SPECIFIC AUTOIMMUNITY IN RHEUMATOID ARTHRITIS - T CELLS, ANTIBODIES AND GENETIC REGULATION

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssalen CMM L8:00

Tisdag den 7 Juni, 2011, kl 09.00

av
Omri Snir

Huvudhandledare:
Docent Vivianne Malmström
Karolinska Institutet
Institutionen för
Medicin, Enheten för Reumatologi

Bihandledare:
Professor Lars Klareskog
Karolinska Institutet
Institutionen för
Medicin, Enheten för Reumatologi

Docent Christina Trollmo
Karolinska Institutet
Institutionen för
Medicin, Enheten för Reumatologi

Fakultetsopponent:
Associated Professor Gunter Steiner
University of Vienna
Division of Rheumatology

Betygsmäntnd:
Docent Kristina Lejon
Umeå Universitet
Institutionen för klinisk mikrobiologi
Enheten för Immunologi

Docent Jan Wahlström
Karolinska Institutet
Institutionen för Medicin, Solna
Enheten för lungmedicin

Docen Per Eriksson
Hälsouniversitet; Linköping,
Institutionen för klinisk och experimentell medicin, Reumatologi

Stockholm 2011
ABSTRACT

Complex interactions between genes and environmental factors may result in destruction of the body’s own cells and tissues by the immune system, i.e. autoimmunity. Rheumatoid arthritis (RA) is a chronic joint inflammation mediated by all arms of the immune system that can lead to tissue destruction and functional disabilities. Many genetic variants and environmental factors that affect the immune system in RA have been revealed in recent years, however it is still not known precisely how they regulate and control autoimmunity. In this work I studied the function and specificity of adaptive immunity in RA, and also addressed influences from known genetic variants that predispose for disease.

First, autoantibody responses to several RA-associated citrullinated autoantigens were studied in a cohort of patients with established RA. Antibody responses and their interrelationships were examined, both in the whole study cohort and following stratification to HLA-DRB1 types, since HLA-DRB1 alleles are the strongest genetic risk factors known for RA. The autoantibodies were found to be highly specific for RA and displayed only limited cross reactivity. HLA-DRB1*04 alleles strongly associated with the presence of these autoantibodies both in sera and synovial fluid.

T cells are believed to be central mediators of RA pathogenesis, however studying T cell specificity has been proven difficult. The stinking HLA-DRB1*04 association with different anti-citrulline antibody responses encouraged us to revisit T cell recognition and responses to citrullinated proteins. We identified an epitope from vimentin that binds HLA-DRB1*0401 in its citrullinated but not in its native form and T cell recognition and function were investigated. CD4 T cells from both HLA-DRB1*0401 RA patients and healthy donors recognized citrullinated vimentin. However, T cells derived from RA patients secreted higher levels of cytokines, suggesting previous activation and/or cytokine dysregulation in RA. This study required a development of an assay sensitive enough to allow detection of rare antigen-specific CD4 T cells. Having such a tool, we further applied the same method to functionally examine type-II collagen (CII)-reactive CD4 T cells from peripheral blood and synovial fluid from HLA-DR*04 RA patients. T cells indeed recognized different variants of the immunodominant T cell epitope of CII and displayed epitope spreading throughout the disease. Synovial fluid derived T cells produced higher levels of inflammatory cytokines as compared to blood suggesting local reactivation.

Many more RA predisposing genetic variants have been identified outside the HLA-DRB1 locus in recent years. We therefore continued to study the association with autoantibody specificities in two independent cohorts of RA patients. Several genetic variants were found to control autoantibodies formation; some associated with several autoantibodies whereas others exclusively linked with a single fine specificity.

In summary, our data suggest that both B and T cells selectively respond to autoantigens in RA and are controlled by HLA and additional RA-predisposing genes. This work emphasizes the importance of multidisciplinary investigation for the understanding of interaction between genes and immunity in order to functionally explain epidemiological findings. We further hope that our findings regarding T and B cell specificities will encourage others to continue in this direction, which may pave the road towards specific therapy in patients following precise gene-immune investigation.