells and high titre autoantibody production is well understood and represents the cornerstone autoimmune mechanism in most RA cases. This adaptive immunity is sandwiched between the aforementioned tissue specificity and subsequent innate immune activation due to the effect of immune complexes formation and interaction with myeloid lineage innate immune cells with resultant pro-inflammatory cytokine production. 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.

Fig. 4. How therapy helps to classify RA subgroups.
Classification of RA according to the immunological disease continuum and the various components involved is reflected in differential therapeutic targeting. Given the strong link between autoinflammatory RA and inflamasomes and the lack of dependence of IL-1 signaling on JAK-STAT pathway then it is unlikely that what is considered pure autoinflammatory RA will respond to this pathway. 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.

Abbreviations: MMF, mycophenolate mofetil; BAFF, B-cell activating factor; BP, IL-18BO, IL-18 binding protein; JAKi, JAK inhibitors; TNF, tumour necrosis factor; DC, dendritic cells.
15. Conclusions

with canakinumab attests to the population level predominance of autoimmune mechanisms.

The existing clinical classification criteria for RA are partially based on the adaptive immunity pathogenesis disease component including RF and ACPA. The immunological disease continuum based classification described herein is relevant for therapy stratification for different disease groups. The mechanistic immune classification has implications for understanding the complexity of RA and for thinking about therapy in an immune centric way. It relies on clinical features of disease to help identify heterogeneity within the disease.

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Fig. 5. The interaction between innate and adaptive immune system genetics in RA. Mutations/SNPs in both innate and adaptive immune system are involved in RA disease evolution from pre-clinical to early RA and even in chronic established disease.
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