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INNATE IMMUNITY AND PRO-INFLAMMATORY CYTOKINE GENE VARIANTS AS DETERMINANTS OF SUBCLINICAL ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS

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Background

Rheumatoid arthritis (RA) is associated with a 1.5–2-fold increase in cardiovascular morbidity and mortality compared to the general population, representing the leading cause of premature death in RA patients [1]. The mechanisms underlying accelerated atherosclerosis include systemic inflammation, endothelial dysfunction and shared genetic predisposition with autoimmunity. Toll-like receptor 4 (TLR4) recognizes both pathogen-associated and damage-associated molecular patterns; two functional polymorphisms Asp299Gly (rs4986790) and Thr399Ile (rs4986791) are commonly inherited in linkage disequilibrium and modulate ligand recognition [3, 6]. Tumor necrosis factor alpha (TNF- α) plays a central role in RA pathogenesis through activation of NF- κ B signaling [2, 7]. Despite extensive characterization of TLR4 and TNF- α polymorphisms in RA susceptibility, their joint contribution to cardiovascular comorbidity in Central Asian populations remains insufficiently explored [5].

Keywords: rheumatoid arthritis, cardiovascular comorbidity, TLR4 polymorphism, TNF- α G-308A, intima-media thickness, mSCORE, Uzbek population.



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Aim

To investigate the role of TLR4 (Asp299Gly, Thr399Ile) and TNF- α G-308A (rs1800629) gene polymorphisms in the development of subclinical atherosclerosis in patients with rheumatoid arthritis of an Uzbek population.

Materials and methods

100 RA patients verified by ACR/EULAR 2010 criteria and 73 ethnically-matched controls were enrolled. Genotyping of TLR4 Asp299Gly, TLR4 Thr399Ile and TNF- α G-308A was performed by real-time PCR with TaqMan probes. Cardiovascular assessment included blood pressure measurement, echocardiography with systolic and diastolic function evaluation, carotid ultrasonography with intima-media thickness (CCA-IMT) measurement and modified SCORE (mSCORE) calculation. Linkage disequilibrium between TLR4 polymorphisms was estimated by D' and r^2 statistics. Multivariable logistic regression with adjustment for age, sex, smoking, BMI and disease duration was applied to establish independent associations.

Results

TLR4 Asp299Gly G allele was associated with increased RA risk (OR=2.18; 95% CI: 1.11–4.29; AUC=0.68), in line with previous Dutch population data [4]. TLR4 Thr399Ile T allele showed similar association (OR=2.06; 95% CI: 1.02–4.16). High linkage disequilibrium between TLR4 polymorphisms was confirmed (D' =0.84; r^2 =0.52), consistent with the well-described co-inheritance pattern. TNF- α G-308A A allele increased RA risk 1.89-fold (95% CI: 1.09–3.33), confirming meta-analysis data on disease severity association [7]. The combined TLR4 + TNF- α haplotype was associated with the highest RA risk (OR=3.80; 95% CI: 1.05–13.8). CCA-IMT was significantly elevated in TLR4 risk variant



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carriers (1.06 ± 0.05 vs 0.86 ± 0.04 mm; $p < 0.001$) and TNF- α GA/AA carriers (1.02 ± 0.07 vs 0.84 ± 0.05 mm; $p = 0.022$). The 10-year cardiovascular risk by mSCORE was significantly higher in carriers of unfavorable TNF- α genotypes ($8.6 \pm 0.9\%$ vs $4.6 \pm 0.5\%$; $p < 0.001$), in line with the elevated cardiovascular profile previously described in Uzbek RA patients [5]. Multivariable analysis with adjustment for traditional risk factors confirmed independent associations of TLR4 risk variants (adjusted OR=2.62; 95% CI: 1.18–5.82; $p = 0.018$) and TNF- α GA/AA genotype (adjusted OR=2.34; 95% CI: 1.06–5.16; $p = 0.035$) with subclinical atherosclerosis (CCA-IMT > 0.9 mm).

Conclusion

TLR4 and TNF- α gene polymorphisms in RA patients of an Uzbek population are independently associated with subclinical atherosclerosis after adjustment for traditional cardiovascular risk factors. The combined TLR4 + TNF- α haplotype carries the highest disease risk and most pronounced cardiovascular phenotype. Implementation of TLR4 and TNF- α genotyping into pretreatment evaluation of RA patients may inform personalized cardiovascular risk stratification.

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