TGFB1 (RS1800470 AND RS1800469) VARIANTS ARE INDEPENDENTLY ASSOCIATED WITH DISEASE ACTIVITY AND AUTOANTIBODIES IN RHEUMATOID ARTHRITIS PATIENTS

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BACKGROUND

The present study evaluated the association between TGFB1 + 869 T > C (rs1800470) and TGFB1 – 509 C > T (rs1800469) variants with susceptibility, disease activity, autoantibodies, and TGF- β 1 plasma levels in rheumatoid arthritis (RA) patients from Southern Brazilian population.

METHODS

A total of 262 patients with RA and 168 control individuals were tested for the TGFB1 variants using a TaqMan genotyping assay. Anti-cyclic citrullinated peptide (anti-CCP) antibody levels were determined by chemiluminescence immunoassay and rheumatoid factor (RF) by turbidimetric assay. The TGF- β 1 serum levels were measured by ELISA kit. Disease activity score in 28 joints (DAS28) classified RA patients into two groups of disease activity: remission/mild (DAS28 < 3.2) and moderate/severe (DAS28 $\geq$ 3.2).

RESULTS

Patients and controls did not differ in sex, smoking and ethnicity. The median disease duration was ten years (4–9) and 135 (53.1%) patients were in moderate/severe disease activity. Diminished TGF- β 1 levels were found in the RA group ($p < 0.001$). The TGFB1 + 869 T > C and – 509 C > T variants, independently or in haplotype combination, were not associated with RA susceptibility. Regarding the TGFB1 + 869 T > C variant, we did not find association between this variant and autoantibodies status, DAS28, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and TGF- β 1 level in the overall RA group. Besides, patients with the TGFB1 – 509 TT genotype had a higher frequency of patients with DAS28 ≥ 3.2 than those with the CC genotype (OR = 2.58 [1.04–6.42], $p = 0.041$). Patients with RF or anti-CCP positive and TGFB1 + 869 CC genotype had lower TGF- β 1 plasma levels than those with the TT + TC genotype. Besides that, patients with high RF titres (> 90 U/mL) and the TGFB1 + 869 TC + CC genotypes showed a high frequency of patients with DAS28 ≥ 3.2 ($p = 0.037$). However, no differences were observed between disease activity and TGFB1 + 869 genotypes in patients with high anti-CCP titres (> 15 U/mL).

CONCLUSION

The TGFB1 + 869 T > C variant was associated with diminished TGF- β 1 plasma levels and moderate/severe activity disease only in seropositive RF patients. This is the first study showing that TGF- β 1 plasma levels can be modulated by the interaction between the TGFB1 + 869 T > C variant and autoantibodies. However, the TGFB1 – 509 C > T variant was associated with moderate/severe activity disease, independently of autoantibodies positivity. Thus, our findings suggest that TGFB1 + 869 T > C and – 509 C > T variants can predict activity disease in different RA patient subgroups.

KEYWORDS

Rheumatoid arthritis, Genetic variants, Transforming growth factor- β 1, rs1800470, rs1800469.