YW1-01 Colony stimulating factor-1 receptor signaling enhances tumorigenesis and invasiveness of prostate cancer cells.

Department of Urology, Kyorin University

Hisamitsu Ide

Recent evaluation of human prostate tissues by immunohistochemical analysis on tissue microarrays showed predominantly high expression of CSF-1R in prostatic intraepithelial neoplasia (PIN) and prostate cancer. However, the biological function of CSF-1R expression in human prostate cancer cells has not been explored. In the present study, we investigated the tumorigenesis and invasive potential of human prostate cancer cell lines, which were stably transfected with the human wild type CSF-1R or its mutant forms of CSF-1R carrying the green fluorescent protein (GFP) cDNA in the same construct. In comparison with the cells transduced with GFP-vector alone, transfected cells expressing a wild-type CSF-1R formed more colonies in soft agar and invaded more efficiently through a matrigel after the addition of recombinant human CSF-1. The receptor bearing activating mutation (L301S and Y969F) induced anchorage-independent growth in soft agar and invasion into matrigel, whereas the cellular growth rate was not increased. After injection the cells into the intraperitoneum or the tail vein of scid mice, activating mutation clones produced higher incidence of diaphragm invasion or lung metastases than wild type and vector clones. Our results suggest that expression of CSF-1R in prostate cancer can facilitate cellular invasion and anchorage-independent and its interference with CSF-1 receptor function may be potential target for therapeutic intervention.

YW1-02 Identification of tumor suppressor genes through functional complementation of tumorigenicity

Department of Urology, Tokyo University

Hiroshi Fukuhara

The existence of tumor-suppressor genes was originally demonstrated by functional complementation through whole-cell and microcell fusion. Loss of heterozygosity on chromosome 10p was observed frequently in human prostate cancers. Studies have demonstrated that the introduction of the short arm of human chromosome 10 into a human prostate cancer cell line, PPC-1, by microcell-mediated chromosome transfer (MMCT), suppressed the malignant phenotype, suggesting the presence of a prostate tumor suppressor gene (s) within a region of approximately 1.2 Mb at distal 10p.

Transfer of chromosome 11 into a human non-small-cell lung cancer (NSCLC) cell line, A549, suppresses tumorigenicity. Loss of heterozygosity (LOH) on the long arm of chromosome 11 has been reported in NSCLC, prostate cancer, and other cancers. Most of tumor-suppressor activity localizes to a 100-kb segment by functional complementation. We reported that this region contains a single confirmed gene, TSLC1, whose expression is reduced or absent in A549 and other cell lines including prostate cancer. TSLC1 expression or suppression is correlated with promoter methylation state in these cell lines. Restoration of TSLC1 expression to normal or higher levels suppresses tumor formation by A549 and PPC-1 cells in nude mice. TSLC1 encodes a membrane glycoprotein with an extracellular domain homologous to those of immunoglobulin superfamily proteins.

YW1-03 Proteome Analysis of Androgen Independent Prostate Cancer

Kitasato University School of Medicine

Hidetoshi Kuruma

To survey comprehensive protein expression patterns in prostate cancer and to reveal differences in proteomes between androgen dependent and independent ones, we applied a unique two-dimensional electrophoresis method that uses an agarose gel (agarose 2-DE), which was good at separating high-molecular-mass (HMM) proteins. Proteins were extracted from LNCaP in vivo models in male nude mice with or without castration, and separated by agarose 2-DE. Those proteins were identified by LC-MS/MS. We identified 91.0% of 324 spots excised in total, and obtained a non-redundant 234 proteins. Excluding mouse-derived proteins, we considered remaining 226 proteins to be related to the cancer. Functional classification revealed that the distribution of total proteins was similar to the human genome's one. In HMM protein area, the transcription/translation group was dominant, in contrast to low-molecular-mass protein area in which the metabolism group was. 18 proteins changed in content when the tumor progressed from androgen dependent to independent states. In conclusions, studying HMM proteins is important in cancer proteomics, and our results may have clinical applicability.

YW1-04 Regulation of androgen-independent growth of human prostate cancer by c-ErbB-2 and PAcP signaling pathway

Division of Nephro-Urology, Nagasaki University Graduate School of Biomedical Sciences

Tsukasa Igawa

OBJECTIVES. Human prostatic acid phosphatase (PacP), a major protein tyrosine phosphatase in prostate epithelium, plays a critical role in regulating the growth of prostate cancer cells. We investigated the suppression effect of PacP by utilizing cDNA direct intratumoral administration in androgen-independent LNCaP xenograft tumors. **METHODS.** An androgen-independent LNCaP cell model (C-33 and C-81 cells) was used for the experiments. We investigated the growth suppression effect of PacP cDNA intratumoral injection in pre-established C-81 xenograft tumors, and analyzed the expression of PacP, prostate-specific antigen (PSA), PCNA, and c-ErbB-2 in the tumors by immunohistochemistry and Western blotting. **RESULTS.** The single intratumoral administration of the wild type PacP cDNA showed a significant suppression effect on C-81 xenograft tumor growth, compared to vector alone-injected control ($p < 0.05$). In the tumors injected with this PacP cDNA, the PacP expression was inversely correlated with the level of tyrophosphorylated c-ErbB-2 and the degree of cell proliferation indicated by PCNA staining. **CONCLUSION.** Our results clearly demonstrated that cellular PacP has a suppression effect on the growth of androgen-independent LNCaP xenograft tumors. This effect occurs at least partly through the dephosphorylation of c-ErbB-2 by PacP.