THE COMPARATIVE STUDY OF GENE EXPRESSION PROFILE IN PBMC OF SLE DURING ACTIVE AND INACTIVE STAGE, THE SIGNIFICANCE OF APOPTOSIS, AND THE DETECTION OF POLYMORPHISM OF CANDIDATE GENES INVOLVED IN SLE PATHOGENESIS

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The comparative study of gene expression profile in PBMC of SLE during active and inactive stage, the significance of apoptosis, and the detection of polymorphism of candidate genes involved in SLE pathogenesis

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Abstract

The study was designed to investigate the gene expression profile in PBMC of SLE patients during active and inactive stages. The significance of apoptosis and the detection of polymorphism of candidate genes involved in SLE pathogenesis were also studied.

Methods

PBMC samples from SLE patients during active and inactive stages were collected. The gene expression profile was determined using cDNA array. The significance of apoptosis and the detection of polymorphism of candidate genes involved in SLE pathogenesis were also studied.

Results

The study found that the expression of TNF and TNF receptor genes was increased in active stages of SLE. The apoptosis rate was also increased in active stages of SLE.

Conclusion

The study showed that the gene expression profile in PBMC of SLE patients during active and inactive stages is different. The significance of apoptosis and the detection of polymorphism of candidate genes involved in SLE pathogenesis were also found to be significant.
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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disorder which affects various organs and systems. To understand the pathogenic mechanism of such disease, differential gene expression profiles between active and inactive SLE were investigated by cDNA array analysis. Aberrant apoptosis and corpse clearance are thought to have a pathogenic role in SLE. By detection of chromatin condensation, 30% of apoptosis was detected in peripheral blood mononuclear cells (PBMC) from Thai active SLE patients. Using cDNA array screening, 17 apoptosis-related genes were up-regulated in active SLE and were selected for further study. Among those stimulated genes, TNF and the TNF-receptor family were drastically up-regulated in active SLE. Moreover, the degree of apoptosis correlated with the level of TNF-α in plasma, suggesting that TNF family plays a role in induction of apoptosis in SLE. To verify this hypothesis, PBMC from healthy individuals was treated with plasma from active SLE patients in both the presence and absence of etanercept, a TNF antagonist. The etanercept treated active SLE plasma induced 26.43% lower level of apoptosis compared to active SLE plasma alone.

Based on the results from this study, together with those from previous studies, 4 candidate genes i.e. TNF-α, CTLA4, PTPN22, and TP53 were selected on the basis of their significances in SLE pathogenesis. An association study between our candidate genes and SLE susceptibility was done by genotyping in 566 patients and 243 controls. CTLA4 A+49G and an A+49G containing haplotype were found to have associations with the disease. Moreover, an intronic SNP in PTPN22 and its 2 haplotypes were reported to associate with SLE for the first time. However, no association with SLE was observed in TNF-α and TP53.

In conclusion, massive apoptotic death of PBMC occurs during the active stage of SLE. The molecular pathway of SLE PBMC apoptosis is mediated at least via the TNF/TNFR signaling pathway, which is confirmed by functional test of TNF-α in SLE patients’ plasma. The case-control study revealed associations between CTLA4 and PTPN22 and SLE susceptibility, while TNF-α and TP53 did not show any association.

KEY WORDS: SYSTEMIC LUPUS ERYTHEMATOSUS/ APOPTOSIS/ TUMOR NECROSIS FACTOR/ PERIPHERAL BLOOD MONONUCLEAR CELLS/ SINGLE NUCLEOTIDE POLYMORPHISM

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