Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis

Maya H. Buch[1,2,3]✉, *Stephen Eyre*[1,2] *and Dennis McGonagle*[3,4]

Abstract | Despite nearly three decades of advances in the management of rheumatoid arthritis (RA), a substantial minority of patients are exposed to multiple DMARDs without necessarily benefitting from them; a group of patients variously designated as having 'difficult to treat', 'treatment-resistant' or 'refractory' RA. This Review of refractory RA focuses on two types of patients: those for whom multiple targeted therapies lack efficacy and who have persistent inflammatory pathology, which we designate as persistent inflammatory refractory RA (PIRRA); and those with supposed refractory RA who have continued disease activity that is predominantly independent of objective evidence of inflammation, which we designate as non-inflammatory refractory RA (NIRRA). These two types of disease are not mutually exclusive, but identifying those individuals with predominant PIRRA or NIRRA is important, as it informs distinct treatment and management approaches. This Review outlines the clinical differences between PIRRA and NIRRA, the genetic and epigenetic mechanisms and immune pathways that might contribute to the immunopathogenesis of recalcitrant synovitis in PIRRA, and a possible basis for non-inflammatory symptomatology in NIRRA. Future approaches towards the definition of refractory RA and the application of single-cell and integrated omics technologies to the identification of refractory RA endotypes are also discussed.

[1]*Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK.*

[2]*NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester University Foundation Trust, Manchester, UK.*

[3]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.*

[4]*NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK.*

✉*e-mail: maya.buch@manchester.ac.uk*

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Despite advances in the management of rheumatoid arthritis (RA) that have been made over the past 30 years and the availability of effective targeted synthetic DMARDs (tsDMARDs) and biologic DMARDs (bDMARDs), treatment non-response remains an ongoing clinical challenge that can result in treatment-resistant RA[1]. The goal of treatment with existing conventional synthetic DMARDs, tsDMARDs and bDMARDs in RA is the complete abrogation of inflammation. The inability to achieve this goal leads to successive cycling of therapies (BOX 1). Increasingly, the term 'refractory' RA is being used to describe disease that is resistant to multiple DMARDs[2], yet what comprises refractory RA lacks consensus.

In this Review, we discuss the challenges of defining refractory RA and the current literature on the extent and burden of the condition. We posit that refractory RA consists of two overlapping subtypes on the basis of whether symptomatology persists in the presence or absence of inflammation, and that these subtypes have relevance for management strategies. Having defined these subtypes, we examine the heterogeneous overlapping innate and adaptive mechanisms of RA, as well as interrelated factors such as smoking, epigenetic factors and potential somatic mutations, that could contribute to the persistence or evolution of immune responses and ongoing inflammation in individuals with persistent synovitis. We also discuss how perturbations in the joint microenvironment and subtle emergent immune mechanisms linked to pain might contribute to ongoing symptomatology in individuals with little or no discernible inflammation. Finally, we provide some thoughts on how the challenges surrounding refractory RA might be addressed in the future.

Defining refractory RA

Refractory RA is often used interchangeably with 'difficult to treat' RA[3], a working definition of which was provided by a EULAR task force in 2020 (REF.[4]). As illustrated in the results of a survey published in 2018 (REF.[5]), the term difficult-to-treat RA can have a wide variety of interpretations; however, a common theme is the exposure of patients to (but not necessarily a lack of efficacy of) several advanced therapies. Typical reasons for exposing a patient to several DMARDs can include multidrug toxicity and concerns around the safety profiles of complex immunosuppressive therapies in patients with comorbidities (not necessarily directly related to RA).

Key points

- The term refractory rheumatoid arthritis (RA) implies treatment-resistant persistent joint and/or systemic inflammation; however, it is often used interchangeably with broader definitions such as 'difficult to treat' RA.
- Refractory RA could be stratified into two major categories; persistent inflammatory refractory RA (PIRRA), in which unabated inflammation is evident, and non-inflammatory refractory RA (NIRRA), which lacks discernible inflammation.
- Within the category of PIRRA, serological status and HLA associations can provide meaningful stratification that can inform potential therapeutic avenues.
- Epigenetic modifiers, including methylation, microRNAs and long non-coding RNAs, can influence the course of RA and could provide a basis for the emergence of refractory RA.
- NIRRA is typically mediated by ongoing pain and patient-reported outcomes; pain mechanisms might include autoimmune and neuroinflammatory pathways that are independent of joint synovitis.
- The classification of RA and other diseases along an innate-to-adaptive immunological axis can be applied to refractory RA to help discover targets that might be of therapeutic benefit.

Patient compliance and adherence to therapies are also increasingly being recognized as contributors to the overall outcomes for patients.

By contrast, the term refractory RA indicates the inefficacy of multiple agents in conjunction with unabating joint and systemic inflammation — features at the core of the historically poor prognosis of RA[6]. In the real-world clinical setting, a state of genuine refractory RA is considered to exist when all potentially useful available therapeutic options have been exhausted (BOX 1). All of the currently licenced effective therapies for RA target joint inflammation mediated by integrated innate and adaptive immune system mechanisms in an effort to ablate inflammation and normalize inflammatory markers. Thus, implicit in our understanding of true refractory RA is the persistence of joint inflammation (which manifests as a state of high disease activity) and the need to explore alternative anti-inflammatory strategies to target disease. The need for the use of moderately high doses of glucocorticoids alongside DMARD therapy to achieve disease control in patients with RA also implies therapeutic inefficacy and, in the context of the cycling of multiple therapies, is consistent with a refractory disease state. What happens, however, if a patient has a high composite disease activity score that persistent inflammation does not necessarily contribute to? Some patients with RA cycle through multiple DMARDs in an attempt to bring their disease to an acceptable measured disease activity state (be it remission, low disease activity or equivalent) but have little objective evidence of ongoing inflammation. Does this type of disease also constitute refractory RA?

Observations on the effects of therapy, structural progression and patient-centred outcomes that extend back almost two decades can inform how we answer such a question. Many patients with RA who failed to meet the ACR composite outcome measures in a trial of infliximab plus methotrexate still had reductions in swollen joint counts, C-reactive protein (CRP) concentrations and radiographic progression[7], indicating meaningful suppression of inflammation in the face of apparent clinical non-response. A synovial tissue study drew similar conclusions, identifying CRP suppression and synovial tissue improvement in individuals who failed to meet ACR composite measures of response[8]. These findings could be interpreted as joint inflammation and damage being uncoupled and thereby representing two different processes. However, imaging studies have demonstrated that these two processes are coupled, with synovitis thought to precede joint erosion[9,10]. In addition, other studies have confirmed that clinical joint swelling and synovitis, but not tenderness and patient-reported outcome measures (PROMs), correlate with progressive joint destruction[11], and that seemingly controlled disease can be associated with persistent measured disease activity mediated by pain and PROMs[12–14]. Several studies have demonstrated this notion in the context of discordance between the 28-joint disease activity score (DAS28) and the risk of inappropriate escalation of immunosuppressive therapy[15], and also in promoting remission 'near misses'[16]. These data demonstrate that individuals with raised composite disease activity scores might not have underlying joint and/or systemic inflammation.

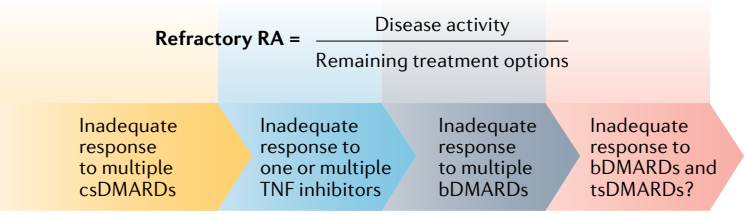
Applying this understanding to individuals who have already cycled through multiple DMARD therapies, we suggest that two types of disease state should be considered: persistent inflammatory refractory RA (PIRRA), in which an individual has unequivocal inflammatory joint synovitis that typically occurs, albeit not exclusively[17], in the presence of raised systemic markers of inflammation, despite the use of therapies with different mechanisms of action; and non-inflammatory refractory RA (NIRRA), in which symptomatology, typically pain, predominantly persists independently of discernible inflammation and is thus not directly amenable to DMARD therapy[2]. For some patients, although apparent joint swelling might suggest refractory synovitis, imaging studies can subsequently show no objective evidence of ongoing inflammation, consistent with the NIRRA subtype, and hence progressive erosion is unlikely[18]. Importantly, these two subtypes of refractory RA are unlikely to be mutually exclusive of one another, and both of these sit within the difficult-to-treat RA population (FIG. 1).

Although this subcategorization is not accepted or validated, and this approach is not without limitations (BOX 2), recognizing these two categories of refractory RA has fundamental conceptual implications for potential management strategies. Identifying PIRRA as the predominant basis for the cycling of multiple therapies will be of central importance for the emergent categorization, prognosis and testing of novel therapies for this condition. Similarly, although we acknowledge the potentially substantial functional incapacity in our suggested category of NIRRA, the prognosis for patients with this type of RA is likely to be very different from those with PIRRA.

Difficult-to-treat RA and the wide group of patients encompassed by this term can include refractory RA, but this concept is not discussed further in this Review. Nevertheless, it is worth acknowledging that a EULAR task force has recommended a threshold of a failure of at least two bDMARDs or tsDMARDs (with different mechanisms of action) as a definition of difficult-to-treat RA[4]. This recommendation is similar to that made in

Box 1 | **Treatment of RA and therapy cycling in refractory RA**

The therapeutic armamentarium for rheumatoid arthritis (RA) has rapidly expanded over the past 20 years with the introduction of biologic DMARDs (bDMARDs). The categorization of therapies in clinical practice and in clinical trials has often been dichotomous, with therapies described as either TNF inhibitors (the first bDMARDs to become available) or non-TNF inhibitor bDMARDs (including B cell-depleting therapies, T cell co-stimulation blockade and IL-6-targeted therapies). Refractory RA has traditionally been represented in the context of persistent disease activity following the exhaustion of all available treatment options (see figure). This concept has inevitably led to a continually expanding and changing definition of refractory RA as the number of available therapies has grown. Patients with refractory RA typically cycle from conventional synthetic DMARDs (csDMARDs), to bDMARDs, usually TNF inhibitors first, and then to bDMARDs with other mechanisms of action. This approach is pragmatic and can provide insights into meaningful pathways of disease. However, it remains to be seen whether the interruption of pan-cytokine signalling by the use of Janus kinase inhibitors, a type of targeted synthetic DMARD (tsDMARD), reduces the burden of refractory RA.



a 2018 viewpoint, which used the term refractory RA[2]; however, the term difficult-to-treat RA (as used by the EULAR task force) also includes the presence of more general signs, symptoms and clinical scenarios that can make the management of RA challenging. Going forwards in this Review, we use the term refractory RA to signify genuine disease that is resistant to treatment with multiple bDMARDs or tsDMARDs (as opposed to patients who are exposed to multiple DMARDs), and PIRRA and NIRRA when discussing data and concepts specific to these subcategories.

How common is refractory RA?

Only a handful of reports have described the prevalence of refractory RA, each of which used a different definition of the condition and none of which was designed to clearly identify PIRRA. A 2018 report from the British Society of Rheumatology Biologics Register for RA on individuals with refractory RA (defined as the failure of a minimum of two bDMARDs owing to toxicity and/or inefficacy) indicated a prevalence of approximately 6%, but the authors only examined patients who had used a TNF inhibitor as their first bDMARD[19]. A 2019 study in which refractory RA was defined as failure of a minimum of three DMARDs, including at least one bDMARD, and thus had a wider population of interest than the British Society of Rheumatology Biologics Register for RA study, reported that 17% of 412 patients had refractory RA[20]. Predictors of refractory RA included delayed initial treatment, being female and having high composite disease activity scores. The same group illustrated that treatment with a large number of prior DMARDs was associated with poor treatment response regardless of disease duration[21]. These results are consistent with the well-established observation that delayed treatment with a DMARD is associated with a poor response[17,22]. In other words, response rates are almost always higher when a drug is used as a first-line therapy than if the same drug is used as a second-line or third-line therapy later in the treatment pathway[1].

The differing definitions of refractory RA used in the studies published to date[19,20] make accurate estimation of the prevalence of this condition challenging. Such studies presume genuine persistent inflammation at each historic treatment failure. However, the difficulties associated with disentangling bona fide persistent inflammation from other factors that masquerade as refractory RA make it likely that the estimated 6–17% of individuals with refractory RA represents the overall proportion of individuals with refractory RA of any type, and that those with PIRRA constitute a smaller proportion of this group. Indeed, one of these studies reported no statistically significant difference in swollen joint counts, CRP concentration, erythrocyte sedimentation rate or radiographic damage between individuals with refractory RA and those with therapy-responsive disease[20], indicating that PIRRA is probably uncommon.

Characteristics of refractory RA

Persistent inflammatory refractory RA

Historically, severe and treatment-resistant (refractory) RA manifested as bulky synovitis, chronic progressive disability, complete incapacitation and loss of independence, accelerated atherosclerosis, tumorigenesis and early death[23,24]. Nowadays, refractory RA has a less aggressive phenotype and, in our experience, rarely emerges after years of sustained drug-induced remission. An individual can immediately and obviously fail to respond to successive treatments or can develop PIRRA more gradually, often as they partially respond to each new therapy before relapsing back into active disease (FIG. 2).

Patients with PIRRA can typically present with one of three clinical categories of refractory joint involvement (polyarthritis, oligoarthritis or monoarthritis), although this pattern of joint involvement has not been carefully studied. Individuals with unambiguously resistant disease generally have polyarthritis, which can become less extensive over time owing to the partial efficacy of targeted therapies. Some individuals can have an oligoarticular pattern of disease, which includes small-joint involvement of the hands and wrists and, very occasionally, patients can have a monoarticular large-joint pattern of disease with extensive synovitis. However, it is debatable whether a single refractory synovitic joint would meet any definition of refractory RA, which was historically a polyarticular disease. Notably, some individuals might have polysynovitis that is atypical and/or has a large-joint pattern but that nevertheless meets the criteria for RA; by designating such patients as having RA, the range of available treatment options is widened according to local eligibility criteria.

Distinct joint patterns in PIRRA might also be associated with autoantibody status. Involvement of large joints is associated with seronegative RA in what might be clinically termed a spondyloarthritis (SpA)-like pattern, whereas seropositive RA is typically associated with a small-joint symmetrical phenotype, although these patterns are not definitive[25]. Studies on the associations

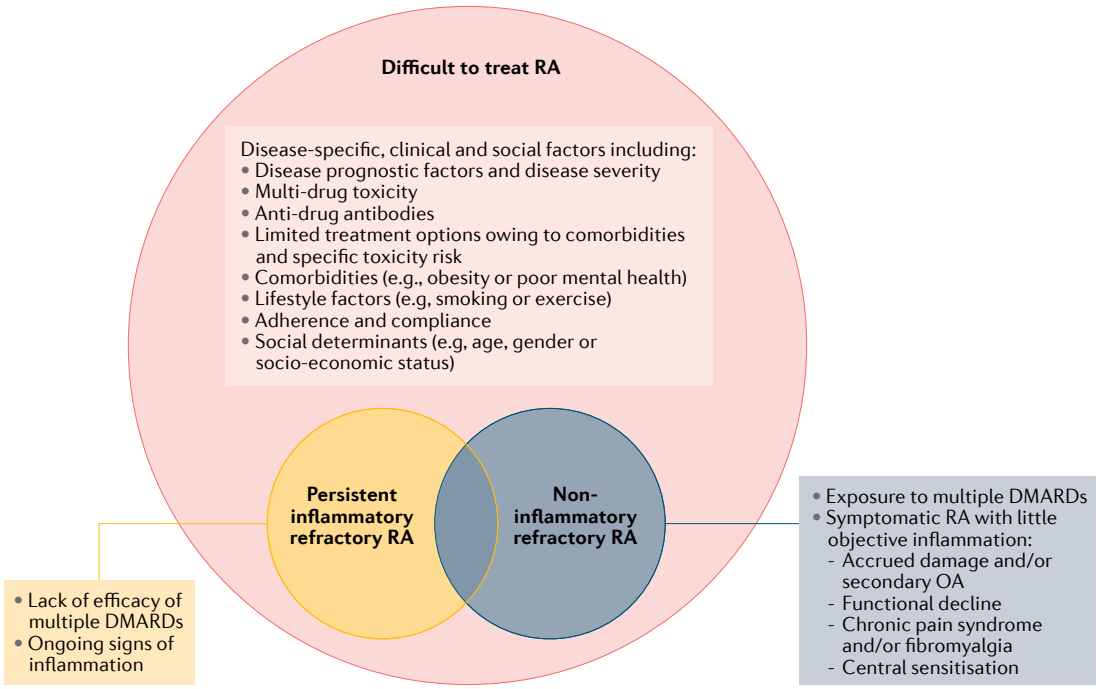


Fig. 1 | **Refractory RA subgroups within the wider context of 'difficult-to-treat' RA.** The term 'difficult-to-treat' rheumatoid arthritis (RA) is often used to describe disease in patients who are exposed to multiple biologic DMARDs and/or targeted synthetic DMARDs, but not necessarily in those for whom they lack efficacy. This group of patients encompasses those with comorbidities that preclude the use of certain therapies, repeated drug toxicity, anti-drug antibody development leading to drug inefficacy, and medication non-adherence and non-compliance. Lifestyle and social determinants might also contribute to lack of treatment efficacy in this group. We propose that the term 'refractory' RA could be defined by the inefficacy (not toxicity) of multiple types of DMARDs. Some individuals in this group will have persistent inflammation in the joints (and potentially systemic inflammation) and would be classified as having persistent inflammatory refractory RA. Other individuals will have symptomatic RA with little objective evidence of ongoing inflammation that can be modulated by DMARDs that principally target innate and adaptive immune system-mediated inflammation. Misdiagnosis of ongoing symptomatology as joint inflammation can lead to individuals in this group cycling though several therapies; such individuals would be classified as having non-inflammatory refractory RA. Importantly, all three groupings can exist in their own right and/or coexist to differing degrees, this latter scenario being the most likely. Although the definitions and terminology suggested here are preliminary, it is clear that the two subtypes of refractory RA would need distinct therapeutic approaches. OA, osteoarthritis.

between anti-citrullinated protein antibody (ACPA) status and clinical manifestations in cohorts of patients with early RA have also suggested possible differences between ACPA-negative and ACPA-positive individuals, including more large-joint involvement in ACPA-negative individuals; however, the data are not altogether conclusive[26,27]. Careful assessment of the site of pathology using ultrasonography can be used to help identify extracapsular disease[28] that would perhaps be more typical of autoantibody-negative RA or SpA-spectrum disorders.

Non-inflammatory refractory RA

With the development of targeted therapies for RA, the expectations of patients and clinicians have changed such that modest levels of inflammation are no longer an acceptable target to settle for. If an individual has only one or two involved joints, local injection or synovectomy can be employed, but for more extensive disease other treatment strategies are clearly needed. Yet some patients designated as having refractory RA can actually have low numbers of (or even no) swollen joints, normal CRP concentrations and erosive disease that is no more extensive than that in individuals who respond well to therapy[20] (in other words, a NIRRA phenotype), raising two questions: what is behind such a clinical profile, and what are the long-term implications for the patient?

Disease activity measures are surrogate indicators of active RA that are used to guide assessment of disease status and treatment response. Refractory RA, including the NIRRA subtype, is identified through a persistently raised disease activity score. Although validated composite disease activity measures have been instrumental in enabling the robust testing of new therapeutics and their introduction into clinical practices, the limitations of such composite measures are well-recognized. The DAS28 is weighted heavily for the tender joint count, yet objective evidence of inflammation does not necessarily correlate with PROMs such as pain[29]. In fact, when patients with RA are split into groups on the basis of the DAS28 and PROMs, a specific phenotype emerges that comprises predominant pain, fatigue and catastrophizing behaviour in the absence of markers of inflammation[30]. The absence of genuine joint and/or systemic inflammation but persistence in measured disease activity and PROMs might be the main factors behind

the futile cycling of DMARDs in this group of patients. Interestingly, in the VEDERA trial, the results of which were reported in 2020, the absence of sonographically determined power Doppler signals in the hands of approximately one-third of participants suggested that in real-world clinical practice, a substantial proportion of even symptomatic individuals with early RA might not have local inflammation to modify[18]. Such patients could be consigned to unnecessary cycling of therapies and falsely thought to be on a refractory disease trajectory.

Individuals with NIRRA are unlikely to require attention from the wider health services in the same way that those with PIRRA would owing to the well-known sequelae that emerge following chronic systemic inflammation[23]. The number of swollen joints, CRP concentration and presence of erosive pathology are the main prognostic determinants of future joint damage and adverse outcomes[31], and are usually low or absent in those with NIRRA. Thus, although PROMs clearly indicate an impaired quality of life that needs addressing for individuals with NIRRA, the long-term prognosis for these patients is likely to be radically different to that for those with PIRRA.

Biological basis for refractory RA

Very few studies have specifically investigated the mechanisms of refractory RA. Nevertheless, current knowledge of the pathogenesis of RA, together with experimental studies that implicate important pathways in the development of pain, provide meaningful insights that can be applied to the development of refractory RA.

Persistent inflammatory refractory RA

In this section, we review the relevance of serological status to the understanding of PIRRA and the distinct genetic associations of autoantibody-positive and autoantibody-negative RA. We discuss epigenetics in relation to two potentially distinct processes: the effect of chronic inflammation on mediating epigenetic changes that thus render RA resistant to treatment; and the increased recognition of age-related epigenetic changes. And finally, we review the immune pathways implicated in RA, including those that have demonstrated redundancy through unsuccessful clinical trials but that might be relevant for specific subgroups of patients, such as those with PIRRA.

Autoantibody status. The fundamental hallmark of RA is the production of autoantibodies such as rheumatoid factor (RF) and antibodies that recognize post-translationally modified proteins, including ACPAs and anti-carbamylated protein antibodies. Autoantibody-positive and autoantibody-negative RA are considered to be distinct disease subtypes that might be associated with specific pathogenic mechanisms[32]. Seropositive RA is associated with severe disease and poor outcomes, including increased mortality[33–35], and several strands of clinical and experimental data indicate that positivity for both RF and ACPAs has an amplifying effect on disease and results in an aggressive phenotype[33,36,37]. However, there is no evidence linking this combination of autoantibodies with the development of PIRRA. A positive autoantibody status is also linked to good responses to rituximab and to other therapies that target B cells and T cells[38,39], further supporting the pathogenic relevance of serological status in RA. Studies looking at synovial tissue and fluid have also suggested discrete tissue characteristics and/or cytokine profiles for seropositive and seronegative disease[40,41], but these results have not yet been translated into personalized medicine approaches, and autoantibody status has not been evaluated in cohorts of individuals with refractory RA of any type, let alone in those with PIRRA (or indeed NIRRA).

Genetics. Autoantibody status (particularly ACPA status) has emerged as the most effective way of stratifying patients with RA owing to distinct genetic and environmental associations with autoantibody-positive and autoantibody-negative disease[42,43]. Clear evidence exists that specific genetic loci, most convincingly those within the HLA region but also those within shared and specific non-HLA genetic regions, contribute to ACPA-positive and ACPA-negative RA[44,45]. For example, specific HLA-DR alleles within the so-called 'shared epitope' (a five-amino acid sequence motif in residues 70–74 of the HLA-DR chain, encoded by several *HLA-DRB1* alleles, that is over-represented among patients with RA) are only associated with the risk of ACPA-positive RA and not with ACPA-negative disease[43,46]. In ACPA-negative RA, associations have been reported with *HLA-DRB1*03* and *HLA-B*08* (REFS[47,48]), and associations with HLA-A alleles have been reported for ACPA-positive RA[44]. The authors of a fine mapping study identified distinct sets of amino acid residues in HLA-DRB1 at position 11 that were either protective for or conferred a risk of ACPA-positive and ACPA-negative RA[44]. Specific residues and amino acid sites explained the HLA associations with ACPA-positive and ACPA-negative RA and the amino acid positions mapped to the peptide binding

Box 2 | Proposed terminology for refractory RA

Persistent inflammatory refractory RA

- **Advantages**
  - Confident of active rheumatoid arthritis (RA) pathology in the face of multiple therapies
  - Identifies a group of patients with a poor prognosis
  - Accurate basis for investigation and target validation
- **Disadvantages**
  - Status can change over time as drugs with different mechanisms of action are trialled
  - Could dismiss inflammatory or autoimmune pain mechanisms

Non-inflammatory refractory RA

- **Advantages**
  - Mitigates against unnecessary treatment changes or cycling
  - Identifies a distinct cohort for investigation of residual patient-reported outcomes and alternative pain mechanisms
- **Disadvantages**
  - Risk of missing low-level inflammation
  - Unclear basis
  - Possible overlap with entheseal pathology, osteoarthritis and pain syndromes

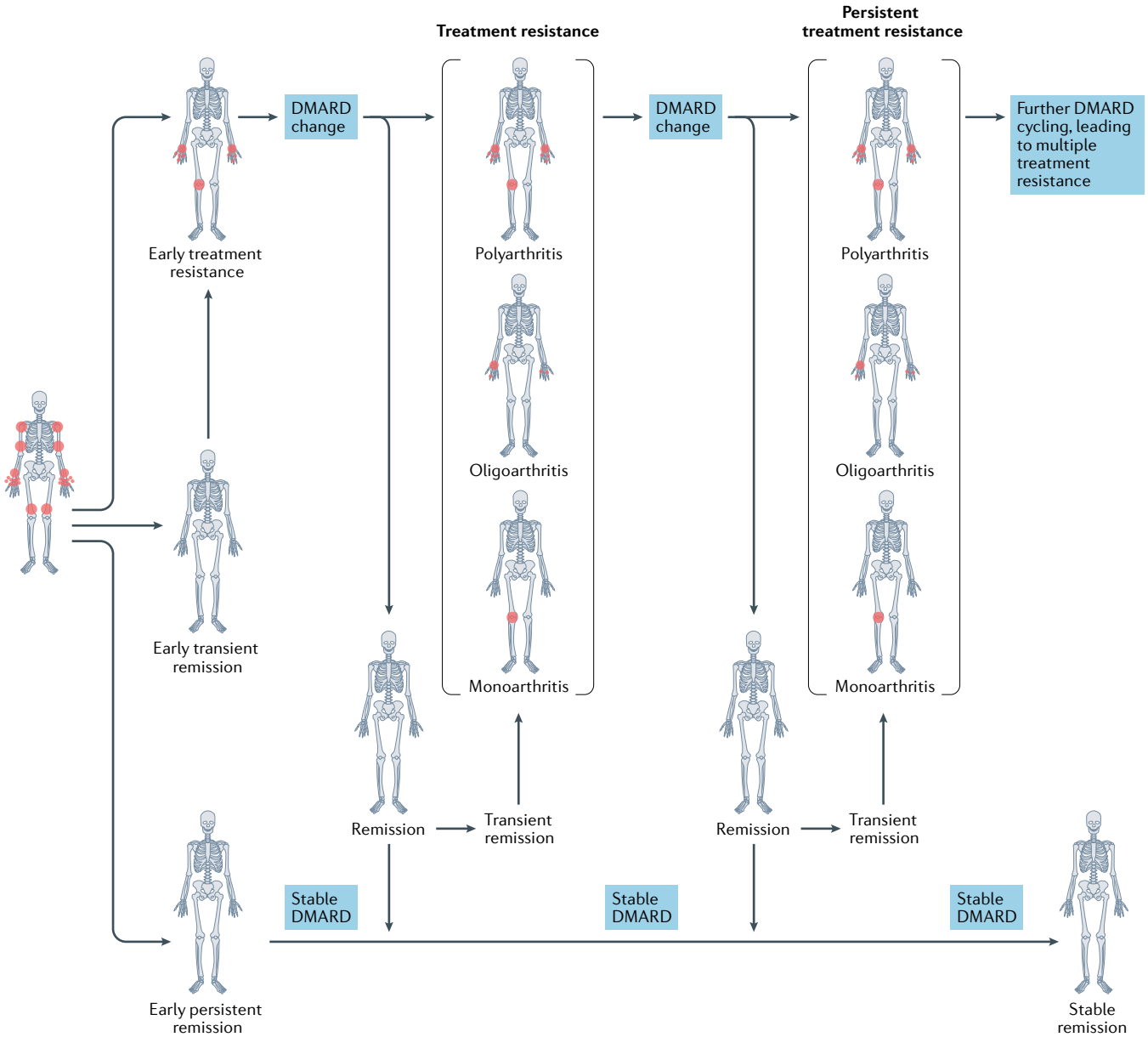


Fig. 2 | **Proposed trajectory and distribution of joint involvement in refractory RA.** Patients with rheumatoid arthritis (RA) who have a refractory disease course can follow this course from the outset, with early failures to successive therapies within the first 2–3 years. Often however, a varying depth of response initially occurs and an acquired loss of response is observed, such that refractory RA emerges after a period of several years. Although patients with untreated RA typically exhibit a symmetrical polyarthritis, individuals with refractory disease of a persistent inflammatory type might have a less extensive pattern of polyarthritis than at the time of diagnosis owing to the partial efficacy of successive therapies. A relatively oligoarticular pattern of disease that includes the small joints of the hands and wrists is also often seen in patients with refractory RA. Very occasionally, patients might have a monoarticular disease with extensive synovitis, although it is debatable if this type of disease would meet any definition of refractory RA, which was historically considered a polyarticular disease. Although some patients can have an intractable refractory disease course, the course of RA more often comprises several periods of stable or partial disease control (or remission) with a particular treatment, followed by a later relapse to active disease. The changes to treatment regimens that are associated with this disease course, often over a prolonged period of time, can also lead to a state of multiple-treatment-resistant refractory RA. In addition, some patients can have stable remission from the earliest time point and maintain this course over a long period of time.

grooves of the HLA molecules, implicating their relevance in antigen recognition and suggesting that different antigens might promote disease in ACPA-positive and ACPA-negative RA. HLA loci thus remain the genetic region with the strongest association with both autoantibody-positive and autoantibody-negative RA, albeit with distinct alleles for each type of disease.

Interestingly, in addition to being associated with ACPA-negative RA, *HLA-B*08* is also associated with susceptibility to psoriatic arthritis (PsA)[49]. Notably, several MHC class I associations have been reported for PsA, pointing to a specific $CD8^+$ T cell immunopathology in this disease[50,51]; supporting this notion, functional studies have shown the production of IL-17A by $CD8^+$

T cells from the synovial fluid of patients with PsA, but not from those with RA[52]. We would speculate that the *HLA-B*08*-associated ACPA-negative subgroup of RA might be similar to PsA and also have a predominant $CD8^+$ T cell-mediated immunopathology[53]. No further direct data exist on this putative subgroup of patients and whether it equates to PIRRA and, more importantly, whether therapies licenced for SpA-type disease might have a role in the treatment of some individuals with refractory RA.

No studies to date have reported a genetic architecture specific to PIRRA (or indeed NIRRA) and, given the relatively small proportion of patients with PIRRA, such an endeavour could be challenging despite the extensive amount of genome-wide association study data available from patients with RA[54]. In the post-genome-wide association study world, whole exome or whole genome sequencing could help to elucidate the genetic basis for PIRRA, which is relatively uncommon[55]. For example, in individuals with PIRRA who are autoantibody-positive and have known RA risk-associated HLA genes, genetic variant associations could be investigated to determine if any novel genetic factors are involved in PIRRA. As with other complex diseases, these variants could then be used to gain insights into the genes, cell types and mechanism of genetic influence in PIRRA, through expression quantitative trail loci and mapping of variants onto gene regions, gene regulators and active chromatin regions[56].

Epigenetic alterations. As discussed in the previous section, genomic studies of populations of individuals with PIRRA could potentially be used to identify a (rare and) distinct genetic trait that explains the treatment-resistant nature of the condition. However, it is likely that PIRRA develops over time. Clinical trial data of targeted interventions in individuals with very early RA show how strikingly good disease control can decrease over time[57,58], raising the possibility that accumulated epigenetic changes in chronic RA might help to determine the PIRRA state.

A number of lines of evidence suggest that epigenetic changes, including methylation and changes in microRNAs (miRNAs) and long non-coding RNAs, occur either before treatment or are induced by ageing and/or treatment[59], and thus might have a role in PIRRA. The epigenetic signature of RA can also change as a result of ageing or environmental factors, and treatment regimens that are initially successful in patients with RA can fail later, suggesting a change in mediators of disease in these individuals. Differential methylation has been observed between RA and osteoarthritis (OA)[60,61], between early and late RA[60], between individuals who respond to treatment and those who do not[62] and between different joint sites[63]. These results give an indication not only of the role of methylation in disease but also its plasticity, and potentially help to explain some of the heterogeneity that occurs in RA in terms of disease course and treatment response. Therefore, the reported unique 'DNA methylome signature' found in the early stages of RA, the ongoing alterations in DNA methylation as the disease progresses[60] and the signatures associated with RA or disease subgroups point towards epigenetic changes contributing to the development of a treatment-resistant pathology. Similar observations have been made for miRNAs and long non-coding RNAs, epigenetic modifiers of gene expression and cell state[64–67]. In particular, the miRNAs miR-146a and miR-155 have been extensively studied and are differentially expressed in patients with RA compared with those with OA or healthy individuals in a wide range of cell types, including cells in the blood, synovial fluid and synovial tissue[65–67].

Therefore, strong evidence now exists for how environmental factors can influence epigenetics, how epigenetics can influence cellular phenotype and how these epigenetic changes can be fluid among different cell types, disease stages and ages. Drug exposure and environmental influences such as smoking[68] are therefore probable contributors to changes in epigenetic states and immunopathogenesis that result in a PIRRA phenotype. A bidirectional relationship is thought to exist between inflammation and epigenetics, with the local inflammatory milieu inducing epigenetic alterations that lead to subsequent immune alterations, and vice versa[69–73]. Specific epigenetic markers contribute to the regulation of gene expression in RA and can be found in both immune and stromal cells[74]. These epigenetic changes potentially explain non-genetic risk factors in RA, and possibly have roles in the chronicity and perpetuation of inflammation. However, it is unclear if such epigenetic alterations occur as stochastic events, in response to specific environmental triggers or as a result of chronic inflammation. The largest study conducted to date suggested that an altered DNA methylation status might partially underlie the genetic effect of HLA risk by acting as an intermediary in the regulation of gene expression by disease variants[73]. Although these observations suggest potential epigenetic mechanisms in continued inflammation, they have not been specifically looked for in patients with PIRRA and thus remain speculative.

De novo mutations that affect epigenetic programming. Epigenetic changes might also be promoted through somatic mutations in RA. These mutations could affect adaptive and/or innate immune cells to contribute to the immunopathogenesis of RA, or could act in a manner that is completely independent of the effects of tissue inflammation. The expansion of haematopoietic clones carrying recurrent somatic mutations has been well described in older individuals, and such clones have also been identified in increased amounts in individuals with myelodysplastic syndrome (MDS) or acute myeloid leukaemia[75,76]. For example, whole-exome sequencing has enabled the identification of somatic mutations in genes involved in epigenetic regulation, including those involved in DNA methylation (*DNMT3A*), DNA hydroxymethylation (*TET2*) and histone methylation and ubiquitylation (*ASXL1*), in individuals with acute myeloid leukaemia[77].

Identical mutations are evident in the dynamic evolution of the haematopoietic system in individuals without clinical haematological disease, but who are at a high risk

of developing MDS and other haematological cancers, in a process known as clonal haematopoiesis of indeterminate potential (CHIP)[78]. Cardiovascular disease is strongly linked to inflammation; therefore, it is of particular interest that CHIP is associated with an increased cardiovascular mortality in individuals without MDS or evidence of tumorigenesis[79]. Thus far, only preliminary reports have been published of common CHIP associations in RA. One study reported the prevalence of CHIP in 59 patients with RA compared with 12 patients with MDS or aplastic anaemia and two healthy individuals and, within the RA group, attempted to ascertain if individuals with severe RA (typically considered a surrogate for a refractory state, although this is not necessarily the case) had a greater degree of CHIP than individuals with milder RA[80]. Overall, the authors of the study noted an expected age-related increase in CHIP in patients with RA that was substantially lower than in those with MDS. No association with severe disease was noted but the need for further studies was acknowledged. CHIP in RA synovial fluid macrophages has also been reported in the preliminary results of a small study of CHIP in patients with arthritis[81].

Certainly, the idea of a genetically evolving somatic mutation burden as a mediator of refractory RA is novel and is supported by evidence of somatic mutations in other RA settings. For example, *STAT3* mutations are associated with Felty syndrome (although this phenotype is not necessarily linked to refractory RA, including PIRRA)[82], and somatic mutations have been reported in $CD8^+$ T cells from patients with newly diagnosed RA[83]. Further studies in well-characterized cohorts of patients with RA are needed to understand the possible functional and mechanistic relevance of somatic mutations in the perpetuation of inflammation and recalcitrant pathology. A French study of inflammatory polyarthritis in patients with MDS showed that for most individuals, disease was ACPA negative, generally non-erosive and responded to steroids, perhaps suggesting that age-related myeloid changes might not be major contributors to refractory RA phenotypes[84]. However, many individuals with MDS and seronegative arthritis probably have a polymyalgia rheumatica-like phenotype, which perhaps is conflated with RA but has a distinctive topographical localization to the synovium[84]. Nevertheless, in a newly described syndrome, somatic mutations in patients with MDS have been linked to chronic inflammatory disease phenotypes including vasculitis and inflammatory arteritis, although a specific RA phenotype was not reported[85]. The association of such phenotypes with multiple simultaneous cytokine perturbations could render disease more refractory, whereby bDMARDs and even tsDMARDs might not provide sufficient suppression of all pro-inflammatory mediators.

Smoking. Smoking is an accepted environmental risk factor for RA, both for the development of the disease and also for poor prognosis and treatment-predictive outcomes[86,87]. Cigarette smoke contains over 4,000 chemicals that can elicit numerous effects on cells of the innate and adaptive immune system[88]. In the lungs, cigarette smoke extract promotes the production of TNF and other cytokines by macrophages[89] and has myriad other effects, including the dysregulation of reactive oxygen species and autophagy, which contribute to the inflammatory milieu[90].

The effects of cigarette smoke on refractory disease could potentially be linked to epigenetic and somatic mutations. In smokers, methylation levels in ACPA-positive individuals were able to account for the interaction between the rs6933349 genotype and smoking, which was not found in ACPA-negative individuals[91]. In addition, an association has been reported between smoking and CHIP[92] that extends the known relationship between smoking and the risk of MDS[93,94]. A relationship between CHIP and atherosclerotic disease, an inflammatory disorder with prominent myeloid cell involvement, has also been shown[76]. These changes most typically occur via somatic mutations in the DNA methylation pathways. Smoking might also epigenetically regulate immunity through other mechanisms, such as changes in DNA methylation status[68], as well as inducing cellular changes through oxidative stress and apoptosis, and promoting ACPA production[88]. Given the independent link between smoking and chronic pain[95], smoking seems to be a common denominator that could also contribute to the persistent and residual symptoms of a subgroup of patients with NIRRA[96]. Such data could, in the future, lend further support to a role for smoking cessation as part of a wider management strategy to improve long-term outcomes.

Immune pathways. Clinical trials of DMARDs for RA have been enormously instructive and have enabled the development of a more refined understanding of the relative roles of cytokines, their signalling pathways and their hierarchy within the immune system[97,98]. The great success of therapies directed against TNF or IL-6, especially in patients with early RA[57,99], with the achievement of high remission rates, supports their importance in the cytokine network; results that are consolidated by reports of an IL-6-mediated $CD4^+$ T cell signal transducer and activator of transcription 3 (STAT3) signature in the earliest stages of disease[100,101]. Granulocyte–macrophage colony-stimulating factor (GM-CSF) is also implicated in the pathogenesis of RA, as confirmed by positive results in early-phase studies of GM-CSF blockade[102]. However, the inflammation in individuals with PIRRA is likely to be independent of such cytokines, assuming resistance to therapies that target these cytokines is not mediated by neutralizing antibodies or poor drug compliance. Similarly, therapies that target B cells or T cell co-stimulation pathways validate RA as a prototypic autoantibody-mediated disease[103,104]. By contrast, although preclinical studies suggested roles for several cytokines in RA, including IL-17 (REFS[105,106]) and IL-1 (REFS[107,108]), clinical trials and studies of inhibitors for these cytokines lacked the non-redundancy needed to enable effective targeting[109,110]; however, these cytokines might still be relevant in specific subgroups of patients with refractory RA. A commonly cited hypothesis for the development of refractory disease is that of an escape mechanism and the emergence of a new mediator

following chronic blockade of an immune pathway, possibly through alteration of the tissue microenvironment and/or the systemic environment. Aside from a preliminary report of improved treatment response in mice with collagen-induced arthritis by targeting the IL-23–IL-17 axis alongside TNF blockade[111], no studies currently support this theory. Thus, it is unclear which immunological pathways typify PIRRA and whether targets outside of those pathways highlighted above remain to be discovered.

Non-inflammatory refractory RA

Several scenarios, some conjectural, can be considered to explain the pain and joint symptomatology that occurs in patients with NIRRA, which cannot all be comprehensively reviewed here. Coexistent or disease duration-dependent secondary OA is an obvious scenario. Reports of refractory RA associated with swollen joint counts, CRP concentrations and radiographic damage that are no more severe than in individuals with RA who respond well to treatment, and that is more common in young women than in men[20], might be linked to the multifaceted differences in pain perception that have been reported between men and women[112]. The persistence of pain in patients with RA is a well-recognized phenomenon that has not abated with the introduction of powerful anti-inflammatory agents. Studies suggest that such residual pain is attributable to persistent central sensitization and the development of maladaptive pain processing[113] (FIG. 3a). The effects of pain sensitization and poor outcomes in individuals who have delayed initiation of therapy[17,22,114] and secondary fibromyalgia are also obvious factors that could contribute to the development of NIRRA.

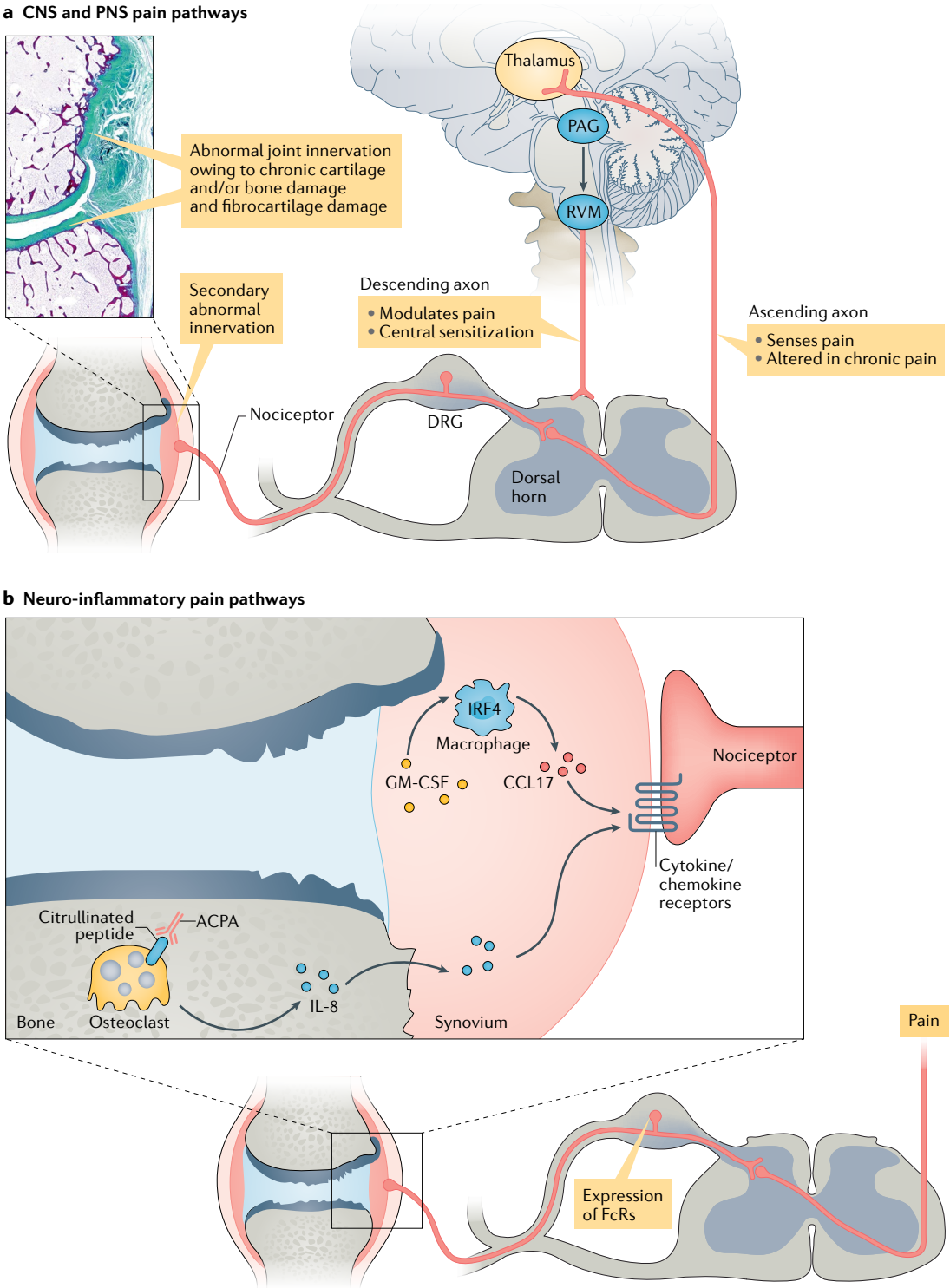
A potential role for autoimmunity and inflammation as an unconventional mediator of pain in RA (not related to acute or chronic joint synovitis) has attracted much research interest (FIG. 3b). ACPAs might directly contribute to osteoclast activation and are associated with bone pain in experimental models of RA[115], a scenario that could conceivably occur without discernible clinically or imaging-defined joint synovitis. A second area of research pertains to type II collagen-related immune complexes, which seem to be capable of activating Fc receptors expressed on dorsal root ganglion afferent nerve fibres. The injection of anti-type II collagen autoantibodies into mice was associated with pain behaviour in advance of discernible joint pathology[116]. Although anti-type II collagen autoantibodies are not specific to RA, this research provides a possible mechanism for peripheral nociception that is linked to joint inflammation in general. Several signalling pathways, including the TNF pathway and phosphoinositide-3 kinases, are known to have direct roles in dorsal root ganglion-related pain and inflammation in experimental arthritis[117,118]. In addition, a GM-CSF axis linked to the CC-chemokine ligand 17 (CCL17) pathway has been described in experimental arthritis, in which CCL17 was involved in pain development both dependently and independently of joint inflammation[119]. Accordingly, if this axis was able to promote pain independently of inflammation in RA, then mavrilimumab, an anti-GM-CSF antibody, would be predicted to improve outcomes in patients with RA, which was not the case[120].

We would speculate that such putative neuroimmunological effects could take place in conjunction with abnormal small joint innervation, secondary to inflammation-mediated damage to the normally avascular, ligamentous, fibrocartilaginous tissue that abundantly lines the proximal interphalangeal and metacarpophalangeal joints. The sites of small joint erosion in RA are actually covered with cartilage and form elaborate synovio-entheseal complexes that, once damaged by inflammation, might contribute to abnormal joint innervation[121,122]. Although the concept of abnormal joint enthesis innervation is well established in the spine in intervertebral disc degeneration disease[123], it remains to be established in small-joint RA.

Experimental studies in mice have also shown a central effect of TNF in mediating pain[124] and, in a pilot brain functional MRI study of patients with RA, treatment with a TNF inhibitor reduced activity in thalamic, limbic and associative areas of the brain before clinical improvements were seen[125]. A sophisticated multi-modal MRI study that included 54 patients with RA found that high levels of peripheral inflammation were associated with an increased number of positive connections between specific areas in the brain, and that these patterns of connectivity could predict fatigue, pain and cognitive dysfunction[126]. Intriguingly, post hoc analysis of a clinical trial of the Janus kinase (JAK) inhibitor baricitinib in RA suggests an effect on pain symptoms that might be independent of clinically evident joint swelling[127]. Comparative trials between JAK inhibition and TNF inhibition suggest that, despite comparable reduction of swollen joint counts and radiographic joint erosion retardation, JAK inhibitors produce superior composite disease activity scores to TNF inhibitors[128,129]. This superiority is thought to be mediated by an as yet poorly understood effect on pain. Curiously, the emergent JAK inhibitor therapies for RA might have serendipitously stumbled into the NIRRA arena to good clinical effect. Although entirely speculative, this apparent benefit of JAK inhibition could indicate an as yet unrecognized systemic neuro-inflammatory component of pain, an autoantibody-mediated mechanism of pain or could implicate JAK–STAT signalling in the pathogenesis of complex pain that is completely independent of inflammation.

Stromal cells in refractory RA

The role of stromal cells, namely synovial fibroblasts, across the refractory RA spectrum is also worthy of comment but is at a speculative stage of research. Stromal cells are relevant in the early stages of RA by virtue of their antigen-presenting capabilities and their ability to interact with the immune system to support the functional roles of adaptive immune cells[130,131]. The production of IL-6, prostanoids and matrix metalloproteinases by stromal cells also perpetuates synovitis and enables destruction of the extracellular matrix and subsequent joint damage[132]. However, these processes could conceivably be part of a stromal cell-mediated pathway



that is shared with other diseases such as OA[133,134], which might exist in isolation but might also be classified as autoantibody-negative RA and/or coexistent RA and OA. Interestingly, some individuals in an early RA inception cohort, in which patients' disease was characterized by synovial tissue pathotype, had a pauci-immune or fibroid 'non-inflammatory' type of disease[135]. Individuals in this fibroid group, approximately half of which were negative for ACPAs and RF, showed the lowest acute phase reactant levels, swollen joint counts and power Doppler ultrasonography scores[135]. This clinical profile, coupled with the near complete absence of immune cells in the synovium, would be consistent with a clinical disease pattern characterized by little or no inflammation that would not be expected to respond to immune-targeted DMARDs, which is indeed what was reported[135,136].

We would speculate that this phenotype of RA with low levels of inflammation might reflect a milder disease state or a post-inflammation resolution state if it

Fig. 3 | **Speculative pain mechanisms in non-inflammatory refractory RA.** Pain in rheumatoid arthritis (RA) arises from the interactions between joint pathology and the processing of pain signals by peripheral, spinal and supraspinal pain pathways. **a** | Dysregulation of central nervous system (CNS) pain pathways can contribute to hyperalgesia and allodynia, which are associated with chronic pain. The primary CNS pain regulatory mechanisms comprise descending modulatory pathways via the periaqueductal grey (PAG), the rostral ventromedial medulla (RVM) and central sensitization. In the joints, chronic inflammation, malalignment and damage to the cartilage, bone, capsule and fibrocartilage can lead to secondary abnormal joint innervation and the development of local pain. This type of pain is more likely to develop in chronic RA. **b** | Theories are emerging of neuro-inflammatory mechanisms of pain in RA. Autoimmune mechanisms contribute directly to pain in settings where there is no measurable synovitis, which might have relevance for non-inflammatory refractory RA (and might also occur in persistent inflammatory refractory RA). Putative mechanisms from experimental models of arthritis include anti-citrullinated protein antibody (ACPA)-mediated activation of osteoclasts and associated bone pain mediated by IL-8, and immune complex-mediated activation of neuronal Fc receptors (FcRs) expressed on the dorsal root ganglion (DRG). Inflammatory mediators such as CC-chemokine ligand 17 (CCL17) can also have central effects on nociceptive pain. A granulocyte–macrophage colony-stimulating factor (GM-CSF)–CCL17 pathway mediated by interferon regulatory factor 4 (IRF4) has been demonstrated in experimental models of arthritis that could have implications for humans. These mechanisms could be pervasive in RA, contributing to pain in both inflammatory and non-inflammatory RA phenotypes. Such mechanisms could operate during the earlier phases of the disease, when minimal clinical joint swelling is present. PNS, peripheral nervous system. Part **a** adapted with permission from McGonagle et al.[121], Wiley. Copyright © 2009 by the American College of Rheumatology.

were to emerge after therapy, or might be a result of diagnostic overlap and/or misclassification with OA. Alternatively, a neat explanation for progression from early RA to later RA, in which responses to therapy are less robust, is the evolution to a non-immune stromal pathology. Such a theory would explain resistance to the currently available anti-inflammatory DMARDs, which fail to address fibroblastic disease. An ongoing study of cyclin-dependent kinase inhibition[137] was conceived on the premise that active stromal pathology underlies the residual ceiling effect of bDMARDs and that additional targeting of fibroblasts might further close the disease activity gap. However, if stromal cells are indeed responsible for refractory RA, stromal pathology might be expected to confer a site-specific disease (such as persistent monoarthritis or oligoarthritis); it is more difficult to conceptualize multi-joint PIRRA in terms of dysregulated stromal biology unless chronic inflammation can elicit abnormal stromal function in multiple joints[138]. A study of patients with RA in which a circulating fibroblast-like cell type was identified during a flare[139] needs to be validated, and other studies have failed to detect stromal cells in the blood[140]. Anatomical and functional heterogeneity in fibroblasts has been reported across different diseases[63,141] and specifically in RA[142], possibly implicating roles for fibroblasts across the refractory RA spectrum. A study in mouse models of resolving and persistent arthritis revealed two distinct subsets within the fibroblast activation protein-α (FAPα)-positive synovial fibroblast population: one that assumed an immune-effector role by sustaining inflammation through its distinct chemokine and cytokine profile; and one that mediated joint damage through bone effector cells[143]. However, it is unclear if these mouse fibroblast phenotypes can be translated to the human setting.

Management of refractory RA

As discussed at the beginning of this Review, we believe that placing the paradigm of persistent joint swelling and raised acute phase reactants (which are clearly linked to progressive joint destruction and poor outcomes)[4,19] at centre-stage helps to identify which patients with refractory RA belong to the two major (but overlapping) sub-categories — PIRRA and NIRRA. The ability to classify these two categories strongly argues for a more attentive approach and for the precise evaluation of persistent disease activity and PROMs (FIG. 4). Careful clinical assessment to demonstrate the absence of extensive joint synovitis, including the use of power Doppler sonography (if available) and a targeted examination of painful and tender joints, can be used to support a clinical impression that DMARDs are appropriately targeting inflammation. These assessments can also serve to reassure patients that their lingering treatment-resistant symptoms might not require a change in DMARD therapy. Where sonography is not available, definite clinically defined 'boggy' joint swelling, raised acute phase reactants and progressive radiographic damage can be used to differentiate PIRRA from NIRRA and to mitigate against the erroneous perception of continued underlying synovitis.

We further believe that an important determinant in the assessment of refractory RA should be in relation to identifying an individual's RF, ACPA and HLA status. As a first line of stratification, PIRRA could be considered to comprise three groups: autoantibody-positive RA that has an HLA association; autoantibody-negative RA (for both RF and ACPA) that has an HLA association; and autoantibody-negative RA with no HLA association (which would be more autoinflammatory in nature).

Given the heterogeneity of refractory RA and the current understanding of the pathogenesis of RA[144], the vital question for therapeutic strategies is whether the inflammation in PIRRA is predominantly humorally mediated, T cell-mediated or innate cell-mediated (autoinflammatory)[53] (FIG. 5). Identifying the principal mechanism of inflammation has obvious ramifications for the choice of therapeutic approach. B cell-targeted therapies and T cell costimulation-targeted therapies need to be considered for autoantibody-positive disease[38,145]. By contrast, autoantibody-negative refractory RA (in particular, potentially non-HLA-associated disease) would be predicted to be more innate immune cell-mediated or autoinflammatory in origin, and might also include other differentials such as crystal deposition disease[146] that can coexist with or be confused with RA. Thus, reappraisal for alternative (and/or coexistent) conditions or other rare innate immunopathologies or autoinflammatory mechanisms should also be undertaken. Cytokines that are seemingly less relevant to RA (such as IL-1) might actually be biologically pertinent[147,148] in a subgroup of patients with refractory RA despite IL-1 antagonism having minimal efficacy in patients with a typical autoimmune pattern RA following TNF inhibitor failure[110].

The possibility also remains that an as yet unidentified treatment target exists that is not covered by current advanced therapies for RA. Experimental studies

to identify new, tractable targets and stratified treatment approaches are therefore urgently needed. For individuals with persistent seronegative refractory RA, a potential role for the IL-23–IL-17 axis could be considered, as the RA phenotype might potentially be a presentation of PsA without psoriasis. Looking further afield, evidence exists that anti-IL-18 strategies might be beneficial for autoinflammatory disease phenotypes such as adult-onset Still's disease[149]. A seronegative refractory RA more akin to autoinflammatory conditions or adult-onset Still's disease could be a future candidate for targeting cytokines such as IL-18, type I interferon[150] and IFNγ[151].

As well as being an important mediator of early RA[99], IL-6 seems to also be relevant in later stages of the disease, as an IL-6-targeted therapy was effective in patients who had previously failed to respond to multiple TNF inhibitors[152]. These results are consistent with a non-redundant role for IL-6 and distinct intracellular signalling pathways for TNF and IL-6. However, it is important to acknowledge that the participants in this trial[152] did not clearly have refractory RA, but instead either had inadequate responses to one or more TNF inhibitors and/or an intolerance to two or more TNF inhibitors. In addition, a genuine form of multidrug-resistant refractory RA that evades targeting of both TNF and IL-6 is clearly seen

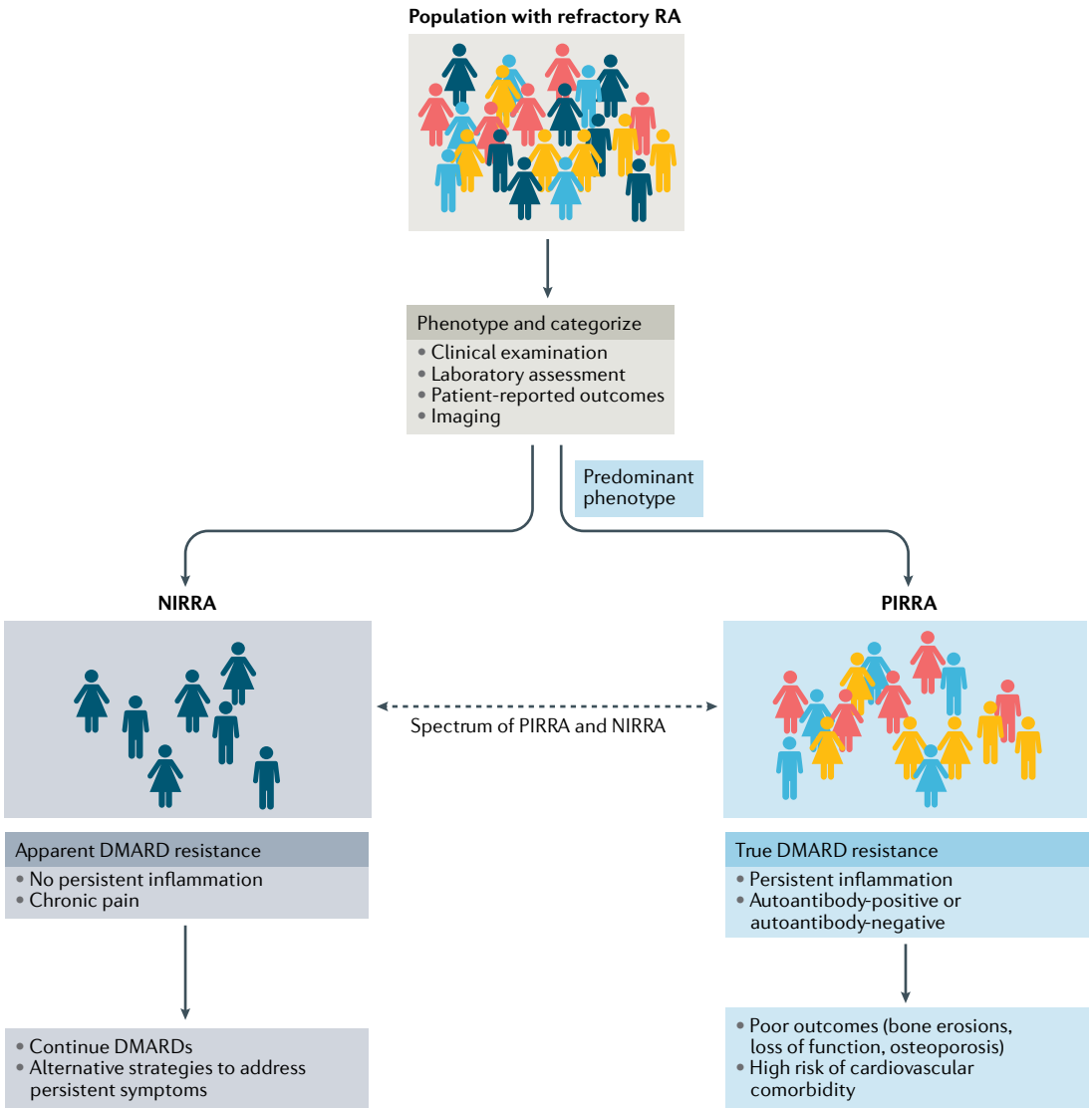


Fig. 4 | **A first step in the stratification of refractory RA.** A fundamental first step in stratifying individuals with refractory rheumatoid arthritis (RA) should be to confirm the presence of a genuine, persistent inflammatory pathology. Clinical examination, biochemical evidence of systemic inflammation and patient-reported outcomes can be supplemented with sensitive imaging (such as ultrasonography, which can be readily used at most disease sites) to verify recalcitrant disease. This strategy splits patients into two broad categories that we have called persistent inflammatory refractory RA (PIRRA) and non-inflammatory refractory RA (NIRRA). Those in the PIRRA group have a poor prognosis and the highest risk of comorbidities such as cardiovascular disease. A greater understanding of PIRRA immunopathogenesis will be central to identifying existing or emergent therapies. Those in the NIRRA group are likely to be receiving appropriate targeted therapy but have poor quality of life and patient-reported outcomes such as pain and fatigue, highlighting the need for alternative strategies for addressing the persistent symptomology that promotes the measured disease burden.

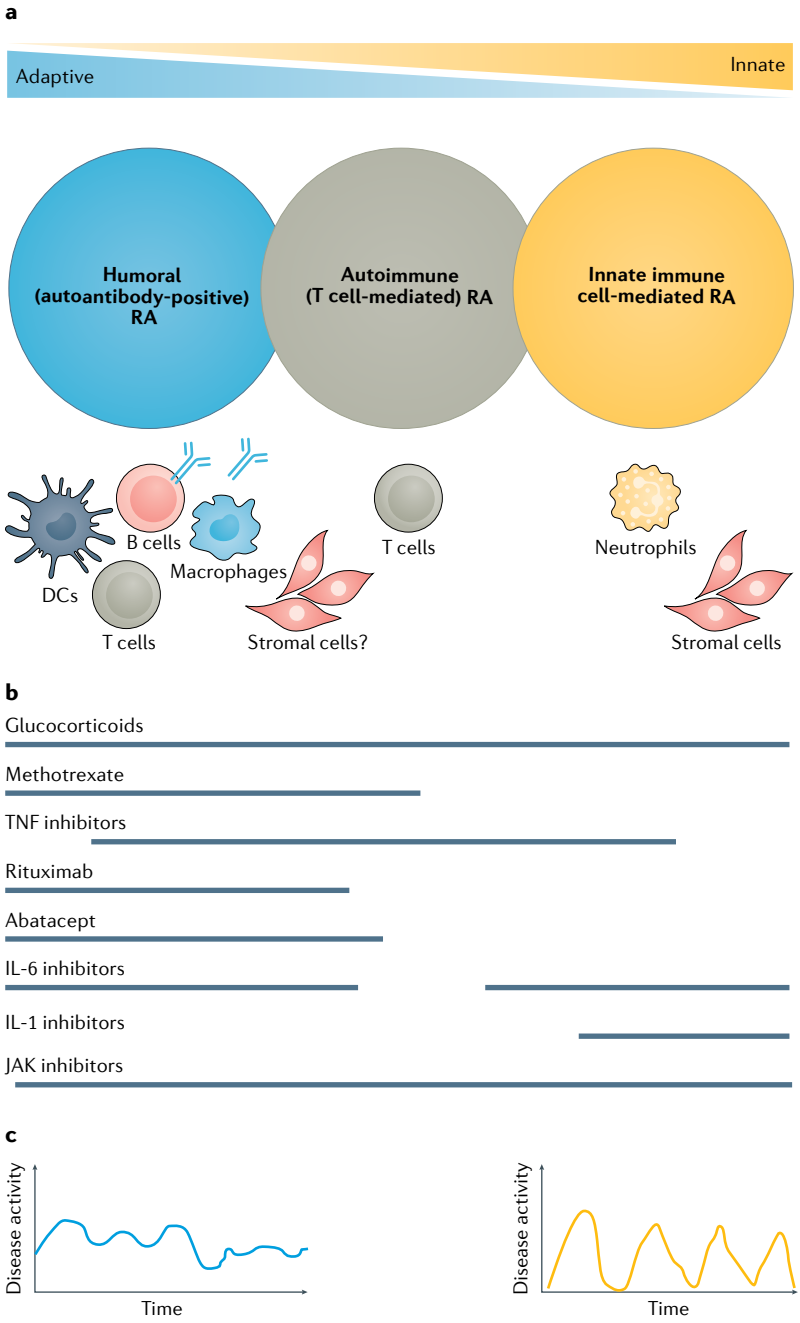


Fig. 5 | **Therapeutic approaches to targeting inflammation in refractory RA. a** | Inflammation in refractory rheumatoid arthritis (RA) can be predominantly humorally mediated, T cell-mediated or innate immune cell-mediated, or can involve a combination of all three owing to the functional integration of innate and adaptive immunity. A cellular hierarchy is likely to exist between more autoimmune RA and more innate immune cell-mediated RA. Humorally mediated disease relies on the triune axis of follicular helper T cells, dendritic cells (DCs) and B cells. Macrophages mediate much of the pathology of autoimmune RA following immune complex activation and also probably have a major role in seronegative (potentially more T cell-mediated) RA. Neutrophilic inflammation is important in innate immune cell-mediated RA. The role of stromal cells or joint fibroblasts in the pathogenesis of RA could be multifaceted and awaits elucidation in refractory RA, so we have placed stromal cells as primarily facilitating innate pathways, although speculate that they might have a role in adaptive processes via epigenetic mechanisms. **b** | Therapeutic approaches to refractory RA such as targeting B cells (rituximab), T cells (abatacept) or the IL-6 pathway affect adaptive immune cell-mediated disease, as does the use of Janus kinase (JAK) inhibitors. TNF inhibitors are effective across most of the range of RA. JAK inhibitors are beneficial in innate immune cell-mediated diseases, as are glucocorticoids, which are effective across a wide range of both innate and adaptive immune pathways. IL-1 blockade is licensed for use in RA, but has proven ineffective at a group level; however, IL-1 blockade might be beneficial in refractory RA that is innate immune cell-mediated. It remains to be seen whether some individuals with seronegative refractory RA actually have a psoriatic arthritis-type phenotype, and therefore if inhibiting the IL-23–IL-17 axis warrants consideration. **c** | Different disease activity courses can be observed over time for adaptive immune cell-mediated and innate immune cell-mediated RA. Whereas adaptive immune cell-mediated RA might typically demonstrate persistent, albeit varying, levels of disease activity, innate immune cell-mediated RA might show the episodic spikes in inflammation (disease activity) that are characteristic of autoinflammatory pathology.

in the clinic. Nevertheless, previous drug exposure and the stage of disease at which these cytokines are targeted might be relevant in mitigating against future refractory disease[1]. Delayed treatment and suboptimal targeting of RA near onset might favour the development of refractory RA, which, in humorally mediated PIRRA, might be mediated by secondary lymphoid organ development and an accompanying increased autoantibody titre in the joint[153]. Planned exploratory analysis of a trial of methotrexate with or without a TNF inhibitor in patients with early RA[18] suggested a reduced responsiveness to TNF inhibition following methotrexate exposure, implicating a change in the biology of the disease to a more refractory form. If credible, the importance of disease suppression at the very earliest stages of RA in mitigating against the development of refractory disease could alter the current perspective that methotrexate should be used as a generic first-line treatment for all patients.

The comparable response profiles to JAK inhibitors in patients with established RA who have previously failed to respond to bDMARDs with those observed in patients with an earlier stage of disease[154–156] make a persuasive argument for the additional benefit of simultaneously inhibiting multiple cytokine signalling pathways with JAK inhibition. The use of JAK inhibitors, combined with effective targeting of RA-related inflammation at an early stage, could limit epigenetic changes and somatic mutations, and might preclude the development of PIRRA. The ability of JAK inhibitors to target the multiple cytokines that mediate autoantibody-positive and autoantibody-negative RA, as well as the overlapping connective tissue diseases that can coexist, provides the coverage needed to capture the heterogeneity of RA and refractory RA (FIG. 5). For example, JAK inhibition with tofacitinib[157] might be effective in adult-onset Still's disease, which overlaps with seronegative or autoinflammatory types of RA, suggesting that JAK inhibition might

overcome treatment resistance in individuals with these types of refractory RA. Although at an early stage of evaluation, and in the absence of data in individuals with clearly confirmed PIRRA, it is still tempting to speculate that JAK inhibition could help to treat this group of patients.

Aggressive treatment strategies might also have a role in severe PIRRA. Historically, the use of TNF inhibitors and anakinra (which targets IL-1) to treat severe RA was limited by toxicity and no clear efficacy[158]. Nevertheless, the potential for combinatorial cytokine antagonism has been reinvigorated by the possibility of antagonism of the synergistically acting cytokines TNF and IL-17A[159] or TNF, IL-17A and IL-17F[160]. This approach offers a potential future option for treating individuals with PIRRA. Finally, radical strategies that reset the 'immunostat', such as autologous haematopoietic stem cell transplantation, have proved disappointing in RA[161]. Whether an allogeneic bone marrow transplant might be more fruitful for inducing long-term remission in individuals with truly refractory RA who otherwise have good health remains speculative[162,163].

Future research needs

On the basis of the literature discussed in this Review, patients with genuine refractory RA are likely to be genetically heterogeneous and to even show complex overlaps between innate and adaptive immune mechanisms[147]. We would postulate that ostensible non-autoantibody-associated disease is likely to be molecularly heterogeneous and to involve unrecognized humorally mediated disease, $CD8^+$ T cell-mediated disease and predominantly innate immune cell-mediated disease. By contrast, the basis for resistant seropositive refractory RA pathology in individuals with PIRRA despite the use of current humorally targeted approaches remains unclear. Single-cell RNA sequencing and mass cytometry have been used to delineate the transcriptomic and cellular basis of joint synovitis in RA, although the samples used for these studies were procured from arthroplasty, as well as from ultrasound-guided biopsy[164]. Systems biology, although powerful, has thus far only pointed towards broad homogeneity in cell populations and cytokine biology in RA, potentially reflecting the diversity of the patient populations studied to date. Modern technologies have enabled the discovery of rare disease-relevant subpopulations of cells in patients with RA[165], but the relevance of these cells to refractory RA remains unclear. Also, the cardinal molecular events that mediate autoantibody-positive PIRRA might take place in the primary and secondary lymphoid organs outside of the joint, which are not investigated by taking tissue samples by synovial biopsy. Nevertheless, characterization of individuals with PIRRA using an integrated omics approach involving serological status, whole genome sequencing, RNA sequencing and epigenetic modifications could help to identify underlying endotypes and inform a personalized medicine approach to multiple therapy-resistant RA.

Conclusions

Overall, although a substantial amount of the ongoing symptomatology of individuals with refractory RA might be related to persistent pain mechanisms, prototypic autoimmune and inflammatory mechanisms that lead to ongoing synovitis in patients with refractory RA clearly exist. In this Review, we suggested that distinguishing those with multiple therapy-resistant refractory RA (PIRRA) from those with persistent measured disease activity and cycling of therapies in the absence of inflammation (NIRRA) is fundamental to understanding and managing refractory RA. Refined clinical phenotyping will be essential to aid in the identification of those with genuine persistent inflammatory disease and, thus, to reveal specific molecular pathways associated with disease subtypes. Epigenetic mechanisms and acquired somatic mutations, together with environmental cues such as smoking, might influence the dynamic genetic and epigenetic landscape of RA, leading to changes in the biology and relative roles of immune and non-immune pathways. Suboptimal or delayed treatment of RA near onset might favour the development of refractory RA that is generally resistant to DMARD strategies. Therapies that target TNF or IL-6 are of central importance for the treatment of RA and, when used early, lead to highly impressive outcomes. But whether the sequence in which targeted therapies are used is relevant to the development of refractory RA (including persistent symptoms in the absence of clear inflammation) is not clear. For individuals with truly treatment-resistant disease, the tools are now available for interrogating immune and stromal cells in the joint and beyond in order to explore therapy resistance mechanisms, and for interrogating the genomic architecture and epigenetic changes in distinct cell types at single-cell resolution. Precise clinical phenotyping to identify genuine refractory RA, which we have termed PIRRA, combined with a multi-omics approach, should lead to greater mechanistic insights into the cellular heterogeneity and differentiation behind the development of refractory disease.

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M.H.B. and D.M. researched data for the article. All authors provided substantial contributions to discussions of content, wrote the article and reviewed or edited the manuscript before submission.

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Review criteria
A search for original articles was performed in PubMed. The search terms used were "refractory" and "rheumatoid arthritis" in combination. We also searched the reference lists of identified articles for further relevant papers.