Why remission is not enough: underlying disease mechanisms in RA that prevent cure

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Abstract | Cure is the aspirational aim for the treatment of all diseases, including chronic inflammatory conditions such as rheumatoid arthritis (RA); however, it has only been during the twenty-first century that remission, let alone cure, has been a regularly achievable target in RA. Little research has been carried out on how to cure RA, and the term 'cure' still requires definition for this disease. Even now, achieving a cure seems to be a rare occurrence among individuals with RA. Therefore, this Review is aimed at addressing the obstacles to the achievement of cure in RA. The differences between remission and cure in RA are first defined, followed by a discussion of the underlying factors (referred to as drivers) that prevent the achievement of cure in RA by triggering sustained immune activation and effector cytokine production. Such drivers include adaptive immune system activation, mesenchymal tissue priming and so-called 'remote' (non-immune and non-articular) factors. Strategies to target these drivers are also presented, with an emphasis on the development of strategies that could complement currently used cytokine inhibition and thereby improve the likelihood of curing RA.

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Treatments for acute illnesses are usually aimed at producing a cure. In the context of infections, recovery from clinical symptoms usually parallels the elimination of the microorganism by the patients' immune system. Patients can therefore be cured from the likes of bacterial pneumonia, appendicitis or influenza. By definition, however, cure is rare in degenerative or inflammatory chronic illnesses, for which remission is generally a more realistic treatment goal. Cure and remission are distinct (TABLE 1); although both lead to cessation of symptoms, the underlying disease process remains active in remission but is absent in cure. This differentiation is important, as remission, in contrast to cure, generally requires continuation of treatment, regular follow-up with a clinician and carries the risk of relapse, particularly if treatment is interrupted or stopped. Notably, the absence of symptoms cannot be used to differentiate between remission and cure.

Perhaps surprisingly, the concept of cure has not been widely discussed in rheumatology, let alone defined. Yet, we should remember that remission only became a recommended aim of treatment over the past 20 years as a consequence of early diagnosis, treat-to-target algorithms and targeted therapies[1]. Furthermore, the mechanisms that underpin rheumatic diseases such as rheumatoid arthritis (RA) are less clearly defined than those in infectious diseases or cancer. Thus, no single microorganism (such as in infectious disease) or cell (such as in cancer) has been identified as causal for most rheumatic diseases. Rather, these are complex conditions in which environmental and genetic factors interact to promote pathophysiology in distinct tissues, sometimes involving currently undefined mechanisms. For example, in RA, synovitis can coexist with fatigue, pain and extra-articular nodules, which are distinct pathologies that presumably have a common underlying mechanism[2]. Individual disease manifestations might be understood relatively well, such as inflammation in synovitis, which can be effectively blocked by directly targeting cytokines or their signalling pathways; yet, without an understanding of the underlying mechanisms, cure of RA as a whole remains elusive[2].

In this Review, we address the challenges of achieving a cure in RA. We first clarify the differences between remission and cure. We then discuss the fundamental mechanisms that underpin the disease process and trigger long-standing inflammation in RA. We conceptualize these underlying mechanisms as 'drivers' in this Review, meaning the processes that stably fuel immune activation and effector cytokine production in RA and thereby prevent cure. Our focus is on drivers such as aberrations of the adaptive immune system, changes in resident synovial cells and their inter-relationships, and factors remote from the joints (including mucosal barrier

Key points

- The term cure indicates the principle absence of disease, whereas remission indicates that disease is still present but is adequately controlled by therapy.
- Although effector cytokines involved in rheumatoid arthritis (RA) are well-defined and can be effectively neutralized by current treatment modalities, cure is still rare.
- Underlying disease mechanisms (referred to as drivers) are thought to continuously promote effector cytokine production and thereby prevent cure of RA.
- Aberrant T cell activation related to autoimmunity, microenvironmental changes associated with local mesenchymal cell priming and so-called 'remote' factors such as intestinal barrier function all serve as drivers of RA.
- To attain cure of RA as an ultimate treatment goal, strategies need to be developed to therapeutically tackle drivers of RA and enable a sustained interruption of the disease process.

function and neuroendocrine circuits), rather than on the well-described downstream pro-inflammatory effector pathways that are critical for defining remission but not cure. Any of these drivers, whilst active, can prevent the achievement of cure. We also discuss current and future possibilities for therapeutic interventions, as well as consequences for the design of future experimental medicine studies to probe these drivers.

Remission versus cure

By definition, cure describes the complete absence of disease and its manifestations, whereas remission addresses the absence of symptoms (TABLE 1). In this Review, we focus specifically on the challenges of achieving cure in RA, a prototypic chronic inflammatory disease. Notably, despite advances in molecular medicine, the current perception is that cure remains a distant goal for such diseases. This perception stands in stark contrast to the large number of effective therapies that are available for RA[2] and the continuous increase in the proportion of patients who are achieving disease remission[3]. Hence, a large discrepancy seems to exist between remission and cure in RA. But what underpins this discrepancy?

Remission in RA is defined as the (almost complete) absence of signs and symptoms of disease[1]. In daily clinical practice, rheumatologists usually define RA remission as the absence of tender or swollen joints, with an emphasis on swollen joints. Composite indices such as the 28-joint Disease Activity Score (remission defined as a score of <2.6)[4], the Simplified Disease Activity Index (remission defined as a score of <3.3)[5], the Clinical Disease Activity Index (remission defined as a score of <2.8)[6] or the ACR–EULAR remission criteria[7] are also widely used to describe remission, and are particularly useful for research studies. All these indices, although differing slightly in their stringency, are essentially based on the same parameters and require or mandate the absence of or very low numbers of tender and swollen joints. Remission in RA is therefore determined on the basis of sufficiently deep control of synovitis. As synovial inflammation largely results from cytokine-triggered innate and adaptive immune cell influx, appropriately targeted cytokine-blocking therapies (such as those that target TNF, IL-6, granulocyte-macrophage colony-stimulating factor and Janus kinases) are powerful remission-inducing tools[8]. If such treatments are used appropriately, >50% of patients with RA reach remission in real-life settings, as demonstrated by data from large registries[3]. Furthermore, when combined with early intervention and treat-to-target strategies, cytokine blockade can be used to achieve remission in the majority of patients with early RA[9].

Although reaching remission undoubtedly represents an important milestone in RA management, it does not equate to cure because the absence of clinical signs and symptoms in patients in remission usually depends on the continuous use of anti-rheumatic treatment. This notion does not diminish the achievements of current RA treatment strategies, which provide relief of signs and symptoms of the disease and gains in quality of life, but does demonstrate the current limitations of the field. Indeed, remission often means the effective suppression of inflammation rather than true eradication of disease. From a clinical point of view, it is not easy to distinguish patients with RA in whom inflammation is only suppressed from those in whom disease might indeed be cured. However, it might be possible to differentiate between remission and cure when treatment is stopped in patients with RA who achieved remission. Attempts to stop treatment are often followed by disease relapses, suggesting that the underlying pathophysiology remains active in these individuals, despite effective suppression of synovitis[10]. Furthermore, patients with RA in whom synovitis has been effectively suppressed can still have debilitating fatigue that is not explained by coexisting conditions such as fibromyalgia[11]. Relapse rates after stopping therapy for RA vary between 40% and 80%[10], indicating that underlying pathophysiological processes (or drivers) remain active and, upon removing the therapeutic brake, cause disease to relapse (FIG. 1). Factors such as the presence of broad-spectrum autoimmunity (which can manifest as multiple autoantibodies), subclinical synovitis detected by imaging and the duration of remission have all been suggested to increase the likelihood of disease recurrence if therapy is stopped[10].

Sustained drug-free remission (>12 months) is far less common than remission in the context of continuous treatment, and is thus a closer scenario to a 'cure' of RA[12,13]. In most cohorts of patients with early RA that have been studied, sustained drug-free remission is rather rare, ultimately being achieved by ~9–15% of all patients[12,13]. The relationship of this state to cure remains uncertain, but individuals with sustained drug-free remission seem to have no relevant progression of joint damage[14].

Drivers of RA that influence cure

The potential pathophysiological drivers of RA that might need to be controlled to achieve cure are discussed in the following sections. Needless to say, such factors differ from the effector cytokines involved in RA and their respective downstream pathways. We propose the presence of three main types of drivers that impair the transition from remission to cure in RA: adaptive immunity-related drivers, resident synovial tissue-related drivers and so-called 'remote' drivers (FIG. 2).

Adaptive immune factors

Clinical observations have shown that widespread autoimmunity towards multiple modified antigens (in the form of anti-modified protein antibodies (AMPAs)) not only facilitates the onset of RA[15–17] but also make sustained drug-free remission less likely[18]. These findings indicate that underlying adaptive immune system dysfunction, which promotes autoimmunity, might function as a driver of RA. Indeed, this idea underpins the fundamental concept that an inability to restore immune tolerance, such as occurs with most of the current treatments for RA, might prevent the achievement of cure. Supporting this notion is the genetic risk factor profile of RA[19], which bears a dominant adaptive immune system signature of T cell activation (genes such as *PTPN22* and *CTLA4* and specific HLA associations) rather than innate immunity, indicating that T cell-mediated immunity has a disease-promoting function in RA, rather than directly determining the amount of inflammation. The regulation of adaptive immune system activation can therefore influence the achievement of cure in RA in several ways (FIG. 2).

Continuous antigen exposure and antigen-related immune responses. The most evident mechanism by which the adaptive immune system affects cure is the regulation of antigenic exposure; for example, the expression of modified proteins on the mucosal surfaces of the lungs and the gum, which is increased by smoking and potentially also by other environmental or microbial stimuli, can lead to continuous antigen processing and T cell stimulation[20]. Cessation of smoking mitigates the risk of developing RA as well as improving the response of patients to treatment[21]. Therefore, counselling for cessation of smoking represents a feasible approach to moving remission in RA closer to cure. Whether antigenic exposure can also be influenced by inhibitors of peptidylarginine deiminases (enzymes that modify proteins by citrullination)[22] that are currently in development remains to be determined. Such compounds could limit underlying adaptive immune responses by controlling the citrullination of proteins and the subsequent antigenic load.

Table 1 | **Remission versus cure in chronic disease**

Attribute	Remission	Cure
Definition	Absence of symptoms	Absence of all disease manifestations
Disease state	Present	Absent
How to achieve	Suppression of symptoms	Elimination of disease-mediating pathological mechanisms
Subclinical disease	Detectable	Absent
Relapse	Possible	Not possible
Prognosis	Disease can progress (clinically or subclinically) and require therapy	No progression possible, no treatment indicated
Follow-up	Necessary	Unnecessary
Management	Continuation of treatment (sometimes intermittently)	Cessation of treatment

Altered homeostasis between effector and regulatory T cells in RA. Continuous T cell activation and the support these cells provide for B cells and antibody generation is a step further down the pathway from antigen exposure. Early studies suggested that a circulating effector T cell signature was present in patients with RA in remission; cells termed 'inflammation-related cells' were associated with relapse of RA but were incompletely characterized[23]. Despite limitations, these data support the concept that aberrant T cell stimulation could remain present in patients with RA in remission and act as an initiator for downstream inflammation.

Studies of conventional T cell subsets in RA have not always produced consistent results, possibly owing to differences in the tissues studied. For example, some studies have found reduced numbers of regulatory T (T_{reg}) cells in the peripheral blood of patients with RA[24], whereas others have shown heightened numbers of these cells in synovial fluid[25]. The issue is further complicated by the instability and plasticity of T_{reg} cells and other T cell subsets in autoimmune disease[26]; for example, the pro-inflammatory microenvironment in experimental autoimmune arthritis promotes FOXP3$^+$ T_{reg} cells to convert to pro-inflammatory IL-17-expressing T cells[27]. Cytokines such as IL-7 and TNF can impair the suppressive function of T_{reg} cells in patients with RA[28–30]. Moreover, essential functional molecules for T_{reg} cells such as cytotoxic T lymphocyte-associated protein 4 (CTLA4) are recruited with delay to the immunological synapse, thereby enabling enhanced co-stimulatory activation of T cells[31]. The consensus is that effector T cell dominance exists in RA, at least in the synovium, for a number of reasons, including metabolic dysfunction[32,33]. Consequently, attempts are currently underway to stimulate T_{reg} cell function in various forms of autoimmune disease including RA, for example, by the therapeutic administration of low-dose IL-2, a well-known growth factor for T_{reg} cells[34,35].

The generation of T follicular helper (T_{FH}) cells in lymph nodes and the spleen is also relevant to antibody generation. These cells produce IL-21 and engage B cells to trigger their activation, maturation and the production of (auto)antibodies[36]. Such cells are not targeted by most current RA therapies and could therefore be responsible for maintaining the continuous autoantibody production that occurs in patients with RA, even when they are in remission. Notably, previous studies have shown that neither cytokine blockers nor methotrexate affect autoantibody concentrations in patients with RA, even if they are in remission, supporting the notion that T_{FH} cells remain active in most patients[37]. In the past couple of years, similar cells have been discovered in the synovial membrane of patients with RA, termed T peripheral helper (T_{PH}) cells; these cells have a molecular profile that is distinct from that of T_{FH} cells, but share essential molecules that are involved in providing B cell help, such as IL-21, CXC-chemokine ligand 13, the transcription factor MAF and inducible T cell costimulator[38]. T_{FH} cells and T_{PH} cells could thus serve as critical checkpoints for maintaining autoimmunity.

Data on the role of ethanol in T_{FH} cell function are also of interest, as alcohol consumption has emerged

as a consistent protective factor in RA[39]. Interestingly, ethanol exerts a potent inhibitory function on T_{FH} cells through its metabolite acetate, which blocks IL-21 secretion, thereby leading to a reduction in autoantibody production and selectively interfering with adaptive immune system activation[40]. Whether regular moderate alcohol intake in addition to conventional anti-inflammatory treatment could act as a cure for RA remains to be determined; however, these data provide a potential molecular rationale for such an approach. Abatacept, a fusion protein of CTLA4 and the Fc portion of an IgG molecule, also has an effect on T_{FH} cells[41] and, in turn, autoantibody concentrations in patients with RA[37]. In addition to its effect on cytokine production by monocytes (which is responsible for its quick anti-inflammatory effect in RA)[42], abatacept interrupts the stimulation of T_{FH} cells and thereby the T cell–B cell axis in RA[41]. Notably, in post hoc analysis of a clinical trial of abatacept in treatment-naive patients with early RA, a small number of participants became autoantibody negative when treated with abatacept[43]. Furthermore, intervention with abatacept in patients with early RA could induce sustained drug-free remission in a subset of individuals, indicating that early intervention in the adaptive immune response in RA might be a strategy for inducing cure[44].

Enhanced effector function of antibodies. In addition to T_{FH} cell activation, antigenic stimulation is required for robust B cell activation, antibody production and affinity maturation in RA. Hence, B cell depletion not only inhibits RA but also blocks the formation of autoantibodies[37] and delays disease onset[45]. Strategies to inhibit B cell activation, such as targeting Bruton's tyrosine kinase (necessary for B cell receptor signalling), could emerge as valuable future tools to interrupt autoimmunity at the B cell level in RA[46]. At the effector level, linking autoimmunity to inflammation, autoantibodies remain relevant as they can trigger pro-inflammatory cytokine production by binding to Fc receptors on monocytes; for example, immune complexes containing rheumatoid factor and AMPAs can trigger cytokine release in monocyte-derived macrophages[47]. The potency of this effect is influenced by the amount of Fc sialylation on the autoantibodies[48]. Low amounts of sialylation (induced by IL-23-mediated down-regulation of the sialylation

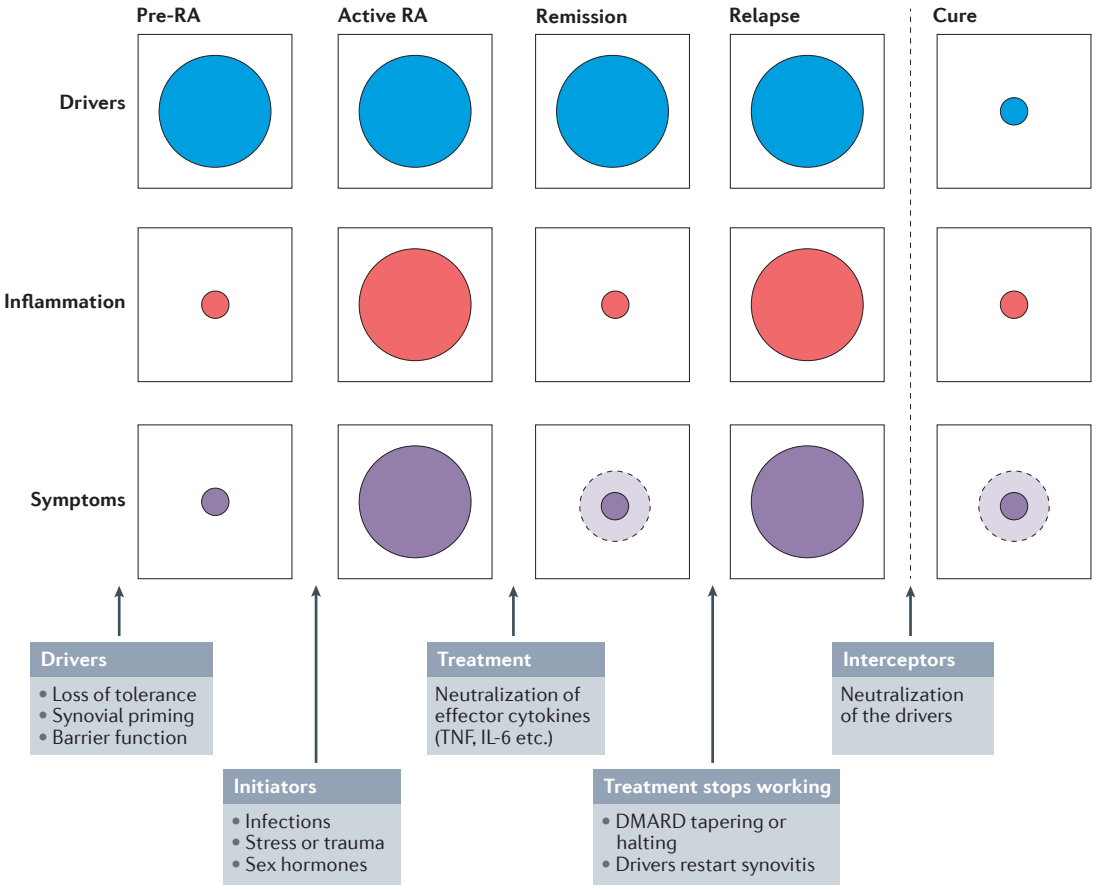

Fig. 1 | **Modular analysis of rheumatoid arthritis disease states.** Patterns of disease-causing mechanisms (drivers), inflammation (effectors) and clinical symptoms are shown for rheumatoid arthritis (RA) in different disease states (pre-RA, active RA, remission, relapse and cure). Processes involved in the shift from one state to the next are indicated in the grey boxes and marked by arrows. The dashed line separating cure from the other disease states indicates that achieving cure is an unmet need that is rarely achieved at present, whereas the other disease states are often observed. The dashed circles in symptoms indicate that damage accrued during the course of disease can impair the patient's condition, despite inflammation being controlled.

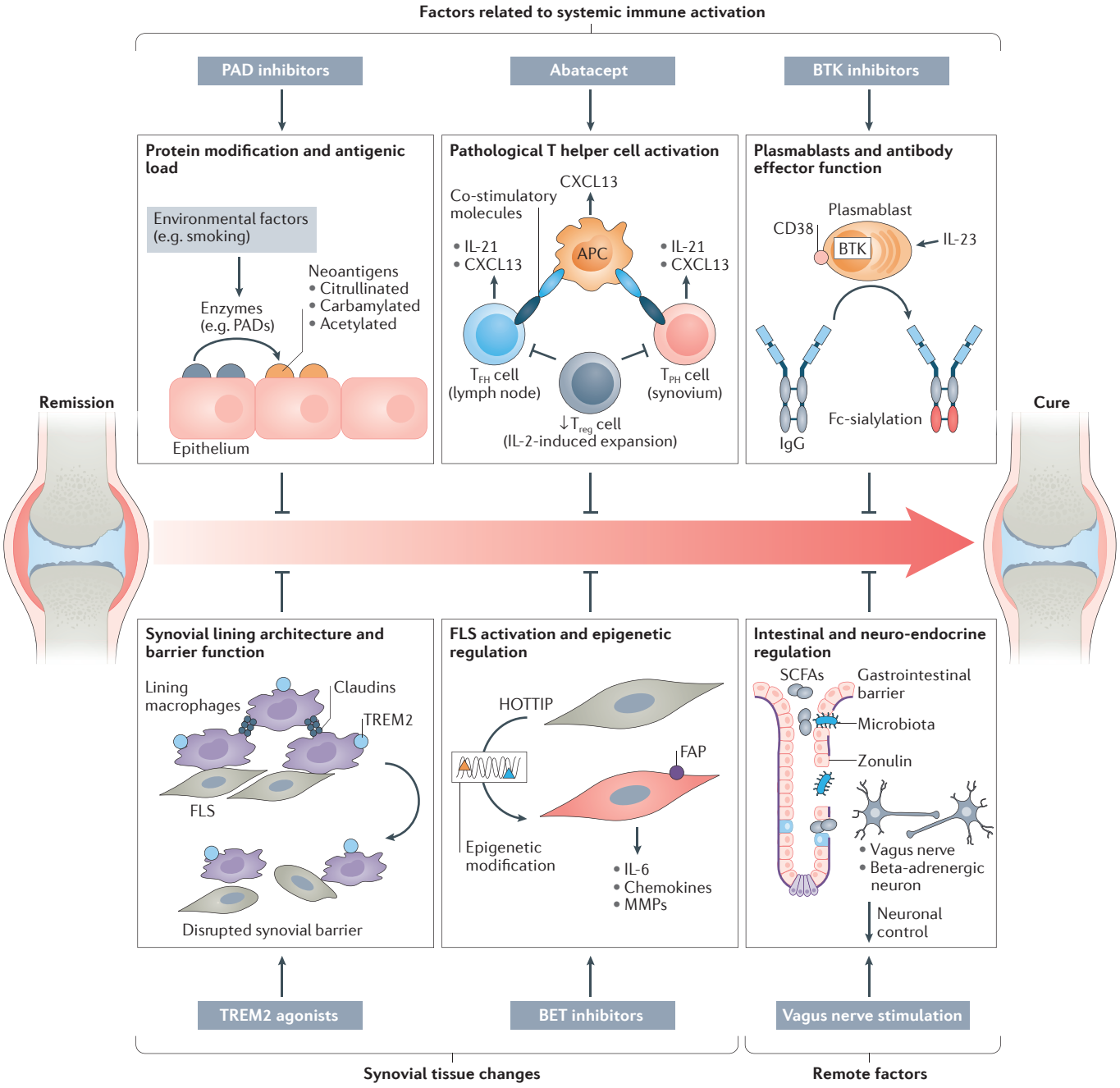

Fig. 2 | **Drivers that affect the transition from remission to cure in rheumatoid arthritis.** In remission (left), disease is present but well controlled, whereas in a state of being cured (right), disease is absent but accrued damage is still present. Processes that impair the transition from remission to cure are shown in the boxes above the arrow and are divided into factors ('drivers') related to systemic immune activation, synovial tissue changes and remote factors. For each process, one example is provided of a therapeutic strategy (grey boxes). APC, antigen-presenting cell; BET, bromodomain and extra-terminal motif; BTK, Bruton's tyrosine kinase; CXCL13, CXC-chemokine ligand 13; FAP, fibroblast activated protein; FLS, fibroblast-like synoviocyte; HOTTIP, HOXA transcript at the distal tip; MMPs; matrix metalloproteinases; PAD, peptidylarginine deiminase; SCFAs, short chain fatty acids, TREM2, triggering receptor expressed on myeloid cells 2; T_{FH}, T follicular helper; T_{PH}, T peripheral helper; T_{reg}, T regulatory.

enzymes in B cells and plasmablasts) enhances the pro-inflammatory functions of antibodies[49]. A shift in antibody effector function towards a pro-inflammatory phenotype, such as that triggered by IL-23, could function as a driver for inflammatory bouts of RA by unleashing the effector function of autoantibodies and triggering cytokine release. Interestingly, oestrogens balance this effector function by increasing the amount of Fc sialylation on autoantibodies via induction of the enzyme β-galactoside α-2,6-sialyltransferase 1 in plasmablasts, thereby potentially explaining the increased risk of RA in postmenopausal women[50].

Synovial tissue factors

Although autoimmunity is an important factor in determining whether cure of RA can be achieved, it might not act alone. Indirect evidence derived from studies examining long-term drug-free remission suggests that, although the initial achievement of drug-free remission depends on the breadth of autoimmunity, in the long run, the importance of autoimmunity might diminish[51]. RA is known to result from a combination of immune cell influx into the joints and resident tissue changes; these synovial tissue changes can precede or, might even be responsible for, immune cell migration into the joints in patients with RA[16], making them a potential driver of RA (FIG. 2).

Changes in synovial barrier function caused by resident lining macrophages. Important insights into the molecular structure and regulatory and pro-inflammatory functions of the synovial membrane have been gained in the past few years. Hence, we now know that the surface of the synovial membrane is covered by a layer of phagocytosing tissue-resident macrophages that provide a physical barrier (and a barrier to immune infiltration) between the synovium and the joint space, ensuring cell-free synovial fluid[52]. The development of RA requires the disruption of this layer, which can be sporadic; however, sustained leakiness of this barrier strongly facilitates the recurrence, and chronicity, of arthritis. The regulatory function of the synovial membrane requires the correct functioning of tight junctions composed of claudins, but also requires TAM receptors such as TREM2, MERTK and AXL, which could be therapeutically fostered to prevent relapses and to support the achievement of cure in RA by clearing the pathological influx of immune effector cells[53]. In addition, in a single-cell analysis of RA synovial membrane published in 2020, two MERTK$^+$ macrophage subpopulations were identified that were transcriptionally enriched in negative regulators of inflammation and that produced inflammation-resolving lipid mediators[54]. These cells were associated with remission (corresponding to resolution of arthritis), involved in synovial repair responses and, when numbers of MERTK$^+$ macrophages were low, relapses of arthritis were more frequent.

Epigenetic changes in fibroblast-like synoviocyte function. Of major importance are the changes that occur in fibroblast-like synoviocytes (FLSs) during RA. Modern technologies such as single-cell RNA sequencing have enabled the categorization of FLSs and the attribution of functional profiles to individual sub-types. Notably, the depletion of FLSs expressing fibroblast-activated protein (FAP) from the joints of mice with serum transfer-induced arthritis suppressed the production of several chemokines and IL-6 by these cells[55]. These data indicate that the FLSs themselves could function as drivers of RA and prevent attainment of cure. Several studies have indeed suggested time-dependent epigenetic changes in FLSs during the course of RA. Chromatin hypomethylation, histone acetylation and microRNAs can all enhance the potential of these resident synovial cells to produce cytokines and chemokines locally, as well as affecting mesenchymal tissue responses within the joint[56]. One example is the transcription factor TBX5, the expression of which is upregulated in RA FLSs by hypomethylation, thereby controlling the expression of a series of chemokines that attract immune cells to the joint[57]. Another example is the increased expression of microRNAs (such as miR-155 and miR-223) in FLSs from patients with RA, which leads to increased cytokine expression by these cells[53,58].

One could speculate that FLSs are epigenetically imprinted by the continuous presence of immune cells and inflammation in the joint, which could essentially change their homeostatic behaviour. In accordance with this concept, the pattern of methylation in FLSs is known to change between early RA and established RA[59–61]. In established disease, FLSs have hypomethylated (and thus activated) genes related to Wnt–β-catenin signalling pathways, integrin signalling pathways and platelet-derived growth factor signalling pathways, all of which are associated with the activation of mesenchymal cells and structural changes to the mesenchyme of the joint[59]. These findings are particularly interesting because drugs that manipulate methylation and acetylation enzymes are being developed for cancer therapy[62] and could, if proved safe in RA, be used to reverse these synovial tissue changes, potentially moving RA one step closer to being cured. Better characterization of the changes to the epigenome in mesenchymal cells will therefore pave the way for new approaches to shutting down the chronic inflammatory process in RA.

Long non-coding RNAs control the positional function of FLSs. Homeobox (HOX) genes determine the positional localization of fibroblasts in the body. Thus, FLSs from distal as opposed to proximal joints, as well as those from lower as opposed to upper extremities, have specific HOX gene expression patterns that are linked to functional differences in the cells, including differences in adhesive, proliferative, chemotactic and destructive behaviours[63]. For example, FLSs from hand joints have more pronounced chemotactic and matrix-destructive characteristics than those from other joints. HOX gene expression is regulated by long non-coding RNAs such as *HOTTIP* and *HOTAIR*, which are among the most differentially expressed transcripts between FLSs from upper and those from lower joints and between FLSs from distal and those from proximal joints. *HOTTIP* and *HOTAIR* are also expressed in FLSs from patients with RA[63]. Moreover, targeting *HOTTIP* or *HOTAIR* in RA FLSs in vitro inhibits their proliferation, invasion and migration capabilities, and can also inhibit inflammatory arthritis in vivo[64,65]. Hence, positional factors related to pro-inflammatory FLS behaviour and associated with long non-coding RNA expression could be responsible for the recurrence of disease in RA and prevent cure.

'Remote' factors

Although already discussed in relation to AMPA-related autoimmunity, smoking is also a remote, non-joint based factor that prevents cure of RA. Effects outside of the joint, such as the induction of citrullination in the bronchial and oral epithelium and recognition by the

immune system of such modified proteins on epithelial structures can explain the prevention of cure by smoking. Other factors at sites outside of the joints might also contribute to the failure of cure in RA. Gastrointestinal microbiota composition is already altered in patients with early RA[66] and can even be altered in individuals during the preclinical phases of the disease[67]. Metabolic products of these microbiota, such as the short-chain fatty acids that are produced during the metabolism of fibre, control gastrointestinal permeability and the migration of immune cells from the gut to secondary lymphoid organs and the joints[68]. Thus, gut leakiness could be a further driver of immune cell influx into the joints, promoting disease relapse.

Central nervous system changes might also influence the possibility of curing RA. Some patients with RA develop hypersensitivity to pain during their disease course; a process that probably involves central nervous system alterations and central sensitization[69]. Furthermore, psychosocial stress is a known trigger for disease flares in RA[70,71]. However, the relationship between stress and RA is unclear. Stress induces the release of glucocorticoids and catecholamines from the adrenal glands, which act through β-adrenergic receptors, yet these mediators reduce cytokine release rather than enhance it[72]. Hence, it remains unclear how stress induces flares of RA. One potential explanation is that, in patients with RA, the stress response is considered to be defective, leading to inadequate immune-regulatory sympathetic signals in the joints, as well as a dysfunctional hypothalamic–pituitary axis, which results in robust, prolonged cytokine release[73].

Potential therapeutic strategies

Although not affected in the most part by current treatments for RA, the drivers highlighted in the previous sections can all be targeted in one way or another (FIG. 2). The continuous adaptive immune system activation characterized by antigen exposure, T_{FH} cell and T_{PH} cell activation and the formation of autoantibodies with pro-inflammatory effector functions, which are not targeted by most currently used RA treatments, might trigger inflammatory disease relapses once anti-rheumatic treatment is stopped. Lifestyle interventions such as cessation of smoking or moderate intake of alcohol might modify these processes. In addition, the limitation of antigen exposure by peptidylarginine deiminase inhibition, the stimulation of T_{reg} cell function via low-dose IL-2, the targeting of T_{FH} and T_{PH} cells with abatacept or IL-21 inhibition, and the modification of antibody effector function by IL-23 inhibition, oestrogens or additional dietary measures[74] all represent strategies that could be adopted to target adaptive immune system activation in RA. Notably, such approaches are not anti-inflammatory per se, as they do not directly block effector cytokines or inhibit synovitis. Furthermore, even if the ultimate immune drivers of RA are T cells, it might still be necessary to target other components of the adaptive immune system independently to achieve cure, such as plasma cells residing in bone marrow niches[75].

Whether it is possible to interrupt the immunological mediators of established RA remains to be seen. Once an immune response has been triggered, it becomes increasingly sophisticated as a result of mechanisms such as epitope spreading[16]. Furthermore, the presence of inflammation generally enhances immune responses, potentially counteracting attempts to switch off, or tolerize[76], autoimmune drivers of RA. Controlling dysregulated immunity might be easiest in the earlier stages of RA, potentially even in individuals at risk of developing RA, rather than in those with manifest disease. In type 1 diabetes mellitus (another chronic autoimmune disease), the application of therapies such as anti-CD3 antibodies in late stages of pre-disease can, at worst, delay disease by several years, and might even be preventative[77]. Similar early interception studies are ongoing with abatacept[78,79], with the aim of preventing the onset of RA in individuals with high levels of anti-citrullinated protein antibodies, and a number of other preventative strategies are also being discussed[80].

Restoration of the phagocytic inner barrier of the joints might also be critical for preventing RA relapses. This concept is supported by the finding that patients with RA in remission have an increased risk of disease flare if they have a low proportion of joint-resident macrophages that express markers of lining macrophages, such as TREM2 or MERTK[54]. However, the restoration of macrophage-mediated barrier function in the joints might require an intact joint anatomy, suggesting an important role for early treatment. To improve the barrier function of the synovial membrane, molecules that foster tight-junction formation targeting claudins or tyrosine kinase inhibitors could be used, as they have been shown to limit arthritis[52,81].

Interventions that tackle the spatially distinct pro-inflammatory FLS patterning in the joint might also represent completely new and powerful tools to reset the local inflammatory environment that is maintained by these cells. Expression of *HOTAIR* and *HOTTIP* can be downregulated by bromodomain and extra-terminal motif (BET) inhibitors[82], which are currently being developed for cancer treatment[83]. In addition, FAP, which is expressed by activated FLSs, could be targeted by antibodies or small-molecule enzyme inhibitors[84]. Other approaches that seem feasible include the inhibition of demethylases that regulate the proliferation and activation of FLSs and the use of antagomirs that target miR-155, although such approaches might not be specific to these cells[85,86].

Tackling remote factors also seems within reach and could emerge as an interesting asset in RA management. For example, fibre-rich diets can change the composition of intestinal microbiota, increase immune-regulatory short-chain fatty acid production, reduce gastrointestinal permeability and potentially relieve the symptoms of RA[68,87]. Fostering efferent immune-regulatory brain signals could be an additional option for improving the chances of achieving cure of RA, building on the concept of an inadequate brain regulatory response to inflammation in these individuals. Along these lines, agonists of β-adrenergic receptors that mimic the activation of efferent sympathetic neurons dampen pro-inflammatory cytokine expression by macrophages[88,89], and the initial results from studies of vagus nerve stimulation have

shown a decrease in inflammatory activity in patients with RA[90].

Outlook

Although remission is a relevant and important therapeutic target, its downside is the need for potentially lifelong therapy if cure is not achieved. In general, more work is required to define the factors that determine the crossroads between remission and cure in RA; however, we should now start to embrace the potential for cure as we better understand the pathophysiology of RA. The move towards cure will require a deeper understanding of the drivers of disease highlighted in this Review and how to target them, and not simply knowledge of the effector cytokines that elicit immediate symptoms. In this context, studies are starting to emerge into the molecular signatures that distinguish remission and cure. Although no predictors of cure in RA have yet been defined, some studies have reported predictors of sustained drug-free remission. One study showed that genetic factors (such as the shared epitope) and autoimmunity (such as the presence of anti-citrullinated protein antibodies) are negative predictors of sustained drug-free remission[91], reflecting the mechanisms discussed in relation to adaptive immune drivers. In addition, an increased serum concentration of IL-27, among other proteins, has been identified as being associated with sustained drug-free remission[92]. Notably, IL-27 inhibits ectopic lymphoid-like structure development in the synovium, and thus reflects the importance of T_{FH} cell activation and B cell maturation as underlying drivers of disease[93]. Finally, immune-regulatory metabolites are preferentially upregulated in patients who reach sustained drug-free remission. These metabolites include amino acids such as L-arginine, a well-known immune-regulatory mediator linked to alternatively activated macrophages, as well as L-proline and L-lysine[94]. In addition, several oxylipids with regulatory immune functions, such as 8,9-DiHETrE, 20-carboxy-LTB4 and 9,10,13-TriHOME, are increased in patients with RA in sustained drug-free remission, some of which are involved in the synthesis of pro-resolving lipid mediators such as lipoxin B4 (REF.[94]).

We will also need to reconceptualize clinical studies by moving away from measuring the anti-inflammatory effects of drugs and towards a true interception of the underlying disease drivers highlighted in this Review. A considerable challenge exists in designing studies to assess curative strategies. Traditional study designs seek rapid effects of therapies on signs and symptoms of RA (such as ACR or EULAR responses), but these outcome measures reflect inflammation and might miss effects on the regulation of autoimmunity, which will only manifest as suppressed inflammation at later time points. To adequately test curative or preventative strategies, outcome measures must reflect the immunological drivers themselves[76]. Moving forwards, clinical studies should include patients with RA in stable remission who are at a high risk of relapse, rather than patients with active disease, and should use targets and outcome measures that embrace the perceived drivers of the disease process. To do so, the outcome measures used for such studies will have to fundamentally change and move away from simple short-term measures of inflammation. Whether cure will be achievable with a single intervention or multiple concurrent (or sequential) therapies awaits clarification. However, it is intriguing that remission, including sustained drug-free remission, becomes easier to achieve if RA is treated earlier[12], suggesting that perhaps not all drivers are activated synchronously. Some drivers might even only kick in once disease is established, such as might be the case with epigenetic factors that are propelled by a defined duration of inflammation. Hence, adequate treatment of early RA, or even of individuals at risk of developing RA, could provide the most tractable route to cure with current therapies.

Conclusions

The treatment of RA should always be primarily aimed at rapidly controlling the signs and symptoms of the disease. We have developed outstanding therapies and tools to accomplish this task; thus, it will consequently be challenging to develop therapeutics with better anti-inflammatory potential than those that currently exist. However, although remission is currently a relevant aim for treat-to-target strategies, cure is highly unlikely to develop just from the increasingly aggressive use of anti-inflammatory therapy in patients with established RA. So what comes next? We propose that shifting focus from remission to cure is the next great challenge for RA treatment, not least because lifelong, albeit effective, control of inflammation cannot be the ultimate target in RA. Targeting the underlying drivers of RA, which are different from the pro-inflammatory effectors, is likely to become a central approach in attempts to attain cure in RA, not least because there is a certain saturation effect of anti-inflammatory drugs in RA and because most of the underlying drivers are not tackled by current therapeutics. Using such approaches, abolishing disease rather than suppressing symptoms could become the principle aim of RA treatment.

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