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MITOCHONDRIAL ANTIOXIDANT DEFENSE DYSREGULATION IN RHEUMATOID ARTHRITIS: GENOTYPE-PHENOTYPE INTERACTIONS IN A CENTRAL ASIAN COHORT

Parpiyeva S. B.
Aleynik V. A.
Vasilevskiy E. A.
Dadabaev O.T.
Andijan State Medical Institute, Andijan, Republic of Uzbekistan
Institute of Immunology and Human Genomics, Tashkent,
Republic of Uzbekistan

Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with a global prevalence of 0.5–1.0% of the adult population and projected 80% increase in incidence by 2050 [6]. Oxidative stress plays a fundamental role in RA pathogenesis through reactive oxygen species generated by activated synoviocytes and infiltrating leukocytes, leading to cartilage degradation, chondrocyte apoptosis and pannus formation [4]. Malondialdehyde (MDA) is the most accessible biomarker of oxidative stress and reflects ongoing lipid peroxidation [4]. Mitochondrial superoxide dismutase 2 (SOD2, MnSOD) is a key enzyme of mitochondrial antioxidant defense; the functional polymorphism Ala16Val (rs4880) reduces enzyme transport into mitochondria with subsequent activity reduction by 30–40% [3, 7]. Significant associations of SOD2 Ala16Val with RA activity have been established in European populations [2], but data on Central Asian ethnic groups remain limited.

Keywords: rheumatoid arthritis, oxidative stress, malondialdehyde, SOD2 polymorphism, Ala16Val, mitochondrial dysfunction, Uzbek population.

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Aim

To investigate associations of malondialdehyde, procalcitonin and SOD2 Ala16Val polymorphism with rheumatoid arthritis risk and clinical activity in an Uzbek population of the Fergana Valley.

Materials and methods

100 patients with verified RA based on ACR/EULAR 2010 criteria [1] and 73 ethnically-matched healthy controls were enrolled. Serum MDA was measured by colorimetric thiobarbituric acid reactive substances (TBARS) assay; procalcitonin (PCT) was determined by electrochemiluminescent immunoassay. SOD2 Ala16Val (rs4880) genotyping was performed by real-time PCR with TaqMan probes. Spearman correlation analysis with Bonferroni correction and ROC analysis with AUC, sensitivity and specificity calculation were applied.

Results

MDA levels showed dose-dependent activation across RA activity subgroups (3.42±0.21 to 7.86±0.42 μmol/L, $p<0.001$) and exhibited strong correlation with DAS28-ESR ($\rho=0.69$; $p<0.001$). PCT increased from 0.082±0.008 to 0.284±0.019 ng/mL across activity subgroups with all values remaining below the conventional septic threshold of 0.5 ng/mL, in line with the systemic inflammatory pattern of RA [5]. Strong intercorrelation between MDA and PCT was observed ($\rho=0.71$; $p<0.001$). The T allele of SOD2 Ala16Val was associated with increased RA risk (OR=1.65; 95% CI: 1.07–2.52; AUC=0.62) and showed clear gene-dose effect on MDA levels: 4.21±0.32 μmol/L in CC homozygotes, 5.48±0.28 in CT heterozygotes and 7.84±0.42 in TT homozygotes ($p<0.001$ for trend; $\rho=0.58$ for genotype-MDA correlation). The mechanism is consistent with impaired mitochondrial import of MnSOD precursor described in functional studies [7].

ROC analysis identified MDA threshold of 5.5 μmol/L as optimal cutoff for prediction of high RA activity (AUC=0.74; sensitivity 71%; specificity 68%).

Conclusion

Oxidative stress represents a central component of RA pathogenesis in an Uzbek population. The SOD2 Ala16Val polymorphism is an independent genetic predictor of RA risk with significant gene-dose effects on MDA levels, providing a mechanistic link between mitochondrial antioxidant capacity and clinical disease severity. The threshold MDA value of 5.5 μmol/L is recommended as a marker of pronounced oxidative stress associated with aggressive disease course and cardiovascular comorbidity.

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