American Urological Association Annual Meeting
May 21 - 26, 2005
San Antonio, Texas, USA

Publishing #: 416

Presentation Title: Comprehensive analysis of genetic polymorphisms involved in prostate cancer development and progression in a high risk Japanese population.

Category: 38 Basic Research

Author Block: *Yoshitaka Sekine*, Haruki Nakazato, Nobuaki Ohtake, Hidekazu Koike, Tatsuya Hamano, Hiroshi Matsui, Seiji Nakata, Yasuhiro Shibata, Kazuto Ito, Hidetoshi Yamanaka, Kazuhiro Suzuki, Maebashi, Japan*

Introduction and Objective: Development and progression of prostate cancer (CAP) are caused by multiple intrinsic and extrinsic factors. Involvement of genetic alterations has been elucidated, and several high penetrance genes and multiple low penetrance genes were reported to affect risks and clinical parameters of CAP. However, most studies reported the effect of a single polymorphism or a few ones on CAP in each study. In the current study, we performed comprehensive analysis of genetic polymorphisms involved in development and progression in CAP in Japanese with high risk of CAP development. Methods: This study included age-matched 144 cases and 119 controls. Cases had a family history of prostate cancer in the first-relative degree. Twenty nine genetic polymorphisms in 22 genes were analyzed. Genes were androgen receptor, CYP 17, 5 alpha-reductase, UGT2B15, PSA, vitamin D receptor, estrogen receptor alpha, CYP19, COMT, CYP1A1, GSTM1, GSTT1, GSTP1, cyclin D1, CDKN1A, CDKN1B, SULT1A1, IGFBP-3, Her-2, p53 codon72, HPC2/ELAC2 and RNASEL. CAG repeat length and [TTTA]n repeat length were assessed by electrophoresis using Spreadex® Precast Gel. GSTM1, GSTT1, UGT2B15 and m2 polymorphism of CYP1A1 were genotyped by allele specific PCR. Genotypes of RNASEL were screened by SSCP and determined by direct sequencing. Other genotypes were determined by RFLP method. Odds ratios (ORs) were assessed by chi-square test in these genetic polymorphisms. Results: Development of CAP was significantly associated with Asp541Glu in RNASEL, Ala541Thr in HPC2/ELAC2, Arg/Pro in p53 codon 72, [TTTA]n repeat in CYP19, A870G in Cyclin D1, C/T in CDKNA1, A/A in IGFBP-3, D/Y in UGT2B15, Val/Val in GSTP1, combination of GSTT1, GSTM1 and GSTP1, and combination of ER, C/T in CYP19 and COMT. Association of clinical stage, i.e., localized or metastatic, was found in Asp541Glu in RNASEL, Arg/Pro in p53 codon72, A870G in Cyclin D1 and combination of M1 and M2 in CYP1A1. Finally, association of pathological grade, i.e., Gleason score <7 or 7<) was found in Asp541Glu in RNASEL, Arg/Pro in p53 codon72, A/A in IGFBP-3 and combination of M1 and M2 in CYP1A1. Conclusions: The present study showed that many genetic polymorphisms affected CAP development and clinical features in Japanese men with family history with CAP. These findings suggested that necessities of multiple approaches to understand genetic susceptibility of CAP.

Keywords: Prostate cancer,Genetics,Family history

Effects of PCBs on steroid xenobiotic receptor (SXR)-mediated transcription

Wataru Miyazaki [1], Toshiharu Iwasaki [1], Izuki Amano[1], Nana Rokutanda[2], Rin Nagaoka[2], Akira Takeshita [3], Noriyuki Koibuchi [1]

[1]Department of Integrative Physiology, Gunma University Graduate School of Medicine, [2]Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, [3]Toranomon Hospital

Polychlorinated biphenyls (PCBs) have been used for many industrial products as insulator from the early 1930s until the beginning of 1970s. PCBs contain 209 congeners, each of which is chlorinated to various degrees. PCBs are known as environmental contaminants that cause various effects in many organs. PCBs undergo little catalysis because of their high stability. They are highly lipophilic, accumulate in many organs such as the liver and adipose tissue and mammary gland. Steroid and xenobiotic receptor (SXR), which bound with steroid hormones, drugs and xenobiotics, is a ligand-activated transcription factor. SXR activates transcription through a responsive element conserved in the promoter of the target gene such as cytochrome P450 (CYP) isoforms. Recently, it has been reported that SXR is expressed in a series of breast cancer cells. Estrogen receptor (ER) is also expressed in breast cancer cells and mediates the effects of estrogens, which may be associated with development and progression. We performed several experiments to clarify the effects of PCBs on mammalian glands in relationships with breast cancer. To investigate the effect of PCB on SXR-mediated transcription, we performed transient cotransfection-based reporter assays using human breast cancer cell line, MCF-7 cells. SXR-mediated transcription was activated in a dose-dependent manner. However, we did not observe transcriptional activation in African green monkey kidney fibroblast-derived CV-1 cells. On the other hand, PCB induced the ERE-mediated transcription through ER alpha. To further investigate the effects of PCB, we cotransfected ER with SXR into CV-1 cells, however ER did not affect the SXRE-mediated transcription. We also performed mammalian two-hybrid assay to examine the binding of SXR to coactivator (CoA: steroid hormone receptor coactivator-1 (SRC-1)), or corepressor (CoR: nuclear receptor corepressor (N-CoR), silencing mediator for retinoid and thyroid receptors (SMRT)). We observed a slight induction of the binding between SXR and CoR (SMRT), but not binding between SXR and CoA. These results suggest that the interaction between SXR and SMRT may be involved in the activation of SXRE-mediated transcription by PCB. Thus, PCB may affect development and progression of breast cancer via both ER alpha and SXR.