Summary
Rikard Holmdahl
Genetics of joint inflammation – problems and possibilities

(No summary and key words available)

Summary
Jane Worthington, Anne Barton and Sally L. John
The epidemiology of rheumatoid arthritis and the use of linkage and association studies to identify disease genes

The epidemiology of rheumatoid arthritis (RA), the most common form of inflammatory polyarthritis, is reviewed with reference to population differences and observed trends in the incidence and prevalence of the disease. Family and twin studies provide evidence that RA has a complex aetiology involving genetic and environmental factors. A brief summary of non-genetic factors is provided.
Both linkage and association-based approaches have been used to investigate the genetic basis of disease susceptibility and in the second part of this chapter linkage and association methodologies are reviewed with particular reference to the genetics of RA. The advantages and disadvantages of these approaches in the context of the current rapid developments in technologies, bioinformatics and genetics are discussed.

Key Words: association, complex disease genetics, linkage single nucleotide polymorphisms, microsatellites, rheumatoid arthritis.

Summary
Cornelis L. Verweij and Tineke C.T.M. van der Pouw Kraan
Heterogeneity in rheumatoid arthritis based on expression analysis: towards personalised medicine

There is growing evidence that rheumatoid arthritis (RA) is a heterogeneous disease. Despite the heterogeneous nature of RA we generally refer to the disease in terms of a group average, which may hamper further progress to increase our understanding of the genetic basis and pathogenesis of the disease, and the treatment success for subsets of patients. An issue of scientific interest for the near future is to identify disease classifiers to define homogeneous groups of patients for genetic, biological and clinical studies. By definition, nearly every aspect of a disease phenotype should be represented in the pattern of genes and proteins that are expressed in the affected tissues and organs. Here, we describe novel developments in genomics and proteomics research for the identification of biomarkers for disease subclassification and prognosis in RA. It is anticipated that this information will also improve our understanding of the underlying biology of RA subtypes. Ultimately this information will help clinicians to select subgroups of RA patients for optimal treatment and research purposes.

Summary
Ryo Yamada and Kazuhiko Yamamoto
Gene-based large scale LD-mapping of rheumatoid arthritis-associated genes

Progress in high-throughput single nucleotide polymorphism (SNP) genotyping has allowed us to perform large-scale linkage disequilibrium (LD) mapping of common disease-associated genes. We designed a whole genome case-control LD mapping for rheumatoid arthritis (RA)-associated genes in Japanese with SNPs distributed mainly in gene-containing regions. Consequently, we identified RA-associated polymorphisms in two genes/loci: *PADI4* and *SLC22A4/A5* cluster. However, these two findings were in contrast with each other. On one hand, the function of PADI4 has been known to be closely related to RA-specific phenomena before our identification of RA-associated variants. On the other hand, the known function of SLC22A4/A5 has not been related to RA, but *SLC22A4/A5* were reported to have multiple polymorphisms associated with multiple autoimmune diseases. This article discusses our LD-mapping strategy and recent findings on *PADI4* and *SLC22A4/A5* as RA-associated genes.

Key Words: Anti-CCP antibody, citrullination, haplotype, haplotype tagging SNP, linkage disequilibrium, linkage disequilibrium block, organic cation transporter, PADI4, PTPN22, *RUNX1*, single nucleotide polymorphism (SNP), SLC22A4.

Summary
Peter K. Gregersen and Robert M. Plenge
Emerging relationships: rheumatoid arthritis and the PTPN22 associated autoimmune disorders

(No summary and key words available)

Summary
Marta E. Alarcón-Riquelme and Sergey V. Kozyrev
Shared genes in rheumatic diseases, the role of PD1 and the RUNX genes in disease susceptibility

Recently, the role of new genes and gene families has been uncovered through the study of the genetics and genetic mapping for several rheumatic and autoimmune diseases. A combination of mouse engineering, human genetics and mutation screening has led to the identification of the *PDCD1* gene and the runt-family of transcription factors in the pathogenesis of such diseases. Much remains to be done.

Key Words: Anti-inflammation, autoimmunity, rheumatoid arthritis, runt domain, systemic lupus erythematosus, TGFβ, transcription regulation.

Summary
Joachim Sieper and Martin Rudwaleit
The role of B27 and other genes associated with ankylosing spondylitis

HLA-B27 is found to be positive in 90–95% of patients with ankylosing spondylitis (AS), which is the highest known MHC Class I association for human diseases. There is a strong correlation between the overall HLA-B27 prevalence in a population and the prevalence of ankylosing spondylitis and other spondyloarthritides, suggesting that additional

environmental factors are rather ubiquitous. Among these bacteria and their interaction with HLA-B27 seem to be most important. Several pathogenetic models have been proposed to explain the association of AS with HLA-b27, however, for none of which a crucial role could be proven. Although HLA-B27 is the major gene involved in genetic susceptibility to AS the contribution to the overall genetic risks is relatively small. Several other additional genes have been described, many of them including genes associated with diseases which predispose to AS, such as psoriasis and inflammatory bowel disease, or being relevant for the immune response.

Key Words: Ankylosing spondylitis, spondyloarthritides, HLA-B27, HLA-B27 subtypes, bacteria, pathogenetic models, other non-HLA-B27 genes.

Summary
Ulf D. Landegren
Emerging tools for dissecting complex disease

Our understanding of the molecular basis of disease increases rapidly, opening radically improved opportunities for prevention, diagnosis, and treatment. The improved possibilities to analyse molecular states of cells and tissues in disease largely relies on the availability of total parts lists of biological systems, and on specific detection reagents and procedures to use these in advanced bioassays. This chapter provides an overview of present and emerging methods for comprehensive studies of molecular states. In particular, I describe a family of molecular tools being developed in our lab to represent specific target molecules as signature DNA sequences for parallel analyses of large sets of molecules, extending to even single target molecules.

Key Words: High-throughput genomics, functional genomics, molecular diagnostics, molecular tools, padlock probes, proximity ligation, DNA microarrays, single-molecule detection, gene expression, molecular etiology, protein detection, protein interaction, DNA detection.

Summary
Thomas Häupl
Expression analysis of rheumatic diseases, prospects and problems

Expression profiling with probes for all human genes has raised the expectation that molecular mechanisms of diseases insufficiently understood may soon be unravelled. Although many profiles have been published on various etiologically unclear rheumatic diseases and comparative analyses have suggested differences which may be applicable for diagnostics, results are still inconsistent and far from comprehensive functional interpretation. In a field between euphoric expectations and disillusion by the jungle of data, we have to face the benefits and the difficulties with these new technologies and we need to define strategies for reasonable application. This chapter tries to depict some of the major hurdles in the beginning of this new era of research in life sciences and will suggest principle strategies for sorting the pieces of this molecular puzzle.

Key Words: Microarray, expression profiling, transcriptome, signatures, cell mixtures, genomics, molecular strategies, functional components, bioinformatics, pathway models.

Summary
Kary A. Latham, Timothy D. Kayes, Zhaohui Qian and Edward F. Rosloniec
The use of humanized MHC mouse strains for studies of rheumatic diseases

Rheumatic diseases are a significant health problem, yet our understanding of the pathogenesis of these diseases is still lacking. In this review, we discuss a number of humanized mouse models of rheumatic diseases developed by transgenic expression of HLA molecules, and we examine how these models have advanced our understanding of the pathogenesis of these diseases. Humanized models for both Class I associated diseases such as ankylosing spondylitis and Class II mediated autoimmune arthropathies have been developed with many sharing a number of clinical and pathological features with their human disease counterparts. One of the advantages of these models is the ability to experimentally test the role of candidate autoantigens for these diseases and to study the development of the ensuing autoimmune response at the cellular and molecular level. In addition, these humanized models are proving to be useful tools for both studying the function of these HLA susceptibility alleles as well as generating new insights into the immunopathogenesis of these diseases.

Key Words: Transgene, rheumatoid arthritis, collagen, proteoglycan, gp39, HLA, ankylosing spondylitis, Lyme disease, mouse model, autoimmunity.

Summary
Shimon Sakaguchi, Takeshi Takahashi, Hiroshi Hata, Hiroyuki Yoshitomi, Satoshi Tanaka, Keiji Hirota, Takashi Nomura and Noriko Sakaguchi
SKG mice, a monogenic model of autoimmune arthritis due to altered signal transduction in T-cells

SKG mice spontaneously develop CD4+ T-cell-mediated chronic autoimmune arthritis that resembles human rheumatoid arthritis (RA) in its immunopathology and extra-articular manifestations. The primary cause of the disease is a point mutation of the gene encoding 70 kDa zeta-associated protein (ZAP-70), a key signal transduction molecule in T-cells. The genetic anomaly affects differentiation and selection of T-cells in the thymus, leading to thymic production of arthritogenic autoimmune T-cells. The arthritogenic T-cells persist in the periphery and elicit arthritis when activated through stimulation of innate immunity. This model is suitable for studying RA as a systemic disease and elucidating the contribution of genetic and environmental factors to the pathogenesis of RA.

Key Words: Animal model, autoimmune arthritis, rheumatoid arthritis, ZAP-70, T-cell selection.

Summary
Peter J. Olofsson
A genetic approach to select and validate new targets for treatment of rheumatic diseases

Large high-throughput screening and pharmacological analyses have identified traditional targets for drug development. Consequently, the pharmaceutical industry has enormous

capacity for high-throughput screening of compound libraries well as large capacity for development of biological and small molecular drugs. However, the bottleneck in drug development is still fundamental understanding of disease mechanisms to identify new and relevant targets for drug development.

The development of high-throughput techniques for analysis of expression and function of genes and proteins, i.e., genomics and proteomics, has been predicted to multiply the identification of potential new targets for drug development. Still, most of the disorders of the population today like RA are multifactorial, with a complex and often so far not well-characterised aetiology, so even with these methods, identification of new molecular targets is complicated.

With the use of linkage and association studies or well designed gene expression analysis the molecular mechanism of arthritis pathology will be addressed with an unbiased mind. This will enable identification of previously overlooked as well as new disease mechanisms that can be targeted by new pharmacological treatments. Incidence and progression of RA is a complex syndrome that for clinical diagnosis and therapy is complicated by the genetic and pathological heterogeneity of the patient population. Hence, statistically reliable data on genes that regulates RA is difficult to obtain from studies in human populations. One way to minimise the complexity of the disease mechanism and the genetic heterogeneity is to first identify new treatment targets in animal models of RA. The relevance of genes identified in animal models is then open for verification in various patient populations. Additionally, efficacy of developed treatments could also be verified directly in these animals to get proof of concept information before initiating analyses in human patients.

Gene expression profiling and pharmacogenomics are developed as powerful tools using accumulating genomic databases. These tools could be used to identify sensitive biomarkers to follow the efficacy of developed drugs that are designed to target the identified gene products. Pharmacogenomics will also be used to stratify patient populations in clinical trials and to segment the market for the prescribed drugs against RA. This will enable a gene profile-based selection of patients that will be more likely to benefit from the treatment as well as to avoid treating patients that are likely to get serious adverse effects of the treatment. Hence, future treatment of RA will use pharmacogenetic profiling to individualise the optimal drug prescription to each patient.

Key Words: Rheumatoid arthritis, linkage, drug development, genetic, expression analysis, animal model, positional cloning, pharmacogenetics.

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