The study on the viral infections and immunological disorders for chronic fatigue syndrome (CFS).

Takeshi Sairenji¹, Kazufumi Ikuta¹, Takeshi Yamada^{1, 4}, Tokio Shimomura², Hirohiko Kuratsune³, Eiko Ohnishi¹, Yoshihiro Sokawa⁵, Ryuzo Kawahara⁴, Teruo Kitani⁸ and Yasuyoshi Watanabe⁷

¹Division of Biosignaling, Department of Biomedical Sciences, School of Life Science, ²Division of Clinical Laboratory Medicine, Department of Pathophysiological and Therapeutic Sciences, and ³Division of Neuropsychiatry, Department of Multidisciplinary Internal Medicine, School of Medicine, Faculty of Medicine, Tottori University, Tottori, Japan; ⁴Department of Molecular Medicine, Hematology and Oncology, Osaka University Graduate School of Medicine, Osaka, Japan; ⁵Department of Physiology, Osaka City University Graduate School of Medicine, Osaka, Japan; ⁶Sakai Hospital, Osaka, Japan.

We have been studying the viral infection and immune response on CFS. We hypothesize that CFS may be caused partly by immunological disorders especially cytokines associated with some infections (Fig. 1). Toward the goal, we studied EBV reactivation and assayed cytokines, such as IL-4, IL-10, vIL-10, and IFN and IgE in CFS patients. The preliminary results suggested that EBV was reactivated and the cytokines were up-regulated in a part of CFS patients. *In vitro* we studied the mechanisms of EBV reactivation and cytokine-up-regulation on EBV infected cells.

Recently we assayed 2', 5'-oligoadenylate synthetase (2-5AS) activities in peripheral blood mononuclear cells from CFS patients in Japan (Ikuta and Sairenji, 2003). CFS patients were diagnosed in two hospitals, H1 and H2 located in distinct areas. The 2-5AS activities were detected in 19 (86%) of 22 patients of H1and 7 (32%) of 22 patients of H2, respectively; while the activities were detected in only 1 (11%) of 9 healthy controls. We assayed the antibody titers against EBV in the patients. The titers of anti-EA-IgG antibodies which indicate EBV reactivation were detected in 2 (9%) and 7 (32%) patient(s) in 22 patients of H1 and of H2, respectively. There was a low correlation between the 2-5AS activities and antibody titers of EA-IgG. The up-regulation of 2-5AS activities suggests the some virus infections including EBV and/or immunological dysfunctions in the CFS patients. 2-5AS activities were also detected in 8 (36%) to 22 and 2 (7%) to 28, of

depression patients and the control in H1, respectively. Our results indicate that the up-regulation of 2-5AS activities is useful for a diagnostic maker of CFS and should be analyzed why 2-5AS is up-regulated constitutively in CFS.

Publications

- 1. Ikuta, K., and <u>Sairenji, T.</u>: Abnormality of 2', 5'-oligoadenylate synthetase-activity and ribonucleace L in chronic fatigue patients. J. Clin. Exp. Med. (IGAKUNO AYUMI) 204: 409-412 (2003).
- 2. Hoshikawa, Y., Satoh, Y., and <u>Sairenji, T.</u>: Evidence of lytic infection of Epstein-Barr virus (EBV) in EBV-positive gastric carcinoma. J. Med. Virol. 66, 351-359 (2002)
- 3. Satoh, T., Fukuda, M., and <u>Sairenji, T.</u>: Distinct patterns of mitogen-activated protein kinase phosphorylation and Epstein-Barr virus gene expression in Burkitt's lymphoma cell lines *versus* B lymphoblastoid cell lines. Virus Genes 25: 15-21 (2002)
- 4. Fukuda, M., Kurasaki, W., Yanagihara, K., Kuratsune, H. and <u>Sairenji, T.</u>: A mechanism in Epstein-Barr virus oncogenesis: Inhibition of transforming growth factor-β1-mediated induction of MAPK/p21 by LMP1. Virology 302: 310-320 (2002).
- 5. Agawa, H., Ikuta, K., Minamiyama, Y., Inoue, M. and <u>Sairenji, T.</u>: Down-Regulation of spontaneous Epstein-Barr virus reactivation in the P3HR-1 cell line by L-Arginine. Virology 304: 114-124 (2002).
- 6. Ikuta, K., Saiga, K., Deguchi, M., and <u>Sairenji, T.</u>: Epstein-Barr virus DNA is detected in peripheral blood mononuclear cells of EBV-seronegative infants with infections mononucleosis-like symptoms. Virus Genes (in press).
- 7. Jiang, R., Kanamori, M., Satoh, Y., Fukuda, M., Ikuta, K., Murakami, M., and <u>Sairenji, T</u>.: Contrasting effects of hydroxyurea on cell growth and reduction in Epstein-Barr virus (EBV) genomes in EBV-infected epihelioid cell lines versus Burkitt's lymphoma cell lines. J. Med. Virol. (in press).