

Supplement Review

Why do we not have a cure for rheumatoid arthritis?

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Chapter summary

There are currently unprecedented opportunities to treat rheumatoid arthritis using well-designed, highly effective, targeted therapies. This will result in a substantial improvement in the outcome of this disorder for most affected individuals, if they can afford these therapies. Yet our lack of understanding of the basic mechanisms that initiate and sustain this disease remains a major obstacle in the search for a definitive cure. It is possible, if not likely, that our best approach will be to identify individuals at risk and devise reliable, safe methods of preventing the disease before it occurs. The means to do this are currently unknown but should serve as a major focus of research.

Keywords: etiology, prevention, rheumatoid arthritis, therapy

Introduction

New therapies have dramatically changed the way both clinicians and patients think about treatment of rheumatoid arthritis (RA). Indeed, it has become realistic to think about improvement defined by the ACR70 (reduction by 70% in the American College of Rheumatology composite response criteria) as the standard of care, and even to consider the possibility of remission and prevention of long-term disability. However, the possibility of cure remains remote. Why we do not have a cure for RA is a question that patients around the world continue to ask their physicians daily but, unfortunately, is no better answered in this millennium than it was in the last. Rheumatologists, the eternal optimists, can now offer their patients confident reassurance that the tragic outcomes of past decades are largely preventable, albeit at considerable ongoing expense. Yet the very fact that chronic, and generally uninterrupted, therapy is needed to suppress the manifestations of this disease is perhaps the clearest indication that a cure is nowhere in sight. Indeed, finding a

cure for established RA is possibly no more likely than finding a cure for hypertension, where control of organ damage is the only realistic goal of therapy. The impediments we currently face in finding a cure for RA are numerous and are considered here. They are summarized in Table 1. In addition, the possibility that RA can be prevented is explored.

Is there a well-defined etiology for RA?

It is hard to find a cure for RA when the cause is unknown. Considerable attention has focused on the possibility that there is an infectious etiology of RA. Most would, however, agree that the possibility of finding a single infectious etiology for this disorder has been all but eliminated. Yet the modest success achieved by the use of minocycline in the treatment of RA continues to be interpreted by some as being indicative of a bacterial etiology that has completely eluded detection by the scientific community. Proponents of this hypothesis have been particularly vocal and visible to the lay community at large. A viral etiology has been

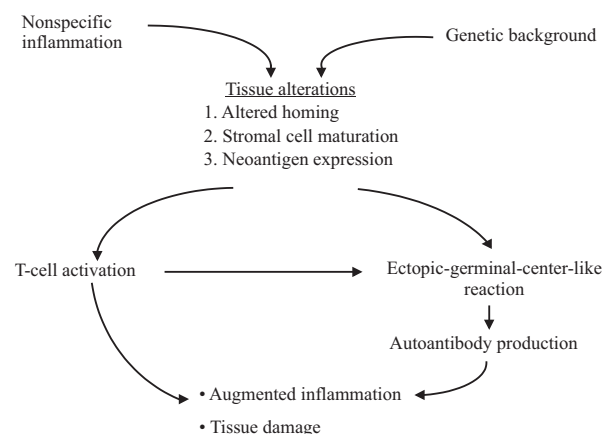
Table 1**Obstacles to curing RA**

Lack of knowledge of etiology
Incomplete understanding of pathogenesis
Lack of means to intervene in most of the relevant processes
Disease heterogeneity
Inability to make an early diagnosis
Limited ability to recognize those at risk

even more difficult to disprove. Perhaps the strongest case has been made for parvovirus B19 and retroviruses. However, recent findings identifying parvovirus-B19 nucleic acid and antigens in a high proportion of RA synovial tissue samples and not in samples of non-RA synovium have not been replicated [1]. The synovial detection of this ubiquitous agent is probably related to the presence of inflammation rather than the cause of it. The RA-like lentivirus arthropathy that affects goats has stimulated interest in a retroviral etiology for the human disease. Studies demonstrating the presence of unique retroviral sequences in genomic material from RA synovial tissues and cells have also been difficult to reproduce [2,3]. Even if a retroviral etiology were to be discovered, the lessons learned from HIV would suggest that the discovery would be unlikely to lead to a cure or a vaccine in the foreseeable future.

If microorganisms are involved in the pathogenesis of at least some cases of RA, it is more likely in an indirect role, such as contributing to the development of autoimmunity through mechanisms such as molecular mimicry. A persuasive case has been made for immune responses to endogenous heat shock proteins that have been shown to share sequences with those of a number of microorganisms [4]. One of the microorganisms incriminated is *Escherichia coli*, a ubiquitous part of the gastrointestinal flora. Intriguingly, these sequences are also present in the HLA-DR4 alleles that are associated with RA [5]. If gut bacteria are indeed involved in precipitating immune responses to endogenous antigens, the elimination of such etiologic agents is obviously not a realistic goal. More viable approaches might be specific immunomodulation using strategies such as oral tolerization, induction of T-regulatory cells, or redirection of T-cell function.

It is now widely believed that the first event in RA may be nonspecific inflammation, which leads to T-cell priming in genetically susceptible individuals as a secondary event, this serving to accentuate and amplify the inflammation. This paradigm is shown in Fig. 1. An alternative hypothesis suggests that autoimmunity is primary in RA, and that autoimmune mechanisms precipitate and sustain the

Figure 1

A current paradigm for the pathogenesis of rheumatoid arthritis that does not require an immune-recognition event of arthritogenic antigens at the induction phase. In this paradigm, nonspecific inflammation from a variety of causes precipitates an aberrant synovial response in a genetically susceptible individual. Subsequent recruitment of immune cells, including B cells, T cells, and dendritic cells, establishes an ectopic lymphoid organ in the synovium that facilitates the local production of autoantibodies to synovial constituents. Autoantibodies, along with activated T cells, serve to amplify the inflammation and the consequent tissue damage. Such a nonspecific onset for the disease is in keeping with the observed heterogeneity in clinical, pathological, and immunological features of RA.

disease. Yet the identification of RA specific autoantigens has been elusive. The most logical place to look for autoantigens is in the joint itself. Antigens derived from cartilage are particularly intriguing candidates. Because of its established role in precipitating a destructive, RA-like arthropathy in susceptible mice, type II collagen has been the most thoroughly studied antigen. The adoptive transfer of murine collagen-induced arthritis using T cells and antibodies has suggested that immune responses to this articular antigen are likely to be of relevance in human RA. Yet extensive studies in RA patients have failed to confirm this hypothesis. Indeed, detailed analyses of T-cell receptor repertoire in RA do not consistently demonstrate evidence of any oligoclonal bias, and when present, the patterns differ from patient to patient. It has been suggested that there may be a global defect in generating a diverse T-cell repertoire in patients with RA, and that this may be a primary defect rather than a result of the disease [6].

Recently, there has been a resurgence of interest in the potential role of autoantibodies in the pathogenesis of RA. Although rheumatoid factor has long been the hallmark of this disease, it has been difficult to incriminate this autoantibody directly in the pathogenesis of either the synovitis or the resultant articular damage. The demonstration that there are other autoantibodies with a higher degree of specificity for RA than that of rheumatoid factor has given

new impetus to the attempts to identify their corresponding autoantigens [7]. In particular, it has been shown that reactivity to citrulline, a residue generated by the post-translational modification of arginine, is critical to a number of the autoantibody responses specific to RA [8]. Whether these antibodies are directed towards a specific articular antigen remains to be seen. In contrast, the need to implicate an antigen specific to joints has recently been challenged by a murine serum-transfer model, in which a ubiquitous cytoplasmic protein, glucose-6-phosphate isomerase (GPI), is the target antigen [9]. Very recent studies suggest that this enzyme of the Krebs cycle is abundant on the surface of the articular cartilage in affected animals [10]. Although anti-GPI antibodies have been detected in patients with inflammatory arthritis, RA specificity remains controversial.

Another issue that may influence the capacity to induce remission in RA patients is the considerable heterogeneity of the disease. The clinical, pathological, and immunological heterogeneity seen in this disorder has been well documented. Yet the underlying basis of this heterogeneity is not well understood. This may well be indicative of the presence of multiple pathogenic factors, operating individually or in combination, in genetically susceptible individuals. Moreover, it is clear that the underlying genetic susceptibility itself may be heterogeneous in different populations. Thus, RA may not be a single disease entity with a well-defined etiology that has yet to be identified, but rather a characteristic clinical syndrome resulting from a complex, and possibly cumulative, interaction of multiple environmental and genetic factors.

Can RA be 'cured' once persistent synovitis is established?

There are now highly effective therapies for RA. Control of systemic and articular inflammation, along with significant retardation of articular damage, are becoming the norm in all but the most resistant patients. This will almost certainly translate into long-term prevention of disability as patients are aggressively treated early in their disease course. Yet the available arsenal of RA therapies rarely, if ever, induces a lasting, drug-free remission in the disease, in other words something akin to a cure. Indeed, there is an almost predictable, often severe, relapse associated with the withdrawal of most of the 'disease-modifying' antirheumatic drugs currently used in clinical practice, including biologic agents that target tumor necrosis factor (TNF)- α and IL-1. The exceptions to this phenomenon, observed occasionally in some individuals having taken antimalarials and injectable gold salts, most likely relate to the long tissue half-life of these agents rather than an intrinsic ability to induce sustained remissions.

The most plausible explanation for the phenomenon of relapse after withdrawal of antirheumatic drugs is that these therapies are collectively aimed at suppressing relatively

peripheral pathways of inflammation and not central abnormalities in cell function that underlie the disease. What are some potential candidates for such central abnormalities? There is clearly a wide divergence of opinion regarding the answer to this question. Proponents of the central and primary role of autoimmunity in the pathogenesis of RA conclude that autoantigens, either in intra-articular or extra-articular locations, will invariably reignite inflammation when the effects of suppressive therapy are withdrawn. Even a relatively complete 'overhaul' of the immune system, as achieved by bone marrow transplantation, has been associated with recurrence of disease, albeit in milder form, presumably because disease-specific memory cells are not adequately deleted by these procedures. Proponents of an occult infectious etiology conclude that recurrence of disease is inevitable if the offending agent is not specifically eradicated. Finally, mechanical abnormalities in the joints induced by antecedent inflammation may predispose to subsequent inflammation whenever anti-inflammatory treatments are withdrawn.

A hypothesis that is currently gaining momentum suggests that RA patients may have intrinsic abnormalities in their synovial responses to inflammation and injury, irrespective of the cause. The inability to bring these responses to resolution effectively may lead to the persistence of an aggressive, angiogenic granulation tissue that is highly equipped to reinduce inflammation and remodel the surrounding articular structures. It has been suggested that the primary effectors of this aberrant response are macrophages, osteoclasts, and fibroblasts.

Macrophages and their products, particularly TNF- α , are responsible for many of the inflammatory manifestations of the synovial lesion, including the activation of the synovial endothelium, which results in the ongoing recruitment of other classes of leukocytes. The dramatic and rapid anti-inflammatory effect associated with the inhibition of TNF- α is compelling evidence for its central role in regulating this inflammatory process. Yet, as mentioned above, the almost predictable recurrence of the inflammation with the withdrawal of this therapy clearly indicates that this effector pathway is rapidly reinitiated by more central mechanisms.

Recent evidence suggests that osteoclasts are likely to be the primary effectors of the bone erosions that are typical of RA [11]. Osteoclastogenesis and bone resorption occur from the outside in, i.e. from the synovial pannus into the marginal bone, and from the inside out, i.e. from the subchondral bone out to the bone surface. The importance of the subchondral bone and bone marrow in the pathogenesis of rheumatoid articular damage is becoming increasingly recognized. Strategies targeting osteoclasts and osteoclastogenesis are quite promising as regards preventing erosive damage, even in the absence of associated anti-inflammatory effects [12]. Indeed, the impressive

effects of anti-TNF agents in retarding the progression of erosive damage may well be related to their direct effects on osteoclast formation and/or function rather than their effects on inflammation [13]. Is this bringing us closer to a cure? Most would agree that effective prevention of tissue damage is a major step forward, but that the need to sustain therapy to achieve this cannot be equated with a cure, in which the entire inflammatory/proliferative/destructive process is brought to a complete and sustained resolution. In this latter scenario, although a relapse may still be possible, as it is in the case of tumors and chronic infections, there would be no need for ongoing therapy unless such a relapse did indeed occur.

In contrast to the erosive bone damage, damage to the articular cartilage in RA appears to be mediated by synovial fibroblast-like cells and chondrocytes. 'Transformed' synovial fibroblasts invade articular cartilage by degrading the extracellular matrix of the cartilage through the production of a variety of proteases. Additionally, under the influence of proinflammatory cytokines, particularly IL-1, chondrocytes become major participants in the degradation of the surrounding cartilage matrix, while losing their capacity to repair the damage by synthesizing new matrix components. Inhibiting the effects of IL-1 by changing the balance between this cytokine and its physiological inhibitor IL-1Ra has proven to be an effective strategy in preventing articular damage. Ultimately, because of the avascular nature of cartilage, once damage has occurred, it cannot be repaired, thus making a cure essentially impossible.

It appears that once the inflammatory rheumatoid synovial organ has formed in a specific joint, it is unlikely that this tissue can be brought back to 'normal'. Moreover, the process almost certainly begins before there are clinical signs, and by the time the disease becomes clinically evident, in most cases the synovitis is capable of autonomous perpetuation. Therefore, by the time clinicians perceive that the disease is even present, a cure may have already become very difficult to achieve.

Can RA be prevented before synovitis becomes clinically evident?

One of the major impediments to the development of definitive treatment for RA is the inability to detect, and in turn study, the earliest events that predictably lead to the development of persistent, destructive synovitis. There are virtually no data, epidemiologic or otherwise, regarding the premorbid status of individuals destined to develop RA. It can reasonably be asked: can anyone develop RA given the right circumstances? The available data indicate that a typical high-risk individual would be a perimenopausal woman with a family history of RA or a related autoimmune disease, who is a smoker, who is positive for rheumatoid factor, and who carries at least one HLA-DR4 allele. The risk of such an individual developing clinically detectable

disease, say, within 5 years, has not been established. A conservative estimate would be at least 5% and the actual risk could be substantially higher. Assembling and longitudinally studying a cohort of such individuals would afford the best opportunity to understand how RA starts and, ultimately, how it can be prevented.

If such a 'pre-RA' cohort were to be assembled, early indicators of impending clinical disease would need to be sought in a longitudinal study. Particular attention would be paid to aspects such as the development of specific autoantibodies. Such a strategy has been used effectively to predict the onset of autoimmune diabetes in genetically susceptible children [14]. Although this latter disorder has a more predictable age of onset, thus lending itself better to this type of strategy, a similar approach might be adopted with certain populations of individuals that are at high risk for developing RA. Longitudinal analysis of serum to detect the development of specific autoantibodies may ultimately be too restrictive an approach, and the application of broad-based proteomic approaches may be necessary to identify novel and unsuspected markers.

An important aspect of studying the early stages of RA would be the longitudinal examination of typical 'RA joints' such as the knees and MCPs using sensitive imaging modalities such as MRI, PET, or spectroscopy. The available histopathologic studies of clinically uninvolved joints have demonstrated the presence of subclinical synovitis in affected individuals [15,16]. This can broadly be taken to imply that there is likely an early, subclinical stage in the history of each RA patient in which the synovium becomes abnormal without actually being clinically inflamed. During this initiation stage, it may be possible to prevent the trafficking of specific cells into the synovial microenvironment, thereby averting the deleterious downstream events that result once these cells provoke aberrant synovial responses. In particular, inhibiting the recruitment of T cells and dendritic cells would be a logical objective. A potentially appealing strategy involves the use of chemokine inhibitors. The inhibition of candidate chemokines such as stromal derived factor-1 (CXCL12), which is an important mechanism by which stromal cells recruit lymphocytes, has been shown to be quite effective in animal models [17]. Alternatively, strategies that serve to bias the immune system away from Th1 responses towards Th2 responses may also prove to be effective in preventing the disease, although there has been a suggestion that patients with RA may have defects in Th2 differentiation [18]. The key would be the detection of early events, before the establishment of the chronic inflammatory synovial organ.

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