GENOMIC STRATIFICATION BY HLA-DRB4 EXPRESSION IDENTIFIES DIFFERENTIAL INNATE AND ADAPTIVE IMMUNE PATTERNS – A STRATEGY TO IDENTIFY PREDICTORS OF METHOTREXATE RESPONSE IN EARLY RHEUMATOID ARTHRITIS


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Background and objective:
Selecting effective drugs for individual patients is the current challenge in rheumatoid arthritis (RA). When methotrexate (MTX) as first line drug fails, targeted therapies with different modes of action may be necessary. Thus, MTX response prediction in early RA provides the opportunity to investigate these different RA immunopathologies without prior modification by treatment.

Materials and Methods:
For a global approach, whole blood transcriptomes of early RA patients (n=50 for selection, n=18 for validation) were analyzed before initiating MTX treatment. Functional interpretation of differential expression was performed with own and public reference transcriptomes of various cell types, cytokine stimulated conditions and bone marrow precursors. Selection statistics were validated with qPCR and functional patterns with independent samples.

Results:
Comparing all responders with non-responders revealed no adequate separation. Assuming heterogenic pathomechanisms, subgroups by gender, genetic, and immunologic characteristics were tested. HLA-DRB4– patients revealed most distinctive transcriptional differences (100% sensitivity; 92% specificity). Response was associated with transcripts related to phagocytes and bone marrow activation while non-response was observed when T- and B-lymphocytic markers were increased. In contrast, HLA-DRB4+ patients were more heterogeneous but also suggested that increased adaptive immune stimulation reduced responsiveness. Technical validation by RT-qPCR confirmed the selection of reliable gene candidates. Independent samples of responders and non-responders confirmed the functional patterning.

Conclusions:
Genomic stratification may be an important tool to improve transcriptional interpretation and supports that molecular pathomechanisms in early RA may be used to find indicators of response to MTX therapy. The data also suggest an important contribution of innate triggers in addition to adaptive immune pathomechanisms in RA.