The functional importance of HTLV-1 Rex in viral replication and its influence on the host cell homeostasis.

Laboratory of Tumor Cell Biology: @Immunology, Institute of Medical Science, University of Tokyo
4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
http://ltcb-mgs.umin.jp/access.html

Supervisors: Kazumi Nakano (Assistant Prof.) and Toshiki Watanabe (Professor)

Key words: Retrovirology, HTLV-1, host-pathogen interactions

Background and summary of the project:

The human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus causing an aggressive T-cell malignancy, adult T-cell leukemia (ATL). Although HTLV-1 has a compact RNA genome, it has evolved elaborate mechanisms to maximize its coding potential. The structural proteins Gag, Pro, and Pol are encoded in the unspliced form of viral mRNA, whereas the Env protein is encoded in singly spliced viral mRNA. Regulatory and accessory proteins, such as Tax, Rex, p30II, p12, and p13, are translated only from fully spliced mRNA. For effective viral replication, translation from all forms of HTLV-1 transcripts has to be achieved in concert, although unspliced mRNA are extremely unstable in mammalian cells. It has been well recognized that HTLV-1 Rex enhances the stability of unspliced and singly spliced HTLV-1 mRNA by promoting nuclear export and thereby, removing them from the splicing site. Rex specifically binds to the highly structured Rex responsive element (RxRE) located at the 3′ end of all HTLV-1 mRNA. Rex then binds to the cellular nuclear exporter, CRM1, via its nuclear export signal domain and the Rex-viral transcript complex is selectively exported from the nucleus to the cytoplasm for effective translation of the viral proteins. Yet, the mechanisms by which Rex inhibits the cellular splicing machinery and utilizes the cellular pathways beneficial to viral survival in the host cell have not been fully explored. Furthermore, physiological impacts of Rex against homeostasis of the host cell via interactions with numerous cellular proteins have been largely left uninvestigated.

In our laboratory, we extensively investigate the biological importance of HTLV-1 Rex in the HTLV-1 life cycle by using cellular and molecular biology techniques. Also, recent interests of ours are focusing on how Rex influences on the host cellular homeostasis, since all functions of Rex for viral replication are dependent on the host cellular machinery.

Techniques used: PCR, human cell culture, protein expression in human cells, Western blotting, immunoprecipitation assay, immunocytochemistry

Recent publications from our laboratory:

1. Nakano K, Ando T, Yamagishi M, Yokoyama K, Ishida T, Ohsugi T, Tanaka Y, Brighty DW, Watanabe T. (2013). Viral interference with host mRNA surveillance, the nonsense-mediated mRNA decay (NMD) pathway, through a new function of HTLV-1 Rex: implications for retroviral replication. **Microbes and Infection**, 15(6-7):491-505, 2013 (doi: 10.1016/j.micinf.2013.03.006)

2. Asanuma S, Yamagishi M, Kawanami K, Nakano K, Sato-Otsubo A, Muto S, Sanada M, Yamochi T, Kobayashi S, Utsunomiya A, Iwanaga M, Yamaguchi K, Uchimaru K, Ogawa S, Watanabe T. (2013). Adult T-cell leukemia cells are characterized by abnormalities of Helios expression that promotes T-cell growth. **Cancer Sci** 104(5), 32pp, 2013, in press (doi: 10.1111/cas.12181)

3. Yamagishi M, Nakano K, Miyake A, Yamochi T, Kagami Y, Tsutsumi A, Matsuda Y, Sato-Otsubo A, Muto S, Utsunomiya A, Yamaguchi K, Uchimaru K, Ogawa S, Watanabe T (2012). Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in adult T-cell leukemia and other cancers. **Cancer Cell** 21: 121-135.

4. Nakano K, Watanabe T. (2012). HTLV-1 Rex: the courier of viral messages, making use of the host vehicle. **Front Microbiol** 3:330. (doi: 10.3389/fmicb.2012.00330) Epub