IMSUT Hospital

Department of AIDS Vaccine Development
エイズワクチン開発担当

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We are working on Microbiology and Immunology to elucidate the immune mechanism for retroviral control in vivo. In particular, we are studying virus-host immune interaction and viral evolution using non-human primate models and human clinical samples derived from African and Asian countries as well as Japan. Furthermore, we are developing vaccines eliciting antibody and/or cytotoxic T lymphocyte responses targeting pathogens including HIV-1, HTLV-1, and SARS-CoV-2.

1. Impaired protective role of HLA-B*57:01/58:01 in HIV-1 CRF01_AE infection: a cohort study in Vietnam.

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Human Leukocyte Antigen *HLA-B*57:01* and *B*58:01* are considered anti-HIV-1 protective alleles. HLA-B*57:01/58:01-restricted HIV-1 Gag TW10 (TSTLQEQIGW, Gag residues 240-249) epitope-specific $CD8^+$ T cell responses that frequently select for a Gag escape mutation, T242N, with viral fitness cost are crucial for HIV-1 control. Although this finding has been observed in cohorts where HIV-1 subtype B or C predominates, the protective impact of *HLA-B*57:01/58:01* has not been reported in Southeast Asian countries where HIV-1 CRF01_AE is the major circulating strain. In this study, the effect of *HLA-B*57:01/58:01* on CRF01_AE infection was investigated in a CRF01_AE-infected Vietnamese cohort (N = 280). *HLA-B*57:01/58:01*-positive individuals mostly had HIV-1 with T242N (62/63) but showed neither a significant reduction in viral load nor increased CD4 counts relative to *B*57:01/58:01*-negative participants. *In vitro* and *in vivo* analyses revealed a significant reduction in viral fitness of CRF01_AE with T242N. *In silico* analysis indicated reduced presentation of epitopes in the context of CRF01_AE compared to subtype B or C in 10/16 HLA-B*57:01/58:01-restricted HIV-1 epitopes. These results indicate that the protective impact of *HLA-B*57:01/58:01* on CRF01_AE infection is impaired despite strong suppressive pressure by TW10-specific $CD8^+$ T cells.

2. Plasmacytoid dendritic cells stimulated with Lactococcus lactis strain Plasma produce soluble factors to suppress SARS-CoV-2 replication.

Hiroshi Ishii[2], Kenta Jounai[6], Ryohei Tsuji[6], Konomi Ohshio[6], Daiki Kaneda, Midori Okazaki[2], Shigeyoshi

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Innate immune responses are important in the control of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication. We have previously found a lactic acid bacteria species, *Lactococcus lactis* strain Plasma (LC-Plasma), which possesses specific feature to activate plasmacytoid dendritic cells (pDCs) and thus may affect innate immune responses. In this study, we investigated the impact of pDC activation by LC-Plasma on SARS-CoV-2 replication *in vitro*. Addition of the culture supernatant of pDCs stimulated with LC-Plasma resulted in suppression of SARS-CoV-2 replication in Vero and Calu-3 cells. We confirmed interferon-α (IFN-α) secretion in the supernatant of pDCs stimulated with LC-Plasma and induction of IFN-stimulated genes in cells treated with the pDC supernatant. Anti-IFN-α antibody impaired the suppression of SARS-CoV-2 replication by the supernatant of LC-Plasma-stimulated pDCs, suggesting that IFN-α plays an important role in the SARS-CoV-2 suppression. These results indicate the potential of LC-Plasma to induce inhibitory responses against SARS-CoV-2 replication through pDC stimulation with IFN-α secretion.

3. HTLV-1 proliferation after CD8$^+$ cell depletion by monoclonal anti-CD8 antibody administration in latently HTLV-1-infected cynomolgus macaques.

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HTLV-1 induces chronic asymptomatic latent infection with substantial proviral load but without significant viral replication *in vivo*. Cumulative studies have indicated involvement of CD8$^+$ cells including virus-specific CD8$^+$ T cells in the control of HTLV-1 replication. However, whether HTLV-1 expression from latently infected cells *in vivo* occurs in the absence of CD8$^+$ cells remains unclear. In this study, we examined the impact of CD8$^+$ cell depletion by monoclonal anti-CD8 antibody administration on proviral load in HTLV-1-infected cynomolgus macaques. Five cynomolgus macaques were infected with HTLV-1 by inoculation with HTLV-1-producing cells. Administration of monoclonal anti-CD8 antibody in the chronic phase resulted in complete depletion of peripheral CD8$^+$ T cells for approximately two months. All five macaques showed an increase in proviral load following CD8$^+$ cell depletion, which peaked just before the reappearance of peripheral CD8$^+$ T cells. Tax-specific CD8$^+$ T cell responses were detected in these recovered CD8$^+$ T cells. Importantly, anti-HTLV-1 antibodies also increased after CD8$^+$ cell depletion, indicating HTLV-1 antigen expression. These results provide evidence indicating that HTLV-1 can proliferate from the latent phase in the absence of CD8$^+$ cells and suggest that CD8$^+$ cells are responsible for the control of HTLV-1 replication.

4. Breadth and durability of SARS-CoV-2 specific T cell responses following long-term recovery from COVID-19.

Dang Thi Thu Thao[3], Alitzel Anzurez[2], Kaori Nakayama-Hosoya[2], Shoji Miki[2], Kazuo Yamashita[8], Mark de Souza[2], Tetsuro Matano, Ai Kawana-Tachikawa: [8]KOTAI Biotechnologies, Inc., Japan

T cell immunity is crucial for long-term immunological memory, but the profile of SARS-CoV-2-specific memory T cells in individuals who recovered from COVID-19 (COVID-19-convalescent individuals) is not sufficiently assessed. In this study, the breadth and magnitude of SARS-CoV-2-specific T cell responses were determined in COVID-19-convalescent individuals in Japan. Memory T cells against SARS-CoV-2 were detected in all convalescent individuals, and those with more severe disease exhibited a broader T cell response relative to cases with mild symptoms. Comprehensive screening of T cell responses at the peptide level was conducted for spike (S) and nucleocapsid (N) proteins, and regions frequently targeted by T cells were identified. Multiple regions in S and N proteins were targeted by memory T cells, with median numbers of target regions of 13 and 4, respectively. A maximum of 47 regions were recognized by memory T cells for an individual. These data indicate that SARS-CoV-2-convalescent individuals maintain a substantial breadth of memory T cells for at least several months following infection. Broader SARS-CoV-2-specific CD4$^+$ T cell responses, relative to CD8$^+$ T cell responses, were observed for the S but not the N protein, suggesting that antigen presentation is different between viral proteins. The binding affinity of predicted CD8$^+$ T cell epitopes to HLA class I molecules in these regions was preserved for the Delta variant and at 94 to 96% for SARS-CoV-2 Omicron subvariants, suggesting that the amino acid changes in these variants do not have a major impact on antigen presentation to SARS-CoV-2-specific CD8$^+$ T cells.

Publications

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