公益財団法人 セコム科学技術振興財団

研究成果報告書

研究課題名

健康長寿社会の実現に向けた新たな自己免疫制御療法の確立

Establishment of new anti-autoimmune therapy to facilitate a healthy long-lived society

研究期間

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Abstract

In Japan, the population of the elderly aged 65 years or older is expected to reach about 40% by 2050 due to the declining birthrate and aging society, and it is also predicted that the life expectancy will increase to 100 years by 2050. With this shift to a society with a longer life expectancy, the number of patients with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus is expected to increase. Among these, rheumatoid arthritis, in particular, still affects approximately 700,000 people, and 15,000 people are newly identified as patients every year. Chronic rheumatoid arthritis is characterized by the production of autoantibodies, including rheumatoid factor, and the disease progresses by inflammation of the synovial membrane of joints. The etiology and pathogenesis of the disease have not been fully elucidated, and although there are effective symptomatic treatments, no curative therapy has yet been established.

Follicular regulatory T cells (Tfr cells) play an essential role in suppressing autoimmune diseases such as rheumatoid arthritis by suppressing the production of IgG autoantibodies that recognize self-antigens and IgE antibodies involved in allergic responses. However, the underlying differentiation mechanism remains largely unknown. There is no culture system to induce differentiation of Tfr cells, and clarifying the differentiation mechanism of Tfr cells is important for (1) clarifying the immunological mechanisms that control autoantibody production and (2) developing therapeutic agents for autoimmune diseases that target Tfr cells. To elucidate the mechanisms of Tfr cell differentiation, chemical biology, which seeks to elucidate complex biological phenomena using small molecular compounds, could be a useful research strategy. In developing chemical biology, it is important to create low-molecular compounds with diversity in structure and bioactivity. Such low-molecular compounds can be expected to become lead compounds for therapeutic drugs; however even modern combinatorial synthetic compounds have limited structural diversity. Meanwhile, microbial metabolites, which are rich in diversity of structure and bioactivity, are attracting attention again as a source of bioactive substances. Actinomycetes, in particular, are known to produce a variety of secondary metabolites in their culture medium, and various bioactive substances have been identified and isolated.

In this study, we aim to search for, identify, and isolate bioactive substances involved in Tfr cell differentiation by evaluating the ability of hundreds of actinomycete culture media to induce Tfr cell differentiation using the Tfr cell differentiation induction culture system developed by the applicant. Furthermore, by identifying molecules targeted by bioactive substances and clarifying many molecules involved in Tfr cell differentiation, we aim to elucidate the entire mechanism of Tfr cell differentiation using chemical biology methods. In addition, this study will particularly focus on the role of Tfr cells in suppressing the onset of autoimmune diseases, and will use a rheumatoid arthritis model to evaluate the pharmacological effects of bioactive substances that induce Tfr cell differentiation. In parallel with the identification of target molecules of bioactive substances, we will introduce a library of known active compounds and off-patent drugs and evaluate their ability to induce Tfr cell differentiation in order to develop chemical biology to a high level.

As a result of screening using actinomycete culture extract, we identified an actinomycete strain with potent Tfr cell differentiation inducing activity. Furthermore, a highly lipophilic fraction of the extract showed Tfr cell differentiation inducing activity. We are currently trying to identify the bioactive substances in this fraction.

Furthermore, screening of a preexisting chemical library led to the discovery of an HDAC inhibitor as a compound with Tfr cell differentiation inducing activity. We evaluated each specific inhibitor of HDAC1/2 in autoimmune rheumatoid arthritis models, and found that each inhibitor markedly inhibited the onset of arthritis. These results suggest that specific inhibitors of HDAC isozymes are promising candidates for the treatment of rheumatoid arthritis in the future.