【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project：Development of rheumatoid arthritis-directed human immunology

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Research Area：Medicine, dentistry, and pharmacy
Keyword：Rheumatology, Clinical immunology, Connective tissue diseases

【Purpose and Background of the Research】

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation. Persistent joint inflammation results in the destruction of bone and cartilage, which is associated with the impairment of daily life. RA has a worldwide distribution with an estimated prevalence of 0.5 to 1%.

The pathogenesis of RA has not yet been fully understood. Nevertheless, decades of research revealed that proteins called pro-inflammatory cytokines play important roles in the formation of inflammation. Recently, biologics which suppress the effect of those cytokines are employed as therapeutic drugs. Those biologics are so effective as RA treatment that nearly half of the patients are released from significant impairment in daily life. However, long-term treatment is required even for the improved patients, and many biologics resistant patients remain in active disease. Therefore, more sophisticated treatments based on the advanced understanding of RA pathogenesis are still necessary. Previous mice research had a limitation in analyzing human disease mechanisms because of the difference between mice and human immunology. Therefore, our purpose of this research is investigating human genes and cells in combination with mice system and addressing the pathogenesis of RA.

【Research Methods】

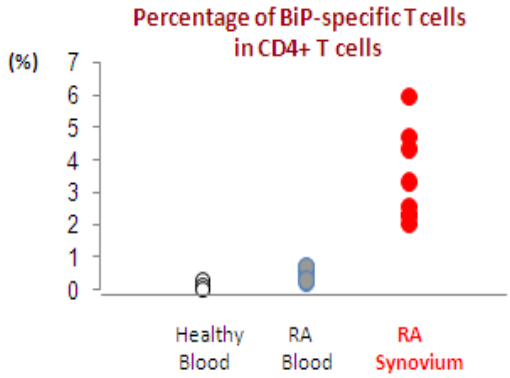
Genes associated with RA development can be identified by precisely comparing gene variation between healthy individuals and RA patients. Our research group has identified several RA-associated genes including PADI4, which is responsible for protein citrullination. Therefore, the molecular roles of these RA-associated genes will be evaluated in various experimental models.

Our group also revealed that T lymphocytes from RA patients respond to a specific part of BiP protein and produce inflammatory cytokine IL-17. Our aim is to elucidate the mode of BiP-responsive T cell induction and to prevent the T cell priming.

In contrast to pathogenic T cells, T cells with suppressive capacity for immune response are called as regulatory T cells. Recently, we have identified a new regulatory T cell subset. The function of this regulatory T cells will be investigated in RA patients to understand the T cell-mediated pathogenesis.

【Expected Research Achievements and Scientific Significance】

Our human based research of RA-associated genes, T lymphocytes activated in RA and regulatory T cell subset will improve our understanding of RA pathogenesis and may lead to the development of new therapeutic strategies based on human immunology.



【Publications Relevant to the Project】

Kochi Y, Suzuki A, Yamada R, Yamamoto K. Ethnogenetic heterogeneity of rheumatoid arthritis-implications for pathogenesis. Nat Rev Rheumatol 6:290-295, 2010

Fujio K, Okamura T, Yamamoto K. The family of IL-10-secreting CD4+ T cells. Adv Immunol 105:99-130, 2010

【Term of Project】 FY2011-2015

【Budget Allocation】 165,200 Thousand Yen