Best Practice & Research Clinical Rheumatology 26 (2012) 225–236

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevier.com/locate/berh

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Taking advances from bench to bedside during the last decade

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Keywords:
Rheumatoid arthritis
Biologicals
Novel treatment
Pathogenesis
Early discovery
Outcome prediction

The remarkable advances in understanding the pathogenesis and therapeutic options for rheumatoid arthritis over the last 10 years are a leap forward in the treatment of this disease. This has led to a shift in focus from established disease to early identification and treatment. Actualisation of treatment guidelines aiming for remission, and a vastly growing arsenal of new synthetic and biological agents have been major achievements. An area of ongoing research is the discovery and development of additional and improved biomarkers for (early) disease with the goal of designing a more personalised treatment regimen to prevent structural tissue damage. Developing valid tools to predict response and outcome for the individual patient remains, however, a great challenge. We will herein summarise some of the major achievements in diagnostic and therapeutic discoveries in rheumatoid arthritis of the past decade.

Introduction

Over the past decade, insights into the pathogenesis and treatment of rheumatoid arthritis (RA) have accelerated at an unprecedented pace. Not only has it become evident that RA is a chronic inflammatory disease requiring active treatment in an early stage of the disease, but great advances have also been made with regard to understanding comorbidities, especially those involving the

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doi:10.1016/j.berh.2012.03.003

cardiovascular system. Based on these insights, targeted strategies have emerged with a substantially better prognosis for a considerable number of RA patients, although constant and stable remission is still not achieved in the majority. The next challenges include unravelling the role of the individual contributors to the development of early disease, translation to more effective treatments for individual patients and elucidating RA's etiopathogenesis.

Advances in understanding the etiopathogenesis of RA

Novel translational methods, including analysis of synovial biopsies, and applied molecular, cellular and genetic technologies, have increased our understanding of the pathogenesis of RA. It has become apparent that years before clinical onset of RA increased levels of autoantibodies, cytokines and chemokines can already be detected, suggesting the advancement of disease long before joint destruction is evident [1], although the primary target of RA, the synovium, is not affected in the earliest stages of preclinical RA [2].

Genetic factors

In 2000, it was estimated that the relative contribution of genetic factors to RA is about 50%, based on twin studies [3]. In 2010 a meta-analysis of genome wide association studies has identified seven new RA risk loci, totalling the known risk alleles to 16% of the estimated 50% of disease variance due to genetic factors [4]. From all genetic data, the risk associations with human leukocyte antigen (HLA)-DRB1-shared epitope alleles and, secondly, PTPN22 alleles are the strongest [5–7]. The next step would be to translate the findings of genome wide association studies to epidemiological and pathogenetic studies.

Anti-citrullinated protein antibodies

Since the beginning of the century anti-citrullinated protein antibodies (ACPAs) have been recognised as a hallmark of RA [8]. ACPAs can be detected years before onset of disease and play a role in the pathogenesis of RA [9]. Citrullination is a biochemical event in which arginine is changed into citrulline by deimination. The basic charge conferred by arginine is then turned into a neutral site in the peptide by citrulline, an event that may alter the tridimensional conformation of the protein. The enzymes catalysing this biochemical reaction are the peptidylarginine deiminases (PADIs). The upregulated expression of PADI enzymes provoked by smoking may promote the citrullination of proteins in the lung, leading to autoimmunity against citrullinated antigens in RA [10]. ACPA-positive disease is associated with unfavourable outcome, and there is an association between ACPA positivity and the presence of the specific genotype encoding the shared epitope, smoking [5–7], and periodontal disease [11]. *Porphyromonas gingivalis* is one of the bacteria causing periodontal disease and may express PADI, allowing the generation of citrullinated peptides. In genetically susceptible (shared epitope-positive) individuals, such citrullinated peptides may interrupt tolerance to endogenous citrullinated antigens, resulting in the generation of ACPA [12].

The notion that RA should be viewed as a syndrome consisting of more than one pathogenetic entity is strongly supported by the differences between patients with detectable ACPA and those who are ACPA negative [13,14]. Taken together, the available data suggest that after initiation of the immune response in, for instance, the lung or the periodontium, leading to production of ACPA, a second 'hit' like a trauma or a viral infection, leading to inflammation and citrullination in the synovium, may result in epitope spreading, and autonomous disease progression, finally resulting in full-blown RA [2].

Insights into synovial inflammation

In established RA, the inflamed synovium is characterised by infiltration with macrophages, plasma cells, T-cells and other cells such as mast cells, B cells, dendritic cells, natural killer cells and neutrophils [15]. Because of their production of matrix degrading enzymes as well their role in attracting and activating immune cells, synovial fibroblasts have gained increased focus. They are stably activated and