

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. Longitudinal analysis of microbiome composition in Ghanaians living with HIV-1.

Lucky Ronald Runtuwene¹, Prince Kofi Parbie¹, Taketoshi Mizutani², Aya Ishizaka³, Saori Matsuoka¹, Christopher Zaab-Yen Abana⁴, Dennis Kushitor⁴, Evelyn Yayra Bonney⁴, Sampson Badu Ofori⁵, Hiroshi Kiyono⁶, Koichi Ishikawa¹, William Kwabena Ampofo, and Tetsuro Matano: ¹AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan; ²Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, University of Tokyo; ³Division of Infectious Diseases, Institute of Medical Science, University of Tokyo; ⁴Department of Virology, Noguchi Memorial Institute for Medical Research, University of Ghana; ⁵Department of Internal Medicine, Eastern Regional Hospital Koforidua, Ghana Health Service; ⁶Institute for Global Prominent Research, Graduate School of Medicine, Chiba University

HIV-1 infection is known to cause gut microbiota dysbiosis. The direct infection of HIV-1 in gut-resident CD4⁺ T cells causes a cascade of phenomena resulting in the instability of the gut mucosa. The effect of HIV infection on gut microbiome dysbiosis remains unresolved despite antiretroviral therapy. In this study, we showed the results of a longitudinal study

of microbiome analysis of people living with HIV (PLWH). We contrasted the diversity and composition of the microbiome of patients with HIV at the first and second time points (baseline_case and six months later follow-up_case, respectively) with those of healthy individuals (baseline_control). We found that despite low diversity indices in the follow-up_case, the abundance of some genera was recovered to be similar to baseline_control. Some genera were consistently in high abundance in HIV⁺ samples. Furthermore, we found that the CD4⁺ T-cell count and soluble CD14 level were significantly related to high and low diversity indices, respectively. We also found that the abundance of some genera was highly correlated with clinical features, especially with antiretroviral duration. This includes genera known to be correlated with worse HIV-1 progression (*Achromobacter* and *Stenotrophomonas*) and a genus associated with gut protection (*Akkermansia*). The fact that a protector of the gut and genera linked with a worse progression of HIV-1 are both enriched may signify that despite the improvement of clinical features, the gut mucosa remains compromised.

2. Prophylactic vaccination inducing anti-Env antibodies can result in protection against HTLV-1 challenge in macaques.

Midori Nakamura-Hoshi¹, Hiroshi Ishii¹, Takushi Nomura¹, Masako Nishizawa¹, Trang Thi Thu Hau¹, Nozomi Kuse¹, Midori Okazaki¹, Akira Aina⁷, Tadaki Suzuki⁷, Hideki Hasegawa⁸, Takeshi Yoshida¹, Kenzo Yonemitsu⁹, Yuriko Suzaki⁹, Yasushi Ami⁹, Hiroyuki Yamamoto¹, and Tetsuro Matano: ⁷Department of Pathology, National Institute of Infectious Diseases; ⁸Center for Influenza and Respiratory Virus Research, National Institute of Infectious Diseases; ⁹Management Department of Biosafety, Laboratory Animal, and Pathogen Bank, National Institute of Infectious Diseases

HTLV-1 infection occurs by cell-to-cell transmission and can induce fatal adult T-cell leukemia (ATL). Vaccine development is critical for the control of HTLV-1 transmission. However, determining whether vaccine-induced anti-Env antibodies can prevent cell-to-cell HTLV-1 transmission is challenging. In this study, we examined the protective efficacy of a vaccine inducing anti-Env antibodies against HTLV-1 challenge in cynomolgus macaques. Eight of ten vaccinated macaques produced anti-HTLV-1 neutralizing antibodies (NAbs) and were protected from an intravenous challenge with 10⁸ HTLV-1-producing cells. In contrast, the two vaccinated macaques without NAb induction and ten unvaccinated controls showed HTLV-1 infection with detectable proviral load after challenge. Five of the eight protected macaques were administered with an anti-CD8 monoclonal antibody, but proviruses remained undetectable and no increase in anti-HTLV-1 antibodies was observed even after CD8⁺ cell depletion in three of them. Analysis of Env-specific T cell responses did not suggest involvement of vaccine-induced Env-specific T cell responses in the protection. These results indicate that anti-Env antibody induction by vaccination can result in functionally sterile HTLV-1 protection, implying the rationale for strategies aimed at anti-Env antibody induction in prophylactic HTLV-1 vaccine development.

3. Characterization of the Proinflammatory Cytokine Profile during Acute SARS-CoV-2 Infection in People with Human Immunodeficiency Virus.

Alitzel Anzurez¹, Lucky Runtuwene¹, Thi Thu Thao Dang¹, Kaori Nakayama-Hosoya¹, Michiko Koga³, Yukihiko Yoshimura¹⁰, Hiroaki Sasaki¹⁰, Nobuyuki Miyata¹⁰, Kazuhito Miyazaki¹⁰, Yoshimasa Talahashi¹¹, Tadaki Suzuki⁷, Hiroshi Yotsuyanagi³, Nat-suo Tachikawa¹⁰, Tetsuro Matano, and Ai Kawana-Tachikawa: ¹⁰Department of Respiratory Medicine, Yokohama Municipal Citizens' Hospital; ¹¹Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases

Persistent inflammation in chronic HIV infection

may affect immune responses against SARS-CoV-2 infection. Plasma levels of multiple proinflammatory cytokines during acute SARS-CoV-2 infection were assessed in people with HIV (PWH) with effective cART. There were no significant differences in any of the tested cytokines between COVID-19 severity in PWH, while most of them were significantly higher in individuals with severe disease in HIV-uninfected individuals, suggesting that excess cytokines release by hyper-inflammatory responses does not occur in severe COVID-19 with HIV infection. The strong associations between the cytokines observed in HIV-uninfected individuals, especially between IFN- α /TNF- α and other cytokines, were lost in PWH. The steady state plasma levels of IP-10, ICAM-1, and CD62E were significantly higher in PWH, indicating that PWH are in an enhanced inflammatory state. Loss of the several inter-cytokine correlations were observed in *in vitro* LPS stimuli-driven cytokine production in PWH. These data suggest that inflammatory responses during SARS-CoV-2 infection in PWH distinct from those in HIV-uninfected individuals, partially due to the underlying inflammatory state and/or impairment of innate immune cells.

4. Virion-surface display of a chimeric immunoglobulin Fc domain facilitating uptake by antigen-presenting cells.

Sayuri Seki¹, Prince Kofi Parbie¹, Hiroyuki Yamamoto¹, and Tetsuro Matano

Antigen-presenting cells (APCs) play an important role in virus infection control by bridging innate and adaptive immune responses. Macrophages and dendritic cells (DCs) possess various surface receptors to recognize/internalize antigens, and antibody binding can enhance pathogen-opsionizing uptake by these APCs via interaction of antibody fragment crystallizable (Fc) domains with Fc receptors, evoking profound pathogen control in certain settings. In this study, we examined phagocytosis-enhancing potential of Fc domains directly oriented on a retroviral virion/virus-like particle (VLP) surface. We generated an expression vector coding a murine Fc fragment fused to the transmembrane region (TM) of a retroviral envelope protein, deriving expression of the Fc-TM fusion protein on the transfected cell surface and production of virions incorporating the chimeric Fc upon co-transfection. Incubation of Fc-displaying SIV with murine J774 macrophages and bone marrow-derived DCs derived Fc receptor-dependent enhanced uptake, being visualized by imaging cytometry. Alternative preparation of a MLV backbone-based Fc-displaying VLP loading an influenza virus HA antigen resulted in enhanced HA internalization by macrophages, stating antigen compatibility of the design. Results show that the Fc-TM fusion molecule can be displayed on certain viruses/VLPs and may be

utilized as a molecular adjuvant to facilitate APC antigen uptake.

Publications

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