Abstract of Presentation

Note: This paper should be typed in "Times New Roman" of 12pt.

Presentation Title(Should be no more than 20 words):

HLA and non HLA genes involved in autoimmune thyroid disease

Abstract :

Autoimmune thyroid disease (AITD), including Graves' disease (GD) and Hashimoto's thyroiditis (HT), is caused by an immune response to self thyroid antigens. GD is characterized by the production of thyroid-stimulating hormone receptor-stimulating antibodies, leading to hyperthyroidism, whereas HT is caused by the destruction of the thyrocytes, resulting in hypothyroidism. Twin studies and family studies indicated that AITD is a complex disease with multiple genetic and environmental factors. We previously demonstrated a tight linkage of AITD with HLA, and further identified HLA-DRB4*0101 and HLA-DPB1*0501 as AITD-associated alleles. In order to identify non-HLA genes responsible for the AITD, we first performed a candidate gene approach to find an involvement of CTLA-4 and FCRL-3 genes. Through whole-genome scan using affected sib-pairs method, we found suggestive evidence of linkage of AITD to chromosome 8q24. We identified a novel zinc-finger gene, designated as ZFAT (zinc-finger gene in AITD susceptibility region), as one of the susceptibility genes in 8q24 through subsequent case-control association analysis using SNPs.

ZFAT encodes a 1243 amino-acid protein that contains 18 zinc-finger and 1 AT hook motifs and has several splicing variants including a 846 amino-acid protein, named TR-ZFAT (truncated form of ZFAT), containing 11 zinc-finger and 1 AT hook motifs. We have revealed that i) ZFAT is highly expressed in all types of peripheral blood mononuclear cells, whereas TR-ZFAT is expressed mainly in B cells and monocytes, ii) ZFAT and TR-ZFAT are predominantly localized to nucleus, and iii) immune-related genes are found to be enriched in the ZFAT-regulated genes by the microarray-based expression analysis using the mouse proB cell line BaF3 and its stable transfectants overexpressing ZFAT. These results indicate that ZFAT functions as transcription factors and regulates the expression of immune-related genes. The findings obtained from ZFAT / TR-ZFAT transgenic mouse and conditional knock-out mouse will be discussed.

Furthermore, recent advance of tagging SNP panels across the whole genome allows for efficient and comprehensive analysis of common genomic variants susceptible to multifactorial diseases. The genome wide association analysis for AITD using 600K SNPs is in progress to identify additional non-HLA genes which might functionally interact with HLA, ZFAT and other genes involved in the disease.