Title of Project : HLA polymorphism, disease and evolution

Term of Project : FY2010-2014

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【Purpose of the Research Project】

The human major histocompatibility complex (HLA) binds to a variety of pathogen-derived peptides and controls antigen-specific immune response at the front line of the host defense. Although the prominent features of HLA, i.e., the formation of a multigene family, extremely high polymorphism, strong linkage disequilibrium and big racial differences, were presumably acquired through the interaction between HLA and large varieties of pathogens, the molecular mechanism of generation of these characteristic features of HLA is still unknown and is an important issue to be elucidated.

Several HLA alleles and haplotypes have been reported to associate with immune-related diseases. However, in many cases, which alleles are the true causative variants on the associated HLA haplotypes and what are the pathogenic peptides bound to the causative HLA molecules, have remained unclear. It is critical to solve these questions for developing the innovative therapies.

In this project, we plan to inovate the HLA research by utilizing advanced technologies in protein and genome sciences as well as newly developed databases of human and pathogen genomes.

Our goal is (1) to reveal the evolution of HLA at the molecular level (HLA molecules versus pathogen peptides), (2) to uncover the etiology of HLA-associated diseases, and (3) to develop the immune regulating small chemical compounds to open the new field for the HLA-targeted therapies of immune-related diseases.

【Content of the Research Project】

In order to achieve the above mentioned purpose,

(1) Identify the whole genomic structure of 10 Mb genomic region including HLA using DNA from the HLA homozygotes of 5 commonest HLA haplotypes in Japanese population
(2) Identify the causative HLA alleles for Graves' disease, Hashimoto disease, Cider Pollinosis, Bechet disease, Harada's disease, Sarcoidosis, SLE, Rheumatoid arthritis, Type I diabetes, Narcolepsy, Hepatitis B and C, and Tuberculosis
(3) Identify the causative peptides bound to the causative HLA for above mentioned 13 diseases
(4) Delineate the tertiary structures of these causative HLA-peptide complexes
(5) Identify the small chemical compound to block the peptide-HLA association and to block the immune response to the peptides

【Expected Research Achievements】

Through this effort by the scientists in different disciplines, we (1) reveal the evolution of HLA at the molecular level (HLA molecules versus pathogen peptides), (2) uncover the etiology of HLA-associated diseases, and (3) develop the immune regulating small chemical compounds to open the new field for the HLA-targeting therapies of immune-related diseases.

Through this project, we also expect to inspire young ambitious scientists in the field of human immunology, molecular evolution, bioinformatics and translational research.

【Key Words】

HLA (human major histocompatibility complex): HLA covers an about 3.6 Mb region on chromosome 6p21.31 and encodes one of the key molecules in immune system. HLA molecules play a crucial role in generation of immune tolerance in the thymus and in antigen specific T cell response in the peripheral lymphoid organs via presenting antigen peptide to T cell. In addition, matching of HLA type plays a crucial role in graft rejection or graft versus host reaction in organ or tissue transplantation.

【Homepage Address】

http://133.5.233.30/