YW2-13 The prognostic value of angiogenesis-related genes for progression of transitional cell carcinoma in the urinary tract

Department of Urology, Kochi Medical School

Keiji Inoue

Purpose : We hypothesized that the expression of angiogenesis-related genes would be novel prognostic markers of transitional cell carcinoma (TCC) in the urinary tract.

Experimental Design : We selected highest and the lowest expressing clone of bFGF, VEGF and IL-8 in human TCC cell line. We evaluated tumorigenicity and spontaneous lymph node metastases 1,2,4,8 and 16 weeks after orthotopic implantation of each clone in athymic nude mice. The transitional changes of the expression of angiogenesis-related genes were determined in the tumors. Moreover, we also evaluated the expression of these genes in human specimens of 81 bladder cancer and 55 renal pelvis and ureter cancer.

Results : In vitro findings indicated that bFGF and IL-8 expression regulated, angiogenesis, tumorigenicity and metastasis of human TCC of the urinary bladder. In vivo findings indicated that the ratio of matrix metalloproteinases to E-cadherin was a strong predictor for disease progression of TCC in the renal pelvis, ureter and bladder.

Conclusion : These genes may be good targets for the therapy of TCC in the urinary tract.

YW2-14 The sialyl-Le^x expression defines metastatic properties of bladder cancer

Division of Urology, Chair of Urology, and Obstetrics and Gynecology, Tohoku University Graduate School of Medicine

Kenji Numahata

Background. Invasive bladder cancer tends to occur a distant metastasis. There is no specific predictor at early stages for metastasis, however.

Recently, it is well known that the sialyl-Le^x (sLe^x) expression correlated with prognosis of patients with lung cancer and colon cancer. In this study, we researched whether the sLe^x expression is indicative of metastatic properties of bladder cancer or not.

Methods. (1) Anti-sLex (SNH3) is used in immunohistological stainings in invasive bladder cancer from 44 patients. These samples were obtained by a special sampling procedure termed "whole-layer core biopsy" (WLCB) (2) Comparison of incidence of metastasis with SNH3-positive vs.-negative primary tumors, and of 5-year survival curves. (3) Comparison of expression patterns of sLe^x in superficial and invasive bladder cancer cell lines. Therefore the investigation for adhesion assays of invasive bladder cancer cell lines to the vascular endothelium has obtained.

Results. SNH3 staining of 44 samples showed that the majority of cases (n = 31) were SNH3-positive and SNH3-negative were the minority (n = 13). SNH3-positive cases had higher lymph node or other metastasis, and lower survival rates by Kaplan-Meier curves (p = 0.001). Bladder cancer cell lines from invasive tumors were SNH3-positive and displayed E-selectin-dependent adhesion.

Conclusions. Sialyl-Le^x expression may be a predictor of metastasis.

YW2-15 Deregulation of apoptotic mitochondrial pathways in transitional cell cancer (TCC) cells and molecular approaches to overcome multidrug resistance in TCC

Division of Molecular Oncology, Department of Signal Transduction Research, Graduate School of Medical and Dental Sciences, Niigata University

Vladimir Bilim

In an attempt to finding approaches for overcoming multidrug resistance in TCC we examined apoptosis-inducing signal-transduction pathways in bladder cancer cell lines. Bcl-2 is an antiapoptotic protein that reside in mitochondrial membrane. Downregulation of Bcl-2 antiapoptotic protein by bcl-2 antisense oligonucleotides sensitized T24 cells to Adriamycin-triggered apoptosis. Adenine nucleotide translocator (ANT) is one of the proteins within the mitochondria permeability transition pore complex (PTPC). Thiol crosslinking agents including diamide cause PTPC opening and cytochrome c release with subsequent apoptosis. Diamide reduced viability of T24 cells in a dose-dependent manner inducing cell death with the features of apoptosis. XIAP regulates apoptosis by inhibiting members of caspase family, thus, acting downstream of mitochondria. Overexpression of XIAP in a multidrug resistant T24 resulted in survival advantage compared to parental cells. Administration of xiap antisense oligonucleotides to T24 cells was able to induce apoptosis, leading to decreased viability. Combined administration with ADM resulted in marked cytotoxicity due to escalation of apoptosis. In conclusion, manipulating molecules, involved in regulation of mitochondrial step of apoptosis may overcome drug resistance in bladder cancer with highly malignant phenotype.

YW2-16 Physical interaction of tumor suppressor p53/p73 with CTF2 and differential regulation of human HMG1 gene expression

Department of Urology, University of Occupational and Environmental Health

Takeshi Yoshida

The success of cisplatin-based chemotherapy may be due in part to apoptosis controlled by cellular levels of DNA damage recognition proteins, DNA repair proteins and tumor suppressors.

The tumor suppressor gene products p53/p73 accumulate in nuclei after DNA damage and control cell proliferation through their activity as transcription factors.

HMG1 (high mobility group 1) is ubiquitously expressed in higher eukaryotes and preferentially binds to cisplatin-modified DNA.

We have previously shown that CTF2, one of the splicing variants of CTF/NF-I, is overexpressed in cisplatin-resistant cells, and overexpression of this transcription factor might be responsible for the transactivation of the HMG1 genes.

In the present paper, we report that p53 downregulates the activity of the HMG1 gene promoter, whereas p73 up-regulates the activity of this promoter.

We also found that CTF2 directly interacts with p53/p73. Thus, HMG1 gene expression is differentially regulated by physical interaction of CTF2 with p53/p73. Our results provide novel informations on the functional interplay between CTF2 and p53/p73 as important determinants of their function in cell proliferation, apoptosis, DNA repair and cisplatin resistance.