TRANSCRIPTOME OF CONGENIC MICE WITH TRANSIENT INFLAMMATORY ARTHRITIS: RESCUE OF C5 COMPLEMENT DEFICIENCY

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INTRODUCTION.

Rheumatoid arthritis and its murine models have a heterogeneous genetic background, but complement cascade activation is considered to be a central and indispensable part of inflammation. Hemolytic C5 component is a converging point of the alternative and classical complement pathways and one of the major chemotactic factors that is essential for leukocytes activation in arthritis. Earlier we found that in the BALB/c x DBA/2 murine cross, proteoglycan-induced spondylitis (PGIS) was under the control of two chromosomal loci *Pgis1* and *Pgis2*. The C5 complement component is located in the middle of the *Pgis2* locus that was genetically linked to the severity of leukocyte infiltration in spine. The goal of the study was searching for genes that rescue the inflammatory phenotype in C5-deficient BALB/c.DBA/2-*Pgis2* congenic mice

MATERIALS AND METHODS.

Age and sex-matched BALB/c and DBA/2 progenitors and *Pgis2*-congenic mice were injected with an arthrogenic monoclonal antibody cocktail (Chondrex Inc.) followed by stimulation with lipopolysaccharide (LPS) to induce Collagen Antibody-induced Arthritis (CAIA). Mice were sacrificed at the acute inflammation phase. Total RNA was isolated from hind paws and analyzed with oligonucleotide genome-wide genechip hybridization (Affymetrix). Gene expression patterns were analyzed with Affymetrix console and dCHIP software.

RESULTS AND DISCUSSION.

Expression chip signals were processed according to robust multi-array analysis (RMA) for background correction, normalization and probe summarization at gene level. Quality of array hybridization was confirmed with signal box plots, and separately with signals from chip's positive control spikes. We found 1040 differentially expressed genes when samples were grouped based on genetic background (wild-type versus Pgis2-congenics). Patterns of expression for 997 genes were most significantly correlated with arthritis severity. Only limited number of genes (n=20) showed expression that was affected with both arthritis and genetics. Hierarchical clustering of 20 signature genes exhibited perfect separation of wild-type from Pgis2-congenic samples. Most strongly downregulated gene was Cacybp calcyclin binding protein (fold change 2.2, $p < 0.008$), most strongly upregulated gene was Wnt9a (forld change 2.3, $p < 0.006$).

CONCLUSIONS.

We found that *Pgis2*-congenic mice that carry genetically-deficient copy of C5(Hc) complement component were susceptible to collagen antibody-induced arthritis while inflammation was transient. Using differential gene expression analysis tools, we identified 20 genes whose down/up regulation in *Pgis2*-congenic mice might rescue C5 complement deficiency or, in a wider sense, rescue the function of the entire *Pgis2* locus.

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