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. Virus-host immune interaction in asymptomatic HTLV-1 carriers.

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Human T-cell leukemia virus type 1 (HTLV-1) induces chronic long-term latent infection that can cause fatal diseases, including adult T-cell leukemia. HTLV-1 production is poor and undetectable during the asymptomatic phase of infection. Virus-host immune interaction in latent infection has not been fully determined. In this study, virus-specific antibody and T-cell responses in asymptomatic HTLV-1 carriers (n = 77) were investigated. Neutralizing antibody responses were significantly higher in individuals with higher anti-Env SU (gp46) antibody levels and positively correlated with proviral loads. Overnight *ex vivo* culture of peripheral blood mononuclear cells resulted in detectable HTLV-1 Gag antigen (p19) expression in $CD4^+$ T cells and interferon-γ (IFN-γ) induction in $CD8^+$ T cells. Frequencies of these p19-expressing $CD4^+$ T cells and non-specific IFN-γ-induced $CD8^+$ T cells were positively correlated with proviral loads, respectively. Tax-specific $CD8^+$ T-cell frequencies were not associated with proviral loads but inversely correlated with the ratios of p19-expressing $CD4^+$ T-cell frequencies to proviral loads, implying the involvement of Tax-specific $CD8^+$ T cells in the control of HTLV-1 replication. These results provide insights into the elucidation of the virus-host immune interaction in latent HTLV-1 infection.

2. SIV-specific neutralizing antibody induction following selection of a PI3K drive-attenuated *nef* variant.

Hiroyuki Yamamoto[1] and Tetsuro Matano

HIV and simian immunodeficiency virus (SIV) infections are known for impaired neutralizing antibody (NAb) responses. While sequential virus–host B cell interaction appears to be basally required for NAb induction, driver molecular signatures predisposing to NAb induction still remain largely unknown. In this study, we describe SIV-specific NAb

induction following a virus–host interplay decreasing aberrant viral drive of phosphoinositide 3-kinase (PI3K). Screening of seventy difficult-to-neutralize SIVmac239-infected macaques found nine NAb-inducing animals, with seven selecting for a specific $CD8^+$ T-cell escape mutation in viral *nef* before NAb induction. This Nef-G63E mutation reduced excess Nef interaction-mediated drive of B-cell maturation-limiting PI3K/mammalian target of rapamycin complex 2 (mTORC2). In vivo imaging cytometry depicted preferential Nef perturbation of cognate Envelope-specific B cells, suggestive of polarized contact-dependent Nef transfer and corroborating cognate B-cell maturation post-mutant selection up to NAb induction. Results collectively exemplify a NAb induction pattern extrinsically reciprocal to human PI3K gain-of-function antibody-dysregulating disease and indicate that harnessing the PI3K/mTORC2 axis may facilitate NAb induction against difficult-to-neutralize viruses including HIV/SIV.

Publications

1. Ujiie, K., Nakakido, M., Kinoshita, S., Caaveiro, J.M.M., Entzminger, C.K., Okumura, S.C.J., Maruyama, T., Miyauchi, K., Matano, T., and Tsumoto, K. Specific recognition mechanism of an antibody to sulfated tyrosine and its potential use in biological research. J. Biol. Chem. 301:108176, 2025.
2. Asigbee, T.W., Nakamura-Hoshi, M., Kuse, N., Ishii, H., Ishikawa, K., Kawana-Tachikawa, A., Horibe, E., Nakashima, M., Yamano, Y., Uchimaru, K., and Matano, T. Virus-host immune interaction in asymptomatic HTLV-1 carriers. Microbiol. Spectr. 13:e0250724, 2025.
3. Yamamoto, H., and Matano, T. SIV-specific neutralizing antibody induction following selection of a PI3K drive-attenuated *nef* variant. Elife 12: RP88849, 2025.
4. Miyakawa, K., Tanaka, K., Ino, Y., Kimura, Y., Kameya, T., Mizukoshi, F., Nishi, M., Yokoyama, M., Nakabayashi, J., Nomaguchi, M., Sato, H., Kimura, H., Akari, H., Miura, T., Takaoka, A., Hasegawa, H., Matano, T., Minamishima, Y.A., and Ryo, A. PHD3-VHL axis controls HIV-2 infection through oxygen-dependent hydroxylation and degradation of Vpx. PLoS Pathog. 21:e1013241, 2025.