Molecular markers in prostate cancer: cytochrome P450 enzymes, CYP4F11 and CYP8A1, new related cytochromes

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ABSTRACT

Introduction: Prostate cancer is the second cause of death from cancer in men worldwide. Various cytochromes in this disease are being studied, but there are few reports in the literature on cytochromes CYP4F11 and CYP8A1. In the present study, the presence of CYP4F11 and CYP8A1 was investigated in prostate cancer and in benign prostatic hyperplasia.

Material and method: Thirty-two hyperplasia and thirty-two cancer samples were obtained and conditions were standardized to detect the presence of CYP4F11 and CYP8A1 in the tissues by means of immunohistochemistry.

Results: CYP4F11 and CYP8A1 were expressed in prostate cancer but not in benign prostatic hyperplasia.

RESUMEN

Introducción: El cáncer de próstata (CaP) es la segunda causa de muerte en hombres, por cáncer a nivel mundial. Se están estudiando varios citocromos en CaP. Para el caso del CYP4F11 y 8A1, existen pocos estudios en la literatura. En este estudio, se determinó la presencia del CYP4F11 y 8A1 en CaP e hiperplasia prostática benigna (HPB).

Material y método: Se obtuvieron 32 muestras de HPB y 32 de CaP. Se estandarizaron las condiciones, para detectar por inmunohistoquímica la presencia de CYP4F11 y CYP8A1 en los tejidos.

Resultados: El CYP4F11 y 8A1 no se expresaron en HPB.

Conclusiones: Los resultados anteriores sugieren que CYP4F11 y 8A1 podrían ser utilizados como factores pronósticos y/o detección temprana, realizando estudios en biopsias de pacientes sospechosos de CaP.
Conclusions: These results suggest that CYP4F11 and CYP8A1 could be used as prognostic and/or early detection factors, by carrying out biopsies in patients suspected of having prostate cancer.

Keywords: Prostate cancer, benign prostate hyperplasia, CYP4F11, CYP8A1, Mexico.

INTRODUCTION

Prostate cancer (CaP) is the second cause of death from cancer in men worldwide, after lung cancer. In Mexico in 2009 the three principal causes of death from malignant tumors corresponded to those of the prostate (17.1%), trachea, bronchi, and lung (16.6%), and stomach (10.4%). Benign prostatic hyperplasia (BPH) is a disease characterized by an increase in epithelial and stromal cells in the perirethral area of the prostate that develops in the transition zone. The specific causes determining the onset and progression of CaP are unknown. However, the progression of this disease is attributed to genetic and environmental factors and its onset and progression are influenced by androgens.

The cytochrome P450 system (CYP450) is an enormous and diverse protein superfamily that in man, is associated with the mitochondrial membrane and the endoplasmic reticulum, where these proteins metabolize hundreds of endogenous and exogenous substances. By means of a combination of cDNA research and rapid cDNA amplification, the analysis and sequencing of a new isoform of the human cytochrome P450 of the 4F subfamily was determined. This 4F isoform is called CYP4F11 and is principally expressed in the human liver, followed by the kidney, heart, and skeletal muscle.

The CYP450 cytochromes play a central role in the oxidizing metabolism of xenobiotics that include medication used to fight cancer, carcinogenic agents, and endogenous compounds. Various therapeutic strategies are being developed to take advantage of the presence, overexpression, and activity of the P450 system in tumors.

Because CYP4F11 is a recently discovered cytochrome, studies that utilize it are few, and even fewer look for its presence in some type of cancer. To date there are a couple of studies that have searched for CYP4F11 expression in colon cancer and in ovarian cancer.

In the comparison of colorectal cancer with the normal colon, there was greater immunoreaction for CYP2S1 in immunohistochemical staining, while it was negative for CYP1A1, CYP2F1, CYP2R1, CYP4F11, CYP4V2, and CYP4Z1 in more than 80% of the nuclei.

In ovarian cancer no protein expression of CYP1A1, CYP4F11, CYP24 and CYP39 was found when compared with the normal ovary.

In regard to CYP8A1, the first time that the existence of this cytochrome was reported was in 1994 by Yokoyama et al., in a descriptive study of the human gene for encoding prostacyclin synthase (PGIS). The function of this gene involves the synthesis of prostaglandin I₂ starting from prostaglandin H₂, and so it has a role in the inflammatory process.

Then, in 2001, Chevalier et al. reported on variants of alleles that affect the region that encodes for CYP8A1, causing changes in the amino acids. There are still no analyses of these variants in relation to the risk for cancer.

In accordance with the above, the objective of the present study was to detect CYP4F11 and 8A1 expression in prostate cancer (CaP) and in benign prostatic hyperplasia (BPH) for the first time.

METHODS

Study subjects: Tissue samples from 64 patients registered in the surgical procedure log book of the urology wing of the Hospital Central Militar within the time frame of 2008 to 2011 were studied, using inclusion and non-inclusion criteria.

Inclusion criteria: (a) Tissue from patients with a histopathologic diagnosis of CaP and (b) Tissue from patients with BPH diagnosis analyzed at the Pathology Department within the time frame of 2008 to 2011.

Non-inclusion criteria: (a) Tissue from patients with CaP diagnosis that had been obtained by any procedure other than radical prostatectomy and (b) Tissue from patients with BPH diagnosis that had been obtained through biopsy.

Palabras clave: Cáncer de próstata, hiperplasia prostática benigna, CYP4F11, CYP8A1, México.
The patients with CaP had a mean prostate specific antigen (PSA) of 9.62 ng and a mean age of 65.8 years. The patients with BPH had a mean PSA of 7.91 ng and a mean age of 68.5 years.

Of the CaP patients, 6% presented with a Gleason score of 3, 3% with a Gleason score of 4, 40% with a Gleason score of 6, 36% with a Gleason score of 7, and 15% with a Gleason score of 8.
On the other hand, in 2005 Kajita et al. analyzed the mRNA expression of COX-2, thromboxane A₃ (TXA2), and CYP8A1 through real time polymerase chain reaction in papillary thyroid carcinoma and in normal tissues. In that study there was a substantial increase in TXA2, there were no differences in COX-2, and there was an important increase in CYP8A1.22

In our study, when analyzing the presence of CYP8A1 and CYP4F11 by immunohistochemistry, we found the presence of those proteins in CaP tissues, as well as their absence in BPH tissues. These results suggest that the area percentages marked for this CYP were higher and more frequent as age, Gleason score, and PSA increased.

In accordance with the above, it is likely that CYP4F11 and CYP8A1 have a regulatory role in oxidative stress during the transformation of normal cells into cancerous cells in the prostate, especially because this regulatory function is involved in the inflammatory pathway.

**CONCLUSIONS**

In this study we demonstrated that CYP4F11 and CYP8A1 are expressed in tissues with CaP and not in tissues with BPH. This finding may indicate that CaP tumor cells are regulated in a certain manner by endogenous and xenobiotic metabolism, as well as by oxidative stress, given the participation of the CYP450 system in these phenomena.

The abovementioned may generate continuous genetic changes that are manifested as an increase in chromosomal abnormalities and in mutations, which in turn, can bring about tumor genesis and propagation. The results of this study suggest that CYP4F11 and CYP8A1 could be used as early detection and/or follow-up markers and as prognostic factors in patients with CaP. However, further studies are warranted for determining the role these cytochromes could play in chemoprevention, lengthening the time throughout the patient’s life before the clinical appearance of CaP, or for establishing their use as real prognostic factors.

**ACKNOWLEDGEMENTS**

This work was supported by a grant from the CONACYT (project: SALUD- 2010-01-140535, del Fondo Sectorial de Investigación en Salud y Seguridad Social) and from the IPN (SAPPI, Proyecto SIP: 20113894). LAOA grant No.241493 and CRB grant No.265693 from the CONACYT. PIFI (IPN) No. 3387, 3391 y 3357; CAVJ, SAPM and JJMH. We wish to thank the Fundación Gonzalo Rio Arronte IAP, Mexico, for donating the Confocal Axiovert 200 M microscope.
Floriano-Sánchez E, et al. Molecular markers in prostate cancer: cytochrome P450 enzymes, CYP4F11 and CYP8A1, new related cytochromes

REFERENCES