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Assessment of baseline expression of genes involved in the metabolic and energy generation pathways in the peripheral blood of DMARD-naïve rheumatoid arthritis patients as an approach to predict treatment response to methotrexate

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Statement of the Problem: Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, which is characterized by erosive arthritis (synovitis) and systemic inflammation. Methotrexate (MTX) is a basic drug for RA treatment. However, presently it is not possible to predict MTX efficacy in every patient. Therefore, identification of patients sensitive to MTX could significantly improve therapy outcome.

Purpose: The purpose of this study is to investigate the importance of baseline expression of genes involved in the metabolic and energy generation pathways in RA patients, which could serve prognostic biomarkers of treatment response to methotrexate.

Methodology & Theoretical Orientation: Peripheral blood of 40 DMARD (Disease modifying antirheumatic drug)-naïve RA patients treated with MTX for two years and 26 healthy age-matched subjects were examined. Clinical response by DAS28, serum levels of ACPA (Anti-citrullinated protein antibody), CRP (C-reactive protein) and RF (Rheumatoid Factor); X-ray analysis of bone erosion and joint space narrowing scores were assessed. Protein concentrations were measured using ELISAs (Enzyme-linked immunosorbent assay). Gene expression studies were performed with quantitative real-time RT-PCR (Polymerase Chain Reaction).

Findings: MTX treatment significantly decreased the disease activity according to DAS28. RA patients, which attained clinical remission after MTX treatment demonstrated significantly higher baseline expression of genes associated with glycolysis (Glut1, PKM), cell cycle (cyclin D1), and hypoxia (HIF1α) compared to other examined RA patients and healthy subjects. RA patients, which retained high disease activity at the end of follow-up demonstrated lower baseline expression of genes related to apoptosis (p21, caspase 3), tissue regeneration (TGFβ1, RUNX2), and cyclin D1 than that in the controls and other examined RA patients.

Conclusion & Significance: Clinical remission attainment in DMARD-naïve RA patients treated with methotrexate is associated with higher baseline expression of genes associated with glycolysis, hypoxia and cyclin D1 compared to other examined patients. Non-responsiveness to MTX is accompanied by lower baseline expression of genes related to apoptosis, tissue regeneration, and cyclin D1 compared to controls.

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