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

Understanding the pathogenesis of infectious and immune diseases through integrated understanding of host-pathogen interactions

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Purpose and Background of the Research

● Outline of the Research

The immune system is a biological defense system that has evolved with pathogens and specifically attacks viruses and other pathogens. However, when the immune system is not regulated properly, autoimmune diseases develop, and infectious diseases become severe. In fact, many autoimmune diseases are known to be triggered by certain types of infection, but the mechanism is not clear. Infectious diseases such as viral infections are closely related to various immune abnormalities, and the elucidation of the interactions between pathogens and host immunity is necessary to determine the causes of these diseases. We have analyzed host-pathogen interactions with a focus on paired receptors in the "Elucidation of Infection and Immune Regulation Mechanisms Mediated by Paired Immune Receptors" Grant-in-Aid for Scientific Research (S) etc. (Satoh et al. *Cell* 2008; Wang et al. *Nature Immunology* 2013; Hirayasu et al. *Nature Microbiology* 2016; Saito et al. *Nature* 2017; Harrison et al. *Nature* 2020; Liu et al. *Cell* 2021). However, it has become evident that pathogens regulate immune responses not only through paired receptors but also through a variety of host molecules. Therefore, in order to elucidate the various immune abnormalities associated with infectious diseases, it would be important to go beyond paired-type receptors and analyze them from a more multifaceted perspective. Therefore, based on previous studies, this study aims to integrate and elucidate host-pathogen interactions targeting antibody-mediated host-pathogen interactions and antigen presentation mechanisms by MHC, in addition to host-pathogen interactions mediated by paired inhibitory receptors. We will integrate the host-pathogen interactions through paired inhibitory receptors, as well as antibody-mediated host-pathogen interactions and host-pathogen interactions targeting antigen presentation mechanism by MHC to elucidate the causes of immune abnormalities caused by infectious diseases (Fig. 1).

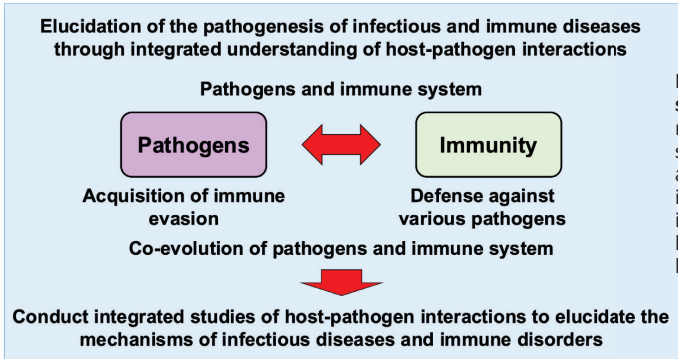

Fig. 1 Overall diagram of this study: To understand the mechanisms underlying the severity of infectious diseases and the pathogenesis of immune diseases caused by infectious diseases, integrated host-pathogen interactions will be elucidated.

● Elucidation of immune evasion mechanisms of pathogens and the immune abnormalities caused by them.

We have shown that inhibitory receptors, which play an important role in the regulation of immune responses, are used not only by viruses but also by *Plasmodium falciparum* in immune evasion. Furthermore, we have revealed immune escape mechanisms of novel coronaviruses using antibodies and targeting the antigen-presenting mechanism of MHC, indicating the importance of multifaceted analysis in elucidating immune escape mechanisms by pathogens. Therefore, we will elucidate how pathogen-induced immune escape mechanisms cause immune abnormalities (Fig. 2).

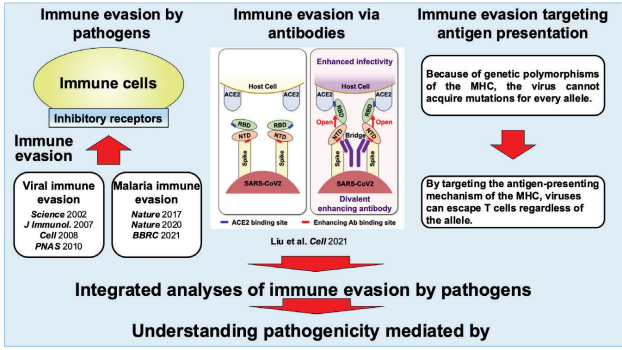

Fig. 2: Causes of immune abnormalities caused by the immune evasion mechanism of pathogens: Pathogens escape from immune responses by regulating the functions of antibodies and MHC, the central molecules of immune responses, in addition to paired inhibitory receptors. Therefore, we will elucidate how immune abnormalities are caused by the immune escape mechanism by pathogens.

Expected Research Achievements

● Elucidation of disease pathogenesis by host-pathogen interactions

By investigating host-pathogen interactions, we aim to elucidate the full pathogenesis mechanisms of many autoimmune diseases whose causes have not yet been clarified. In particular, by elucidating the regulatory mechanisms of immune responses induced by viral infections, we will elucidate the immune evasion mechanisms of viruses involved in severe viral infections and the pathogenesis mechanisms of autoimmune diseases caused by viral infections. Regarding the reasons why various types of autoimmune diseases develop, we will also search for pathogens that can explain tissue-specific autoimmune diseases by analyzing various viral molecules that affect immune regulation. This study is expected to provide completely new insights into how immune dysfunctions are caused by viral infections. Furthermore, by elucidating the mechanism of immune regulation by viruses, we will develop effective treatments for diseases by controlling autoimmune responses (Fig. 3).

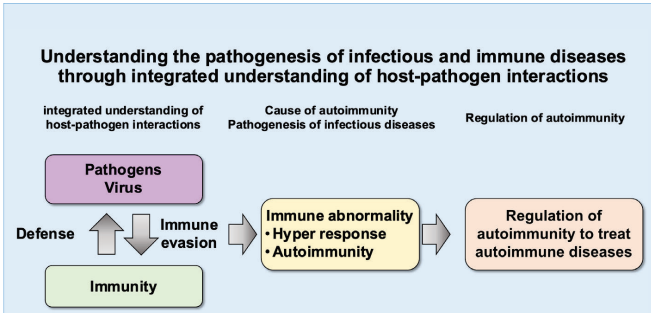

Fig. 3 Elucidation of the mechanisms of disease pathogenesis by elucidating host-pathogen interactions: Elucidation of host-pathogen interactions is expected to elucidate the mechanisms of severity of infectious diseases and the pathogenesis of autoimmune diseases, and based on these findings, development of new therapeutic strategies to control immune responses is expected.

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