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Gene Section

Review

PSCA (Prostate stem cell antigen)

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Identity

Other names: PRO232

HGNC (Hugo): PSCA

Location: 8q24.3

DNA/RNA

Description

The PSCA gene was originally identified by Reiter el al. (1998) through an analysis of genes up-regulated in the human prostate cancer LAPC-4 xenograft model. The PSCA gene is located on chromosome 8q24.2.

Transcription

In normal human tissues, PSCA mRNA expression is found in the prostate, with lower expression in placenta and very low expression in kidney and small intestine (Reiter et al., 1998; Cunha et al., 2006). Within normal human prostate sections, in situ hybridizations by Reiter el al. (1998) demonstrated PSCA mRNA expression in the subjacent basal cells, while Ross et al. (2002) demonstrated PSCA mRNA expression in the secretory luminal cells. These contrasting results may be due to sampling error from relatively small biopsies, since PSCA protein expression was seen in both cell types (see below).

Protein

Description

The PSCA gene encodes a 123 amino acid cell surface protein with a molecular weight of 10-24
kDa (Reiter et al., 1998). Inaccurately named for its 30% homology to stem cell antigen type 2 (SCA-2), an immature lymphocyte cell surface marker, PSCA is neither a marker for a stem cell population nor is it exclusively expressed in the prostate. Like SCA-2 however, PSCA is a member of the Thy-1/Ly-6 family of glycosylphosphatidylinositol (GPI) anchored surface proteins.

Expression

In the human prostate, PSCA protein expression is found in both the basal and secretory epithelial cell layers, along with the neuroendocrine cells. Additionally, PSCA protein expression was demonstrated in the placenta, the bladder, the neuroendocrine cells of the stomach and colon, and weakly in the kidneys excluding the glomeruli (Gu et al., 2000).

Localisation

PSCA is localized to the cell surface, anchored by a GPI linkage.

Function

Although the function of PSCA is currently unknown, PSCA homologues give some insight into possible functions. It has been previously shown that proteins in the Thy-1 family have been reported to function in T cell activation (Presky et al., 1990) and proliferation, stem cell survival, and cytokine and growth factor response (Rege et al., 2006), while the family of Ly-6 genes has been associated with carcinogenesis (Treister et al., 1998; Witz et al., 2000), cellular activation (Malek et al., 1986) and cell adhesion of tumor cells (Eshel et al., 2000). PSCA does not seem to be critical for normal development or urogenital function since a PSCA knockout mouse created by Moore et al. (2008) was viable, grew to adulthood and had normal litters. Additionally, these PSCA knockout mice did not have an increased incidence of carcinogenesis.

Homology

A murine PSCA (mPSCA) homologue was also identified by Reiter et al. (1998) and it is located on chromosome 15. mPSCA has 70% homology to human PSCA at the nucleotide and amino acid levels.

Mutations

Note

While no mutation is known for PSCA, a recent study by the Study Group of Millennium Genome Project for Cancer (2008) found a significant association between two Single Nucleotide Polymorphisms (SNPs) in the PSCA gene and diffuse-type gastric cancer.

Implicated in

Prostate cancer

Note

In human prostate cancer, PSCA over-expression is present in primary human prostate tumors and residual tumors removed after androgen ablation therapy (Reiter et al., 1998; Gu et al., 2000). There is a significant correlation between PSCA expression and seminal vesicle invasion, capsular involvement (Han et al., 2004), Gleason score, tumor stage and progression to androgen-independence (Gu et al., 2000). PSCA expression also correlates with metastasis, with a higher percentage of metastatic tumors expressing PSCA compared to non-metastatic tumors (Ross et al., 2002). In particular, bone marrow metastases show relatively higher intensity of PSCA expression compared to lymph node and liver metastases (Gu et al., 2000; Lam et al., 2005).

Prognosis

PSCA has been tested as a prostate cancer biomarker, with limited but interesting results. One study by Hara et al. (2002) screened for the presence of PSCA mRNA in a milliliter of patient blood via reverse transcription-polymerase chain reaction (RT-PCR) but found only 13.8% of prostate cancer cases positive for PSCA mRNA. However, this study also found that stage IV, PSCA mRNA positive patients correlated with a lower disease-free survival compared to stage IV, PSCA mRNA negative patients. In a separate study by Zhigang et al. (2008), 23.7% of men with benign prostatic hyperplasia (BPH) treated with transurethral resection of the prostate (TURP) who were positive for PSCA mRNA expression went on to develop prostate cancer versus only 1.0% of patients who were negative.

Oncogenesis

PSCA's role in prostate carcinogenesis remains unknown. The location of the PSCA gene at 8q24.2 has some interesting correlations however. Chromosome 8q is commonly amplified in metastatic and recurrent prostate carcinoma, and this amplification is associated with a poor prognosis (Visakorpi et al., 1995; Sato et al., 1999). Additionally, PSCA expression may be a marker for MYC amplification, a common mutation in prostate cancer, since both genes are located close to one another (Qian et al., 1995; Jenkins et al., 1997; Jalkut et al., 2002).

Additional cancers

Note

In addition to the identification of PSCA as a prostate tumor associated protein, several other tumors have shown associations with PSCA expression including pancreatic adenocarcinoma (Argani et al., 2001; Iacobuzio-Donahue et al., 2002; Wente et al., 2005), transitional cell carcinoma (Amara et al., 2001; Elsamman et al., 2006), renal cell carcinoma (Elsamman et al., 2006) and diffuse-type gastric cancer (The Study Group of Millennium Genome Project for Cancer, 2008).

To be noted

Note

The current role of PSCA as a diagnostic, prognostic and therapeutic tool was recently reviewed by our laboratory (Raff et al., 2008). While the use of PSCA as a target in the treatment of human prostate cancer is not covered here, it represents an ideal choice for immunotherapy due to its overexpression in prostate tumors and limited expression in normal tissues. For example, our laboratory recently demonstrated that PSCA vaccination of TRAMP mice that spontaneously generate prostate cancer conferred a 90% survival rate at 12 months of age in contrast to control mice which had all succumbed to prostate cancer or had heavy tumor loads (Garcia-Hernandez et al., 2008).

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