The role of prolactin in prostate cancer

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ABSTRACT

Prostate cancer (CaP) is presently the most frequently diagnosed cancer and represents the second cause of death from the disease in men. The prostate is a hormone-dependent organ and the most important factors in its development, growth and differentiation are androgens and prolactin. This article describes the role of prolactin (PRL) and the androgen receptor (AR) in the development of CaP along with other channels which act separately. The interrelation between PRL and the AR has recently been discovered on a cellular level and potentially will help explain the little-understood hormone-refractory cancer as well as providing new forms of treatment. The authors consider it important to understand these signaling channels and thus were motivated to write this review.

Key words: prolactin, prostate cancer, STAT 5, androgen receptor.

RESUMEN

El cáncer de próstata es en la actualidad el cáncer que se diagnostica con más frecuencia en varones y ocupa el segundo lugar en muerte atribuible a cáncer en el ese género. La próstata es un órgano hormonodependiente que para su desarrollo, crecimiento y diferenciación depende de muchos factores, de los cuales dos son los más importantes, los andrógenos y la prolactina. Este artículo refiere el papel de la prolactina y el del receptor de andrógenos en el desarrollo de la enfermedad maligna prostática. También se detiene en otras vías que actúan por separado. En tiempos recientes se descubrió la interrelación intracelular de estas dos vías, lo que podría ayudar al esclarecimiento del tan poco entendido cáncer hormonorrefractario, así como dar pautas a nuevas formas de tratamiento. El entendimiento de estas vías de señalización parece de gran relevancia y es motivo de esta revisión.

Palabras clave: prolactina, cáncer de próstata, STAT-5, receptor de andrógenos, México.
PRESENT RELEVANT DATA

Endocrinological and urological pathologies are often correlated, as is the case with lithiasis and prostate cancer (CaP).1

Worldwide CaP incidence varies considerably, from 8-103 cases per 100,000 inhabitants and this also holds true for its resulting mortality at 2-32 cases per 100,000 inhabitants. In Mexico, CaP incidence is reported at 23 cases per 100,000 inhabitants and mortality at 7 per 100,000, corresponding to an annual 30.4% of patients with CaP diagnosis. In the United States the mortality rate is 8.7% and in Malaysia it is 46.5% and so in broad terms CaP mortality in Mexico is above the international mean.2,3

In Europe close to 2.6 million new cases of cancer are diagnosed per year and CaP represents 11% of all cancers in men and 9% of all the causes of cancer in the European Union.4

In the United States, CaP is the most frequent tumor in men and represents 25% of all new cancer cases. It is the second most common cause of death by cancer and therefore approximately 1 out of every 6 American men will be diagnosed with CaP and 1 out of every 34 will die from the disease. Thanks to early patient screening, the mortality incidence dropped to 1.6% per year from 1990 to 2005.3

In Mexico, cancer is the second cause of death and CaP is the most common type of cancer, after lung cancer.

THE PROSTATE AS AN ENDOCRINE ORGAN

Towards the tenth week of gestation, the ductal structure of the prostate arises from the epithelial tissue of the urogenital sinus and is taken inside the mesenchyme that is present just below the bladder.6

The prostate is a gland made up of infundibular tubular tissue containing epithelial cells that are organized in the base and apex. The former are moderately differentiated and contain variable quantities of androgen receptor (AR) and have little prostate specific antigen (PSA) production. The latter are well-differentiated and always positive to AR and PSA production.

Anatomically, there are 3 zones: the peripheral zone, corresponding to 70% of prostate volume in the young adult prostate, the central zone, making up 25% and the transition zone, corresponding to the remaining 5%. It is well-known that 70% of prostate carcinomas originate in the peripheral zone, 10-20% in the transition zone and 5-10% in the central zone.7

Ninety-five percent of prostate cancers are adenocarcinomas that grow in the acinar region and near the ductal region. Other histological types include intratubular acinar carcinoma, ductal carcinoma, small cell or cirrhotic pattern carcinoma, mucinous carcinomas and renal cell -like cancer.

Small cell cancers have neuroendocrine characteristics which can be differentiated by markers such as enolase, synaptophysin and chromogranin A.8

CaP histological classification is based on the Gleason scale. It evaluates glandular cell architecture microscopically under 10x and 40x magnification. Five growth patterns are distinguished, going from well-differentiated to poorly-differentiated. Grade 1 corresponds to well-differentiated, with discreet glandular cell formation and grade 5 corresponds to poorly differentiated, with a loss of glandular cell architecture. Gleason score is obtained by adding the two predominant growth pattern grades from the biopsy together and the resulting sums range from 2 to 10. This scale is also prognostic; patients have a better prognosis if tumor Gleason score is under 7 and their prognosis is worse if that score is above 8.9,10

Age is the most important risk factor for CaP and heredity appears to have a significant role in this context. If two or more first-degree relatives are affected, risk increases 5-11 times (some of these alterations are found in the RNASEL, MSR1, AR, CYP17 and SDR5A2 genes as well as in somatic alterations of GSTP1, NKKX3.1, PTEN, CDKN 18 and AR genes).11

In autopsy series, cancer has been found in 0, 5, 15, 41 and 63% of men in their 3rd, 4th, 5th and 7th decades, respectively.12 This is in contrast with CaP clinical incidence, suggesting that there are exogenous factors that affect progression of the so-called latent prostate cancer into clinical cancer.

The most important diet carcinogens are found in red meat that is cooked at high temperatures, producing heterocyclic aromatic amines (PhIP). Diets that are low in protective factor vitamin E, selenium and isoflavonoids, have also been well studied. High levels of lycopene resulting from eating tomatoes have been reported to reduce CaP risk.11

The prostate, like other secondary sexual organs, is stimulated by certain hormones and growth factors during its development, maintenance and secretory function. The principle hormone is testosterone which is converted into dihydrotestosterone (DHT) in the prostate by 5-alpha-reductase, which contributes to its growth and development.
In 1955, Grayhack discovered that prolactin was necessary in order for the prostate to be completely formed. When prolactin was inhibited in rats during embryonic development, only 80% of the prostate was developed.13

The relation between the androgen receptor (AR) and signaling channels produced by prolactin is important for understanding hormone-refractory and disseminated CaP. Research protocols are being developed for treatments with anti-prolactin agents14,15 and other treatments at the genomic level in the search for survival improvement in these types of cancer.

The above-mentioned topics will be briefly developed in order to later see their final relation.16

### THE ROLE OF PROLACTIN IN THE PROSTATE

Prolactin is a hormone produced by the anterior pituitary gland in lactotroph cells and its gene, located in chromosome 6,17 appears to come from the same gene as growth hormone (GH) and placental lactogen hormone (PLH), due to their homology.18 Prolactin is a polypeptide chain of 199 amino acids that contains 3 disulfide bridges and moves about in various sizes: monomeric (small), dimeric (large) and polymeric (large-large). The monomeric form is the most bioactive.19

Inside the prostate, prolactin attaches to its receptor that belongs to the cytokine 1 receptor superfamily and is localized in chromosome 5. In addition the receptor has 2 domains that are separate in the resting state but that become homodimerized once they are joined to prolactin. In this manner intracellular signaling is produced by means of JAK-STAT kinases.20, 21

Once prolactin is attached to its receptor that carries out tyrosine kinase activity, it phosphorylates JAK 2 and STAT-1, 3, and 5a and b. Later on STAT-5 a/b dimers are formed and they are translocated to the nucleus to act on DNA sequences which in turn will activate proliferation, differentiation and survival promoter sequences.21, 22

Two important mechanisms are involved in the adaptation of cancerous cells to hormonal deprivation: the amplification and mutation of the AR and the activation of signaling channels (kinase protein (JAK2-STAT-5 a/b) by peptide hormones (prolactin).23, 24

Although the molecular mechanisms that promote hormone-refractory CaP progression and disseminated disease are not well understood, prolactin seems to play a critical role in them.

There is significant evidence of the existence of prolactin paracrine and especially autocrine action. In other words, there is endogenous prostatic prolactin production and prolactin receptor over-expression has been demonstrated in high grade prostate tumors.25

### PROSTATIC ANDROGEN RECEPTOR

Androgens act through the androgen receptor (AR) and are required for prostate development and function. There is what can be thought of as a hypothalamus-pituitary-gonad-prostate axis because when LHRH is produced, FSH and LH are synthesized and in turn activate Leydig cells in order to produce testosterone. Testosterone is transported to the prostate by 5-α reductase and is converted into dihyrotestosterone, a more active metabolite. Both exert their action upon attaching to their receptor in the cytoplasm. They
**STAT 5A/B FUNCTION IN PROSTATE CANCER**

STAT-5 is one of the 7 members of the family of STAT transcription factors and consists of 2 distinct but highly homologous proteins, 94 kDa (STAT-5a) and 92 Kd (STAT-5b).

STAT-5 a/b is a product of STAT-5a and b phosphorylation by means of JAK once prolactin is attached to its receptor, and it plays a very important role in CaP, especially in hormone-refractory cancer. A study by T.J. Ahonen et al. has shown that STAT-5 a/b activity is increased up to 65% in androgen-independent cancerous cells. The author constructed an adenovirus vector that results in the loss of the STAT-5a transcriptional activation site and that effectively blocks STAT-5a as well as STAT-5b action which in turn induces apoptosis in cancerous cells.

STAT 5 a/b usefulness has been shown as a predictor for high grade tumor and for recurrence.

**SIGNALING CHANNEL INTERRELATION (STAT-5 A/B AND AR)**

As mentioned before, both STAT-5 and the AR have active and important roles in CaP development and are clinically relevant in hormone-refractory cancer. There is also evidence that both prolactin and the androgens have a final point in common. These data were described in a study by Shyh-Han Tan et al.

They demonstrated that STAT-5 a/b and the AR gene sequence interact both directly and indirectly. AR was shown to increase STAT-5 a/b transcriptional activity as well as its intranuclear translocation in cancerous cells. The opposite is also true. That is to say, AR transcriptional activity as well as its translocation to the nucleus increase in the presence of STAT-5 a/b and even more interestingly, their physical interaction results in a new complex with transcriptional activity.

**CLINICAL USE**

Antiprolactin use in previous years, especially bromocriptine, has been described for androgen-independent CaP treatment with unsatisfactory results.

Presently genomic therapies have been created in the search for reducing key intracellular mediators and one of the most important ones includes the STAT family, STAT-3 as well as STAT-5. In regard to STAT-3, techniques have been developed that introduce DNA probes that attach to cellular DNA during replication and end by having a final direct STAT-3 inhibitory
effect which produces apoptosis.\textsuperscript{32} DNA probes have been developed that are introduced into the genome and they produce STAT-5b products without catabolic sites.\textsuperscript{33}

Recently c7Me-IEITC (ethyl thiocyanate) has been used to reduce intracellular channels regulated by pro-oncogenic kinases as well as transcription factors. It causes rapid loss of mitochondrial membrane potential, PARP-1 inactivation and consequent caspase activation. This medicine has been tested in ovarian cancer as well as in neuroblastoma with promising results, but with many side effects.\textsuperscript{34} Although in theory it could be useful, this drug has not been employed in cases of prostate cancer.

\textbf{CONCLUSIONS}

The newly discovered STAT-5-AR complex could be identified in the CaP patient, creating new treatment lines for STAT-5-AR positive patients.

Prolactin appears to play an important role in prostate cancer especially in hormone-refractory tumors.

Genomic therapies have been developed to inhibit these complexes (STAT-3, 5) as well as to block multiple intracellular signaling channels and activate others with ethyl thiocyanate. And finally, there is a need for the development of studies on these types of therapies applied to humans as well as studies on the use of ethyl thiocyanate in the prostate cancer patient.
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