【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Elucidation of the Host's Homeostatic Responses by the Regulation of Immune System and its Application to the Prevention and Treatment of Immunological Disorders

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Research Project Number : 15H05787 Researcher Number : 50133616
Research Area : Molecular Immunology, Infection, Cancer, Inflammation
Keyword : Immune signaling, Homeostasis, Innate Immunity, Inflammation

【Purpose and Background of the Research】

The objective of this research project is to elucidate the underlying molecular mechanisms by which the immune system regulates homeostasis. Immune dysfunction is a critical factor underpinning autoimmune, cancer, and infectious diseases and this project will facilitate the basis for disease prevention and treatment.

Immune system activation in response to invading pathogens, mediated by recognition of pathogen-derived molecules called PAMPs, is critical for pathogen clearance and maintenance of host homeostasis. On the other hands, recent studies have revealed that the immune system also recognizes host-derived molecules, typically released by dead cells, termed DAMPs which have gained much attention for their involvement in various diseases (Rubartelli A. *Trends Immunol.*, 28: 429-436, 2007). Yet, the nature for how DAMPs activate immune responses is not well characterized. As such, little is known about how these DAMP-mediated immune responses contribute to the regulation of host homeostasis.

【Research Methods】

Recent data from our laboratory show that DAMPs and analogue molecules activate immune responses to modulate homeostasis of the host. In particular, we have developed chemical compounds and decoy oligonucleotides which target putative DAMP or DAMP receptors and related molecules. On the basis of these data, we focus on the following four research projects listed below.

(1) Clarify the regulatory mechanisms of inflammation and immune responses by dead cell-derived molecules.

(2) Identify molecules from living host cells recognized by innate receptors that contribute to the maintenance of the host homeostasis.

(3) Describe the role of molecules derived from gut microbiota and their interaction with host molecules for the maintenance of homeostasis.

(4) Identify the targets of host-derived molecules utilizing by newly discovered chemical compounds, and clarify the immune regulatory mechanisms mediated by these compounds.

【Expected Research Achievements and Scientific Significance】

This study will provide new insight into the basic concept of how to modulate immune responses to keep the host's homeostatic responses by self-derived molecules. Expanding on our preliminary, yet advanced research and utilizing our low molecular weight compounds and decoy oligonucleotide will enable us to modulate the immune system in novel ways. The anticipated findings will contribute to our understanding of the pathogenesis of autoimmune, cancer and infectious diseases; and may spawn new concepts and avenues for the treatment of diseases associated with immunity and inflammation.

【Publications Relevant to the Project】

1. Chiba, S. Recognition of tumor cells by Dectin-1 orchestrates innate immune cells for anti-tumor responses. *Elife* e04177 2014.
2. Yanai, H. Conditional ablation of HMGB1 in mice reveals its protective function against endotoxemia and bacterial infection. *PNAS.* 110: 20699-704, 2013.
3. Negishi, H. Essential contribution of IRF3 to intestinal homeostasis and microbiota-mediated *Tslp* gene induction. *PNAS* 109: 21016-21, 2012.
4. Yanai, H. Suppression of immune responses by nonimmunogenic oligodeoxynucleotides with high affinity for high-mobility group box proteins (HMGBs). *PNAS* 108: 11542-47, 2011.

【Term of Project】 FY2015-2019

【Budget Allocation】 132,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.iis.u-tokyo.ac.jp/~mol-immu/