Science, medicine, and the future

Treatment of rheumatoid arthritis

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Rheumatoid arthritis is the commonest form of inflammatory arthritis and affects about 1% of the population. The clinical presentation is heterogeneous with a wide variation in age at onset, degree of joint involvement, and severity. In addition, it is difficult to predict at diagnosis which patients will develop severe disease. Nearly 90% of patients with aggressive disease will become clinically disabled within 20 years. Furthermore, in patients with severe disease or extra-articular symptoms mortality is equal to that for patients with triple artery coronary artery disease or stage IV Hodgkin's lymphoma. Thus the view that rheumatoid arthritis is a benign disease has been discredited.

For the past 20 years the treatment of rheumatoid arthritis has been developed on the premise that the prognosis of the disease is generally good. Treatment has been based on the sequential use of drugs starting with non-steroidal anti-inflammatory drugs progressing to disease modifying agents such as gold, sulphasalazine, and methotrexate. This pyramid approach has had limited success at preventing joint destruction or improving long term outcome. In fact, up to 90% of patients with aggressive synovitis have evidence of bone erosions within two years of diagno-

Possible future developments

- Early identification and treatment of patients at risk of aggressive disease from clinical and genetic characteristics
- Development of more selective non-steroidal anti-inflammatory drugs and cyclo-oxygenase 2 inhibitors
- Treatment with neutralising monoclonal antibodies, designer proteins (immunoadhesins), and naturally occurring inhibitors of cytokines
- Development of drugs to inhibit angiogenesis and leucocyte-endothelial-stromal interactions in the joint
- New drugs to induce apoptosis or prevent accumulation of leucocytes in the joint

sis despite treatment.¹ This has led to a move towards using disease modifying drugs early in the disease.² The future of rheumatoid arthritis is currently at an exciting cross roads with management focusing on early diagnosis, intensive induction therapy, and intensification of treatment for resistant disease. This review highlights how recent developments in our understanding of the pathogenesis of rheumatoid arthritis have led to the discovery of new targets for treatment.

Causes of rheumatoid arthritis

Cellular interactions in the synovium

Although there is abundant evidence that rheumatoid arthritis is immune mediated, it is still not clear whether it is primarily an autoimmune disease; whether the initiating agent is infectious, self antigen, or both; to what extent the course of the disease depends on systemic or joint specific events; or how the cells within the rheumatoid joint interact to produce the invasive and destructive environment observed in the disease.³ Rheumatoid arthritis is characterised by infiltration of the synovium with lymphoid cells (fig 1), formation of new blood vessels, synovial proliferation, and joint destruction. The current view is that chronic inflammation is initiated by antigen induced activation of T cells which accumulate within the joint. Whether the perpetuation of the inflammatory process depends on T cells remains highly contentious, but vascular and synovial cell proliferation as well as cytokine production seem to sustain chronic synovitis and play an important part in joint destruction.⁴⁻⁷ Figure 2 shows

Fig 1 Cellular components and sites of destruction in rheumatoid joint⁷

Fig 2 Relative importance of inflammatory responses, immune responses, and mesenchymal cell transformation during various stages of rheumatoid arthritis¹¹

the stages and cellular components thought to be important in the pathogenesis of rheumatoid arthritis.

Genetic and environmental factors

Epidemiological data support the case for both environmental and genetic factors causing rheumatoid arthritis. Research in twins and other genetic studies suggest that the genetic component is at best 30%. An important genetic determinant for rheumatoid arthritis resides within the groove of the major histocompatibility complex molecule that binds antigen and presents it to T cells (typically the alleles DR4 and DR1).⁸ This region, however, seems to be associated with only the severe forms of the disease. Current studies are exploring whether early screening programmes will be able to identify accurately which patients with early rheumatoid arthritis are likely to develop severe destructive joint disease and should therefore be treated aggressively at an early stage.

The idea that rheumatoid arthritis has an infectious trigger continues to fascinate rheumatologists, but no joint specific antigens have yet been discovered. Recent studies with genetically engineered mice suggest that a breakdown in the mechanisms of self tolerance can lead to joint specific disease without the need for joint specific antigens.⁹ Techniques for rapidly sequencing genes and identifying regions of interest are being used to look for new genetic loci associated with rheumatoid arthritis. Such searches for candidate genes have been effective for other polygenic diseases such as diabetes, and the discovery of predisposing genes outside the major histocompatibility complex may provide future avenues for directed treatment.¹⁰

Role of cytokines

The pattern of cytokine production within the rheumatoid synovium is very different from that observed in other immune mediated diseases. Most of the cytokines produced in rheumatoid arthritis seem to originate from macrophages or fibroblasts rather than activated

leucocytes. Tumour necrosis factor α is thought to be important for controlling the proinflammatory cytokine network in rheumatoid arthritis.¹¹ Neutralising antibody to tumour necrosis factor has a dramatic effect in humans, and recent studies have shown that recombinant soluble forms of the factor's receptor can be used to mop up excess factor.¹² The use of these soluble synthetic proteins (known as immunoadhesins) in conjunction with monoclonal antibodies offers the real possibility of inducing a partial remission in the normally relentless progression of the disease.¹²

Further studies examining the mechanisms by which the production of cytokines is regulated are yielding clues about their role in chronic inflammatory diseases. For example, some people with one polymorphism in an important regulatory region of the tumour necrosis factor α gene seem to produce too much of the cytokine during an inflammatory response and may therefore be predisposed to developing overexuberant chronic inflammatory responses.

New therapeutic targets

Because rheumatoid arthritis is so heterogeneous with a multistep pathogenesis it has proved difficult to treat systematically. Although current treatments have been relatively successful at controlling the symptoms of chronic synovitis, true long term remission in aggressive rheumatoid arthritis has not been achieved. This failure has sparked an interest in the use of early combination drug therapy in patients with aggressive disease. Furthermore, current strategies have been based on the assumption that T cells, antigenic peptide, and the major histocompatibility complex are the most appropriate targets for specific and sustained treatment. The success, albeit experimental, of anticytokine therapy has now focused attention on treatments aimed at alternative targets such as synovial macrophages, fibroblasts, and endothelial cells.

Adhesion molecules, cell matrix, and matrix degrading enzymes

Leucocytes do not have cilia and therefore cannot swim. They move throughout the body from the blood stream through an orderly sequence of molecular interactions involving several cell surface adhesion molecules. The direction of the migration is determined by specialised chemicals or chemoattractants called chemokines. Specialised cell surface proteins called integrins provide the mechanical support that

What cytokines do

- Cytokines are small protein messengers that are important mediators of immune and inflammatory responses
- During an inflammatory response many cytokines are produced by a wide range of cells including leucocytes and fibroblasts
- Some cytokines—for example, interleukin 1—are proinflammatory; others such as interleukin 10 exert anti-inflammatory effects
- During an inflammatory response the balance between proinflammatory and anti-inflammatory cytokines (sometimes called the cytokine network) seems to determine whether chronic inflammation ensues
- Cytokines bind to receptors on target cells (usually leucocytes) and cause biological effects such as cell proliferation, cell death, or enhanced cell killing. Some cytokines enhance the release of other cytokines

allows the cells to migrate over and through the endothelium. During an inflammatory process, agents such as tumour necrosis factor α induce the expression and activation of families of adhesion molecules on both the leucocytes and the endothelium.

The availability of monoclonal antibodies and techniques for rapid cloning of these cell surface molecules has greatly increased our understanding of the molecular signposts or "area codes" that guide leucocytes to discrete compartments within the body. A specific synovial area code has not yet been identified, but it would provide an attractive target for anti-adhesion therapy. The first wave of anti-sticky drugs (a neutralising antibody to the platelet integrin $\alpha\text{IIb}\beta 3$) has recently been licensed for use in preventing coronary artery restenosis after balloon angioplasty.

It is now clear that the extracellular matrix and the presence of other inflammatory cells can influence the behaviour of lymphocytes. For example, culturing monocytes with synovial fibroblasts leads to the production of proinflammatory cytokines such as interleukin 6. In addition, such cellular interactions can lead to the production and secretion of enzymes called matrix metalloproteases, which can remodel the extracellular matrix. Although the controlled expression and regulation of these enzymes is crucial for wound healing and migration of cells through tissues, unchecked expression can lead to joint destruction and scarring. Naturally occurring and synthetic inhibitors of these enzymes are currently in clinical trials for rheumatoid arthritis and show early promise.

Inhibition of angiogenesis

Angiogenesis (the formation of new blood vessels) is a cardinal feature observed in the proliferating synovial membrane in rheumatoid arthritis. Proliferation of endothelial cells requires interactions between adhesion molecules on the endothelial cell (such as integrins) and the extracellular basement membrane or matrix (such as fibronectin). Both antibodies and small chemicals based on the sequence in the ligands recognised by integrins have proved effective in inducing the death (by apoptosis) of endothelial cells.¹³ Clinical trials of anti-angiogenic drugs are now under way in patients with rheumatoid arthritis.

Cell proliferation and apoptosis

Molecular and cellular interactions within the inflammatory site directly modify cell behaviour and cause chronic inflammation. Recent studies have shown that as well as regulating cytokine secretion and cell proliferation, the synovial microenvironment inhibits T cell apoptosis. Other studies have shown that the interaction of immunoglobulin secreting plasma cells with synovial fibroblasts prevents them from undergoing apoptosis in a contact dependent manner, which may account for the continued production of rheumatoid factor during the disease. These studies strongly suggest that the tissue microenvironment is crucial in determining the balance between cell proliferation, survival, and death.¹⁴ They also raise the possibility that one of the main defects in the rheumatoid joint is abnormal environmental cues leading to inappropriate cell survival, cytokine secretion, and cell retention (fig 3). Treatments aimed at enhancing apoptosis or prevent-

Fig 3 Pathogenic processes in synovial proliferation, leucocyte accumulation, and neovascularisation. The microenvironment directly contributes to the persistence of inflammation by preventing apoptosis of leucocytes, promoting the production of cytokines and matrix degrading enzymes, and diverting movement of leucocytes

ing leucocyte accumulation within the rheumatoid synovium may thus turn out to be particularly effective.

Conclusions

Rheumatoid arthritis is not a benign disease. Future treatments will require a radical change in our understanding of the mechanisms involved in initiating and perpetuating the disease. A false sense of security, engendered by better control of symptoms, has been cruelly exposed by studies of long term outcome showing that the prognosis of rheumatoid arthritis remains poor. Newer strategies based on early aggressive treatment, although still in their infancy, show some improvement over conventional treatments. Therapeutic targets such as the synovial fibroblast are now providing exciting possibilities for future treatment. The challenge of the next decade will be to translate some of the potential treatments I have outlined into real benefits for patients with rheumatoid arthritis.

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- 1 Sharp JT, Wolfe F, Mitchell DM, Bloch DA. The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease. *Arthritis Rheum* 1991;34:660.
- 2 Wilske K. Rheumatoid arthritis: evolving concepts in therapy "Don't fiddle while joint burn." *Rheumatology in Europe* 1996;25:145-9.
- 3 Harris FH. Rheumatoid arthritis. Pathophysiology and implications for treatment. *N Engl J Med* 1990;322:1277-89.
- 4 Muller-Lander U. T cell independent cellular pathways of rheumatoid joint destruction. *Curr Opin Rheum* 1995;7:222-8.
- 5 Firestein GS. Invasive fibroblast-like synoviocytes in rheumatoid arthritis. *Arthritis Rheum* 1996;39:1781-90.
- 6 Panayi GS, Lanchbury JS, Kingsley GH. The importance of the T cell in initiating and maintaining the chronic synovitis of rheumatoid arthritis. *Arthritis Rheum* 1992;35:729-35.
- 7 Feldman M, Brennan FM, Maini RN. Rheumatoid arthritis *Cell* 1996; 85:307-10.
- 8 Salmon M. The immunogenetic component of susceptibility to rheumatoid arthritis. *Curr Opin Immunol* 1992;4:342-7.
- 9 Kouskoff V, Korganow A-S, Duchatelle V, Degott C, Benoist C, Mathis D. Organ specific disease provoked by systemic autoimmunity. *Cell* 1996; 87:811-22.
- 10 Ziff M. Rheumatoid arthritis—its present and future. *J Rheumatol* 1990; 17:127-33.
- 11 Maini RN. The role of cytokines in rheumatoid arthritis. *JR Coll Physicians* 1996;30:344-51.
- 12 Moreland LW, Heck LW, Koopman WJ. Biologic agents for treating rheumatoid arthritis. Concepts and progress. *Arthritis Rheum* 1997;40:397-409.
- 13 Stromblad S, Cheresh DA. Cell adhesion and angiogenesis. *Trends Cell Biol* 1996;6:462-8.
- 14 Akbar AN, Salmon M. Cellular environments and apoptosis: tissue microenvironments control activated T-cell death. *Immunol Today* 1997; 18:72-6.