The Fourth CJUA annual meeting

2010

China-Japan urological association

PROGRAM & ABSTRACTS

Date

Oct. 16, 2010

Venue

XIAN GREENLAND PICO

International Convention & Exhibition Center Room 105

http://www.gpcec.com

CJUA Home-page URL: http://www.uro.jp/nichu/index.html

PROGRAM of the Fourth CJUA annual meeting

(2010.10.16　Xian　China)

8:30 to 8:40　Opening Address

Prof. Yanqun Na, President of CJUA (China)

8:40 to 9:10　Special Lecture

Chairman: Prof. Hiromi Kumon, Okayama University

Comprehensive SNP Analyses on Genetic Predisposition for Incidence of 14 Major Cancers in Japan: Special Reference to Urologic Cancers.
Prof. Kenji Shimizu, Department of Molecular Genetics, Okayama University

9:10 to 10:10　Session I (7 minutes presentation following 3 minutes discussion)

Chairmen: Prof. Yukio Homma, Tokyo, Japan
Prof. Xianghua Zhang, Beijing, China

1. Cooperative Research on Genetic Predisposition for prostate Cancer in Asia by Analyzing Cumulative Association of SNPs -The analyses data in Japan-.
Huang Peng, et al.　Okayama University, Japan.

2. Cooperative Research on Genetic Predisposition for prostate Cancer in Asia by Analyzing Cumulative Association of SNPs -The analyses data in Chinese-.
Lei Wang, et al.　Peking University People's hospital, China

3. Complications of Urological Laparoscopic Surgery: A Single Institute Experience of 1,017 Procedures.
Takaaki Inoue, et al.　Kansai Medical University, Japan

4. Percutaneous renal surgery performance on live pigs can be improved by practicing on a biologic porcine kidney model.
Yi Zhang, GangWang, Yanqun Na. Peking University Wu Jie Ping Urology Center, China

5. Primary congenital bladder diverticula in adult.
Wang Jianbo, Sun Xishuang.　Dalian Medical University, China

6. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy.
Toyoaki Uchida et al.　Tokai University, Japan

10:10 - 10:30　Coffee Break

10:30 to 11:20　Session II　(7 minutes presentation following 3 minutes discussion)
Chairmen: Prof. Toyoaki Uchida, Tokyo Japan
Prof. Yi Zhang, Beijing, China

7. Prognostic factors for renal cell carcinoma with bone metastasis: who are the long survivors?
Haruki Kume, et al.　Tokyo University, Japan

8. The expression and clinical value of cytokeratin in peripheral blood of patients with urinary carcinoma.
Xiaoqiang Liu, Sun Guang. Tianjin Medical University, China

9. Systemic T-cell activation following in situ gene therapy in prostate cancer patients.
Shinji Kurosaka, Takefumi Satoh, Makoto Kubo, et al. Kitasato University, Japan

10. The expression and role of transient receptor potential channel A1 in the bladders of rat and human being.
Shuqi Du, the First Affiliated Hospital, China Medical University, China

11. Synergistic apoptosis of lexatumumab and cisplatin against human renal cell carcinoma cells in a caspase-dependent manner.
Xiuxian Wu, et al.　Kagawa University, Japan

11:20 to 11:30　Closing Address
Prof. Hiromi Kumon, President of CJUA (Japan)

11:30 - 12:30　CJUA Leadership Meeting

Special Lecture

Comprehensive SNP Analyses on Genetic Predisposition for Incidence of 14 Major Cancers in Japan: Special Reference to Urologic Cancers.

Kenji Shimizu

Department of Molecular Genetics, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Our aim is to establish a comprehensive strategy for predicting individual's genetic predisposition for most major cancers in Japan through analyzing the overlap of SNP-genotypes at risk on each individual for each cancer.

We have analyzed so far about 270 missense (ms) -SNP with a minor allele frequency (MAF) > 5%, from 225 cancer-related genes for differential distribution of the genotypes between area- and age-matched non-cancer controls (about 970 samples) and 14 kinds of cancer cases (in total, about 2,500 cases).

We have found 44 ms-SNPs from 40 genes are significantly associated with incidence of at least one of 14 kinds of major cancers, which altogether cover approximately 80% of total cancer patients in Japan. Most notably, significant implications of 31 out of these 44 SNP with any cancers were novel findings. In respect to Urologic Cancers, in total of 14, 9, and 6 genes were found to be associated with incidence of Prostate, Renal Cell, and Bladder Cancer, respectively. Of particular interest, stratification analyses revealed that the repertoire of significantly associating SNP genotypes were entirely different between genders (Lung, Colorectal, Pancreatic, and Kidney Cancers) and between age groups (by 70 years; Prostate Cancer, by 55 years; Breast Cancer).

As a way to assess the cumulative effects of the overlapping SNP genotypes at risk, we introduced a measure, MOR (Multiplied Odds Ratio), which is the "product" of each OR value of the overlapping SNP genotypes on each person for each cancer type. Possible bias by gene-gene interactions should be equally applied for controls and cancer cases in case-control studies. Thus, the relative comparison of the MOR value for a single kind of cancer should be substantially reliable for assessing the cumulative risk in a relative sense, albeit the absolute MOR value may be less meaningful.

We have analyzed most of the specimens for most of the 44 SNP genotypes and MOR values were determined on each sample for each cancer. As expected, the MOR value was much higher in cancer cases than in control samples, mean values of which sometimes exceeded ~10 fold difference.

According to the stratification of the MOR distribution for each cancer type and risk-assessment by the likelihood ratio analysis and calculation of the lifetime probability of each cancer incidence, we have found that about 50~80% of Japanese population are relatively cancer-protective, 10~30% are intermediate, 5~20% are high-risk, and 0.5~2% are extremely high-risk on most of the major types of cancer. For example, the highest risk group for Prostate Cancer (PSC) of $\geq$ 70 years onset, based on the overlap of 6 SNP genotypes, was classified as the population with MOR > 6, and constitute only 0.5% of healthy population and 15% of PSC cases, whereas the lowest risk group with MOR < 1.5 occupy 57% of healthy population and 31% of PSC cases. Taking the lowest risk group as the reference, the highest risk group exerts about 64-fold increased risk for PSC (OR = 64.2, 95% CI = 11.5-359, *p* value: 2.28 x 10 -8). Japanese males of this category are predicted to have 33% lifetime probability for incidence of PSC (one in three).

Thus, our way of analysis of the genetic predisposition serves an efficient strategy to predict the susceptibility to specific cancers on each person. We can make use them to prevent cancer by altering life-styles and to detect early cancers by periodic medical checking of the specified organs of the confined individuals at risk. This strategy may eventually be applicable in East-Asian countries sharing similar genetic background with Japanese and these trials are now underway.

Abstract

1. Cooperative Research on Genetic Predisposition for prostate Cancer in Asia by Analyzing Cumulative Association of SNPs -The analyses data in Japan-

Peng Huang [1) 3)], Haruki Kaku [1) 3)], Akiko Sakai [2)],Masami Watanebe[1) 3)], Takashi Saika[1)],Yasutomo Nasu[1)], Hiromi Kumon [1) 3)] & Kenji Shimizu [2)]

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2) Department of Molecular Genetics,

3) The Center of Gene and Cell Therapy, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700, 8558 Japan.

The specific causes of prostate cancer are not known. However, multiple etiologic factors, including genetic profile, metabolism of steroid hormones, nutrition, chronic inflammation, family history of prostate cancer, and environmental exposures are thought to play significant roles. Variations in exposure to these risk factors may explain interindividual differences in prostate cancer risk. Single nucleotide polymorphism (SNP) arrays provide a high-resolution platform for describing several types of genetic changes simultaneously. With the resolution of these arrays increasing exponentially, they are becoming increasingly powerful tools for describing the genetic events underlying cancer.

We have genotyped more than 50 non-synonymous missense-SNP of cancer-related genes between 210 prostate cancer patients and 474 matched healthy males in Japan. Eight SNP of 6 genes were significantly affected the incidence of all-age prostate cancer. These genes included 3 DNA-repair genes, 2 tumor suppressor genes and so on. Compared between age-groups > 70y and <70y, the repertoire of the risk-associating SNPs were largely different each other (7 SNP of 6 genes VS 10 SNP of 9 genes). Cancer-association of these 13 of 15 SNP is novel findings. As result, prediction of the Life-Time Risk for prostate cancer in Japanese Males was done. The highest risk groups exhibited about 33% (mean=1.5%) life-time risk for >70y onset, and 18% (mean=2.8%) for <70y onset.

Thus, our novel way of combining the risk factors of the statistically significant SNP genotypes would be useful for clinical application to predict prostate cancer predisposition of males in Japan and may contribute for prevention and early detection of the disease. This strategy can be applied for other malignancies and for other ethnic populations by choosing proper SNP combinations.

2. **Cooperative Research on Genetic Predisposition for prostate Cancer in Asia by Analyzing Cumulative Association of SNPs -The analyses data in Chinese-**

Lei Wang [1)], Peng Huang [2)], Haruki Kaku [2,3)], Ming Li [4)], Kai Yang [5)], Liping Xie [5)],Akiko Sakai [6)], Kenji Shimizu [6)], Hiromi Kumon [2,3)] & Yanqun Na [1,8)]

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2) Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.
3) Center for Gene and Cell Therapy, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.
4) Department of Urology, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing, China.
5) Department of Urology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China.
6) Department of Molecular Genetics, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Japan.
7) Peking University Wu Jieping Urology Medical Center, Peking University Shougang Hospital, Beijing, China.

BACKGROUND In a recent study of Okayama University, a list of missense single nucleotide polymorphisms (SNPs) had been found to be associated with risk of prostate cancer (PCa) in Japanese population. These SNPs also manifested distinguished accumulative effects in predicting the risk of PCa. AIM To explore whether these SNPs had similar effects in Chinese Han population, which are geographically and genetically close to Japanese population.

PATIENTS AND METHODS One hundred and twenty-five PCa patients and 100 cancer-free controls, which were recruited from four university hospitals in Beijing and one university hospital in Hangzhou between January 2009 and March 2010, were included in the cancer association study. Fourteen missense SNPs, each located in different genes, were genotyped using a Snapshot assay.

RESULTS Seven SNPs were found to be significantly associated with risk of PCa. Among them, 4 SNPs had high-risk associations (Odds Ratio range 1.89-7.84) and the other 3 had protective effects (Odds Ratio range 0.30-0.61). The seven related genes included 4 DNA-repair genes and 1 each of tumor suppressor gene, apoptosis regulator gene and chromosome-segregation gene. Cumulative effects were also revealed for these 7 SNPs in predicting prostate cancer risk. The life-time risk of

PCa occurrence for the highest-risk group we appointed was 31.2 times higher than that of the lowest-risk group (12.8% vs. 0.41%).

CONCLUSIONS According to this small size, case-control study, many missense genetic variants might contribute to the genetic predisposition to prostate cancer in Chinese Han population. These variants also manifested certain effects in predicting PCa occurrence. Larger studies with sufficient power will be needed to confirm our findings.

3. **Complications of Urological Laparoscopic Surgery: A Single Institute Experience of 1,017 Procedures**

Takaaki Inoue, Hidefumi Kinoshita, Masahiko Satou, Naoki Oguchi, Gen Kawa, Kouei Muguruma, Takayuki Murota and Tadashi Matsuda
Department of Urology and Andrology, Kansai Medical University, Osaka Japan

Background and Purpose: We evaluated complications of urological laparoscopic surgery at our institution.

Patients and Methods: One thousand and seventeen urological laparoscopic surgical procedures were performed in Kansai Medical University from December 1991 to January 2009, including 277 radical prostatectomies, 13 donor nephrectomies, 74 partial nephrectomies, 158 radical nephrectomies, 55 pyeloplasties, 97 nephrouretectomies, 54 simple nephrectomies, 128 adrenalectomies, 34 varicocelectomies, and 127 other procedures. Medical records of each procedure were retrospectively evaluated. The difficulty of each procedure was classified according to the European Scoring System. Intra- and postoperative complications were graded according to the Satava and Clavien classifications, respectively.

Results: Among the 1,017 laparoscopic procedures, 148 complications occurred in 123 patients, resulting in a total complication rate of 14.6%. Conversion to open surgery occurred in 20 patients (1.9%). Nephrouretectomy had the highest incidence of complications at 23.7%, which was significantly higher than that of other procedures classified as Difficult Group (D-Group) according to the European Scoring System ($p<0.05$). Clavien grades I and II accounted for 73.8% of all the postoperative complications. We experienced one fatality caused by air embolism.

Conclusion : We evaluated the complications of each procedure using the European Scoring System for classification of technical difficulty. Based on the results of our retrospective study, nephrouretectomy should be upgraded as “very difficult” group according to the European Scoring System. Appropriate grading by technical difficulty is beneficial for the prevention of complications from laparoscopic surgery.

4. **Percutaneous renal surgery performance on live pigs can be improved by practicing on a biologic porcine kidney model.**

Zhang Yi[1)] Wang Gang[2)], Na Yanqun[1)]

1) Wu Jie Ping Urology Center, Peking University
2) Urological institute of Peking University

OBJECTIVES To investigate how the learning and training on a biologic porcine kidney model can improve the performance of percutaneous renal procedure on live pigs

METHODS A previously reported biologic bench model is set up using a porcine kidney. Following instruction and demonstration, novice urologists are asked to practice on this model under X-ray guidance first and then perform percutaneous procedure on live pigs using the same manipulations. The time of successful puncture, tract establishment and intrarenal exploration on the model and on live pigs are compared to investigate if a better performance is achieved.

RESULTS 20 novice urologists were investigated using this method. Significant reduction of time spent on successful puncture($p=0.002$) and tract establishment($p=0.018$). No difference is observed on the time of intrarenal exploration.

CONCLUSIONS Training on the biologic porcine kidney model can help trainees to shorten the crucial step time of percutaneous renal surgery and improve their performance on live pigs. This model is simple and easy to build with readily available materials. It provides realistic and reproducible practice and may be interoperated as one of invaluable teaching tools for percutaneous renal surgery in the laboratory.

5. **Primary congenital bladder diverticula in adult.**

Wang Jianbo, Sun Xishuang.
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Dalian CHINA 116011

Abstract: Congenital bladder diverticula are uncommon, most cases have been described exclusively in male children, they are very rarely found in adults. We report on a case of a 43-year-old man who presented with history of urinary obstruction and recurrent urinary tract infections. Two big congenital bladder diverticula were diagnosed by physical examinations. Open surgical approaches were used in this case and a well healed bladder was made.

6. **High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy**

Toyoaki Uchida, Sunao Shoji, Mayura Nakano, Satoko Hongo, Masahiro Nitta, and Yoshihiro Nagata

Department of Urology, Tokai University Hachioji Hospital, Hachioji, Tokyo, JAPAN

OBJECTIVES: To investigate the use of high-intensity focused ultrasound (HIFU) as a salvage therapy in patients with recurrence of localized prostate cancer after external beam radiation (EBRT), brachytherapy, or proton therapy.

PATIENTS AND METHODS: We retrospectively reviewed the charts of all patients who had undergone salvage HIFU for biopsy-proven prostate cancer after primary radiation therapy. Patient characteristics and oncological outcomes were assessed.

RESULTS: Records of 22 patients with a median (range) follow-up of 24 (5–80) months were reviewed. Patients were men with presumed organ-confined disease who had been treated with salvage HIFU following recurrent disease after EBRT (fourteen patients), brachytherapy (five patients: four with high-dose brachytherapy using In In^{192} and one with low-dose brachytherapy using Au^{98}) or proton therapy (three patients). The median (range) age at salvage HIFU was 65 (52–80) years, with a median (range) prostate-specific antigen (PSA) level before radiation therapy of 14.3 (5.7–118) ng/mL and a median (range) PSA level of 4.0 (1.2–30.1) ng/mL before HIFU. The median (range) period to HIFU after radiation therapy was 36 (4–96) months. The biochemical disease-free survival (bDFS) rate in all patients at 5 years was 52%. Rates of bDFS in low-, intermediate- and high-risk groups were 100%, 86%, and 14%, respectively. One of the twelve patients who received post-HIFU prostate biopsy showed malignancy. Side effects included urethral stricture in four patients, grade I urinary incontinence in four patients, rectourethral fistula and epididymitis in one of each patient.

CONCLUSIONS: Salvage HIFU is a promising treatment option for local recurrence after radiation therapy, with morbidity comparable with other forms of salvage treatment.

7. **Prognostic factors for renal cell carcinoma with bone metastasis: who are the long survivors?**

Haruki Kume[1)], Shigenori Kakutani[2)], Yukio Yamada[3)], Mitsuru Shinohara[3)], Takashi Tominaga[2)], Motofumi Suzuki[1)], Tetsuya Fujimura[1)], Hiroshi Fukuhara[1)], Yutaka Enomoto[1)], Hiroaki Nishimatsu[1)], Yukio Homma[1)]

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3). Department of Urology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital

Purpose: To develop a predictive model for overall survival in renal cell carcinoma (RCC) with bone metastasis.

Patients and method: We retrospectively collected RCC cases with bone metastasis treated at three tertiary referral centers. Clinicopathological parameters and outcome data were analyzed to detect the predictors for overall survival.

Results: The sample comprised of 70 males and 26 females with a median age of 59.7 years. Histological diagnosis was clear cell RCC in 64, papillary RCC in 5, collecting duct RCC in 2, and unclassified cancer in 7. Sarcomatoid differentiation was found in 18. The metastases were detected synchronously (n=44) or metachronously (median interval, 32.2 months; n=52). The median overall survival was 9.25 months. Multivariate analysis identified sarcomatoid differentiation (p=0.012), vertebral bone involvement (p=0.043), extraosseous metastasis (p=0.013), elevated lactate dehydrogenase (1.5 times upper limit, p=0.003), and elevated C-reactive protein (>0.3 mg/dl, p=0.002) as the significant risk factor. According to these risk factors, we reclassified our cases into three groups; low risk (0 -1 risk factor, n=24), intermediate risk (2 - 3 risk factors, n=55), and high risk (4- 5 risk factors, n=17). This grouping clearly separated the survival among these groups (all p<0.001 by log-rank test). The prediction was more accurate than MSKCC classification system.

Conclusions: Our risk classification incorporating five risk factors provides an accurate prediction of survival thus would be helpful for clinical decisions for RCC with bone metastasis.

8. **The expression and clinical value of cytokeratin in peripheral blood of patients with urinary carcinoma.**

Xiaoqiang Liu, Jiang Weifan,Zhang Gaofeng,Sun guang.
Urology Dep. 2nd hospital of Tianjin Medical University,Tianjin Institute of Urology

Objective: In this article, we present our researches in early diagnosis of micro-metastasis by detecting the presence of CK in the circulating peripheral blood supplemented with the detection of CD. Two common urinary carcinomas: renal cell carcinoma (RCC) and bladder transitional cell carcinoma (BTCC) are included in this study. To make the presentation clear and for the convenience of discussion, I'd like to present our studies of RCC and BTCC separately.

First, in the RCC group, when these factors were found, we carried out an analysis of their level in peripheral blood in RCC patients, which was followed by evaluation of the value of CK19 as a marker of CTC.

Methods: We chose 51 patients of renal cell carcinoma (RCC) for this study and 32 healthy volunteers as the control group. We analyzed and recorded the level of CD45- CK19+ of the test group according to age, gender, grade, staging and so on. Follow-up was to get the information of their general condition and location of metastasis. All mRCC cases had received targeted therapy of sorafenib. Diameters of all metastasis before and after treatment were measured. Therapeutic effect was graded as CR, PR, SD, PD. The results were analyzed . Finally, we used SPSS 13.0 to analyze the level of CK19 of different clinical staging and different grading.

Results: 3 cases of 32 in control group are positive with a rate of CK19 at 9.38%. 37 cases of 51 in the test group are positive, with a rate of CK19 at 68.63%. The differences of two groups have statistic significance ($P<0.01$). The numbers of cases of positive and negative in CK19 are 7 and 1 before operation. The numbers of cases of positive and negative CK19 are 5 and 2 after operation. At the end of the experiment, the numbers of CR、PR、SD、PD and dead are 1、3、8、2 and 1 respectively.

9. **Systemic T-cell activation following in situ gene therapy in prostate cancer patients**

Shinji Kurosaka[1)], Takefumi Satoh[1)], Makoto Kubo[2)], Ken-ichi Tabata[1)], Kazumasa Matsumoto[1)], Fumiya Obata[2)], Yasutomo Nasu[3)], Haruki Kaku[3)], Hiromi Kumon[3)], Malcolm K. Brenner[4)], Timothy C. Thompson[5)] and Shiro Baba[1)]

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2) Division of Immunology Kitasato University School of Allied Health Sciences
3) Department of Urology Okayama University Graduate School of Medicine
4) Center for Cell and Gene Therapy Baylor College of Medicine
5) Department of Genitourinary Medical Oncology MD Anderson Cancer Center

Introduction and Objectives: Neoadjuvant in situ cytotoxic gene therapy can potentially trigger a systemic immune response, which could impact occult micro-metastatic disease. We are currently conducting a clinical trial using in situ adenoviral vector mediated Herpes Simplex Virus-thymidine kinese (HSV-tk) gene plus ganciclovir (GCV) therapy. This study evaluates the systemic T-cell response following gene therapy in patients with high-risk prostate cancer.

Methods: This study was approved by the ethical committee of Kitasato University, and by the Ministry of Health, Labour and Welfare Japan. Three patients (Pt1, Pt2, and Pt3) who agreed this Phase I/II trial were repeatedly given 2 weeks of intravenous GCV administration following the intraprostatic HSV-tk injection. PBMC were collected for 7 days from HSV-tk injection and post treatment. PBMC were analyzed by flow cytometry. We also measured intracellular IFN- produced by T cells to responding MHC-I restricted prostate specific antigen (PSA) peptides. Humoral responses were examined by Western blot.

Results: The activated T cells transiently increased in both the first and second HSV-tk+GCV treatments. The activated CD8+T cells of Pt2 and Pt3 markedly increased during second treatment. In Pt1 and Pt2, frequencies of PSA-peptides specific CD8+T cells slightly increased after second treatment. Although the tumor antigen was unidentified, we detected the antibody that increased during treatments in Pt2.

Conclusions: We present evidence of systemic T-cell responses following HSV-tk + GCV gene therapy under clinical trial conditions. There was an increase in activated CD8+ T cells in the peripheral blood following vector injection suggesting the potential for activation of components of cell-mediated immune response in trial conditions.

10. **The expression and role of transient receptor potential channel A1 in the bladders of rat and human being**.

Shuqi Du

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Objectives: Transient receptor potential channel A1 (TRPA1) is a candidate for both mechanosensory transduction and nociception. We investigated its expression in both rat and human bladders, and examined its role in micturition.

Methods: Real-time PCR and immunohistochemistry were utilized to examine the expression level and localization of TRPA1 in both bladder and dorsal root ganglion (DRG). The function of TRPA1 in micturition was analyzed by cystometry in either normal or capsaicin-pretreated rats. The human bladder specimens were divided into normal and bladder outlet obstruction (BOO) groups.

Results: The expression level of TRPA1 mRNA in rat DRG/bladder mucosa/bladder muscular layer was 199:16:1. Of the bladder-innervating DRG neurons, 50.8% showed TRPA1 immunoreactivity. Intravesical perfusion of 600μM *trans*-cinnamaldehyde significantly decreased the intercontraction interval and pressure threshold to 59.8% and 83.8% of their control values, respectively. These effects were reversible by washing out the drug. Desensitization of C-fibers by capsaicin markedly attenuated the *trans*-cinnamaldehyde effects. Similarly, 400μM isothiocyanate reversibly and significantly decreased the intercontraction interval to 64.7% of its control value.

The expression level of TRPA1 mRNA in human bladder mucosa/muscular layer/prostate was in the ratio of 639:1:16. TRPA1 mRNA in the bladder mucosa with BOO was significantly upregulated to 2.32 times of control. TRPA1 protein was localized in the epithelial cells of both urinary bladder and prostate gland.

Conclusions: TRPA1 is expressed in the bladder-innervating primary sensory neurons of rat. Its agonists cause bladder hyperreflexia through C-fiber pathway. TRPA1 is also expressed in the human urinary bladder and prostate. TRPA1 might be involved in the bladder sensory transduction as a mechanotransducer and/or a nociceptor. It might also be involved in the induction process of overactive bladder by BOO.

Reference:

1. Du S, Araki I, Yoshiyama M, et al. Transient receptor potential channel A1 involved in sensory transduction of rat urinary bladder through C-fiber pathway. Urology 70: 826-31, 2007.
2. Du S, Araki I, Kobayashi H, et al. Differential expression profile of cold (TRPA1) and cool (TRPM8) receptors in human urogenital organs. Urology 72: 450-5, 2008.

11. **Synergistic apoptosis of lexatumumab and cisplatin against human renal cell carcinoma cells in a caspase-dependent manner**

Xiu-Xian Wu, Takuma Kato, Hiromi Hirama, Hiroyuki Tsunemori, Xia Zhang, Motoki Yamashita, Masashi Inui, Mikio Sugimoto, and Yoshiyuki Kakehi

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Introduction and Objectives: Lexatumumab is a human agonistic antibody against TNF-related apoptosis-inducing ligand-receptor 2 (TRAIL-R2), which induce apoptosis specifically in cancer cells. In this study, we investigated whether chemotherapeutic agents enhance lexatumumab-mediated apoptosis against human renal cell carcinoma (RCC) cells.

Methods: Cytotoxicity and synergy was assessed by MTT and isobolograpic analyses, respectively. TRAIL-R2 expression was detected by real-time RT-PCR, flow cytometry, and western blotting. Apoptosis was assessed by DNA Ladder and caspase assays.

Results: Treatment of ACHN human RCC cells with cisplatin in combination with lexatumumab had a synergistic cytotoxicity. Synergy was also achieved in six primary RCC cell cultures. Lexatumumab and cisplatin also synergistically enhanced apoptosis. Pretreatment with cisplatin followed by lexatumumab resulted in high cytotoxicity compare with the reverse sequence. Cisplatin significantly increased TRAIL-R2 expression at both mRNA and protein levels. Furthermore, the combination of lexatumumab and cisplatin significantly enhanced caspase-8 activity, Bid cleavage, up-regulation of Bax, cytochrome *c* release, and caspase-9, caspase-6, and caspase-3 activities. Importantly, the activation of capase-8 was significantly abrogated by the specific inhibitors of caspase-9, caspase-6, and caspase-3. Furthermore, combination-induced cytotoxicity was significantly suppressed by DR5:Fc chimeric protein and the specific inhibitors of caspase-8, caspase-9, caspase-6, and caspase-3. Conclusions: Cisplatin sensitizes RCC cells to lexatumumab-induced apoptosis by potentiation of the extrinsic and intrinsic apoptotic pathways that lead to enhancement of caspase activation, particularly caspase-8. These results suggest that combination of cisplatin plus lexatumumab is promising against RCC.