ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 272–279

UROLOGIC ONCOLOGY

Review article

The prostate-specific membrane antigen: Lessons and current clinical implications from 20 years of research

Benjamin T. Ristau, M.D., Denise S. O'Keefe, Ph.D.*, Dean J. Bacich, Ph.D.

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Received 29 July 2013; accepted 1 September 2013

Abstract

Objective: Despite a multitude of detection and treatment advances in the past 2 decades, prostate cancer remains the second leading cause of deaths due to cancer among men in the United States. Technological evolution and expanding knowledge of tumor biomarkers have invigorated exploration in prostate cancer therapeutics. Prostate-specific membrane antigen (PSMA) was one of the first prostate cancer biomarkers successfully cloned. Since then, it has been characterized as the prototypical cell-surface marker for prostate cancer and has been the subject of intense clinical inquiry. In this article, we review the relevant research in PSMA on the 20th anniversary of its cloning.

Methods and materials: A PubMed search using the keywords "prostate-specific membrane antigen" or "glutamate carboxypeptidase II" provided 1019 results. An additional 3 abstracts were included from scientific meetings. Articles were vetted by title and abstract with emphasis placed on those with clinically relevant findings.

Results: Sixty articles were selected for inclusion. PSMA was discovered and cloned in 1993. Its structure and function were further delineated in the ensuing decade. Consensus sites of expression in normal physiology are prostate, kidney, nervous system, and small intestine. PSMA has been implicated in the neovasculature of several tumors including urothelial and renal cell carcinomas. In prostate cancer, expression of PSMA is directly related to the Gleason grade. PSMA has been tested both in imaging and therapeutics in a number of prostate cancer clinical trials. Several recent approaches to target PSMA include the use of small molecule inhibitors, PSMA-based immunotherapy, RNA aptamer conjugates, and PSMA-targeted prodrug therapy. Future study of PSMA in prostate cancer might focus on its intracellular functions and possible role in tumor neurogenesis.

Conclusions: Twenty years from its discovery, PSMA represents a viable biomarker and treatment target in prostate cancer. Research to delineate its precise role in prostate carcinogenesis and within the therapeutic armamentarium for patients with prostate cancer remains encouraging.

Keywords: Prostate cancer; Prostate-specific membrane antigen; Folate; Cancer therapeutics; Tumor markers

1. Objectives

Prostate cancer is the most prevalent noncutaneous malignancy in men in the United States and remains the second leading cause of deaths due to cancer in this population [1]. Recently, as a result of well-publicized large randomized controlled trials [2,3], the use of prostate-specific antigen (PSA) as a screening tool has come under fire. This has culminated in the publication of guidelines aimed at reducing or in some cases eliminating the use of PSA as a screening tool for prostate cancer [4,5]. The necessary consequence of this reduction in screening is a decrease in the number of cancers detected. As a result, some have expressed concern that the abandonment of PSA screening may harbinger a return to prostate cancer presenting as symptomatic local or metastatic disease [6]. It is clear, then, that innovative biomarkers for the detection and treatment of prostate cancer are sorely needed. Prostate-specific membrane was one of the first prostate cancer biomarkers successfully cloned and has been the subject of intense clinical inquiry as an imaging and therapeutic agent since 1993 [7]. In this article, we review lessons learned from 20 years of research on prostate-specific membrane antigen (PSMA) with a focus on the current clinical implications in prostate cancer imaging and therapeutics. Further, potential novel avenues of research taking advantage of PSMA biological function are proposed.

* Corresponding author. Tel.: +1-412-623-3916; fax: +1-412-623-3907.
E-mail address: okeeds@upmc.edu (D.S. O'Keefe).

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.09.003

2. Materials and methods

A PubMed search using the keyword "prostate-specific membrane antigen" or "glutamate carboxypeptidase type II" yielded 1019 results. An additional 3 abstracts were included from scientific meetings. Articles were vetted by title and abstract with emphasis placed on those with clinically relevant findings. Articles not written in English were excluded. A total of 85 articles were selected based on abstract and the full text was read in entirety. From this, 60 articles were selected for inclusion in the review (Fig. 1).

3. Results

3.1. Discovery, structure, and physiology of PSMA

PSMA was first cloned in 1993 [7]. Since then, it has been shown to be identical to both folate hydrolase 1 found at the jejunal brush border and N-acetyl-alpha–linked acidic dipeptidase (NAALADase) in the nervous system [8]. The multiple names have led some to argue for standardization of nomenclature based on function (e.g., glutamate carboxypeptidase type II), however, this has not been widely accepted. Regardless of name, PSMA is a type II transmembrane protein with an N-terminal cytoplasmic tail, a helical transmembrane structure, and an extracellular C-terminus. The extracellular portion, existing as a dimer, makes up most of the protein and includes a binding motif featuring 2 zinc ions. This extracellular binding domain has been shown to bind glutamate and glutamate-like structures, hence its natural substrates (N-acetyl aspartylglutamate and folyl-poly-γ-glutamates) both have C-terminal glutamates. Internalization mechanisms for PSMA have been characterized and are believed to be mediated by cytoplasmic N-terminal tail interactions with calveolin-1 and clathrin-coated pits [9].

As aforementioned, PSMA has been called many different names based largely on its location of discovery. Four consensus sites of expression in normal physiology exist: prostate (secretory acinar epithelium), kidney (proximal tubules), nervous system glia (astrocytes and schwann cells), and the small bowel (jejunal brush border) [10,11]. Despite accepted expression in these tissues, the function is only well defined in nervous system glia and small bowel.

At the jejunal brush border, PSMA is called folate hydrolase 1. Here, it is responsible for assisting in folate absorption for transportation to the rest of the body. Dietary folates exist in the form of folyl-poly-γ-glutamates, but only monoglutamated folates can be absorbed by jejunal enterocytes [12]. PSMA is responsible for removing the C-terminal glutamates from dietary folates to allow for enteral absorption in humans and pigs. Interestingly, although rats do not express PSMA at the brush border, a similar folate hydrolase is released in murine pancreatic secretions allowing for enteral absorption of dietary folates [13].

In the nervous system, PSMA has been termed NAALADase, which is responsible for hydrolyzing N-acetyl aspartylglutamate (NAAG). NAAG is the most abundant peptide neurotransmitter in the mammalian nervous system

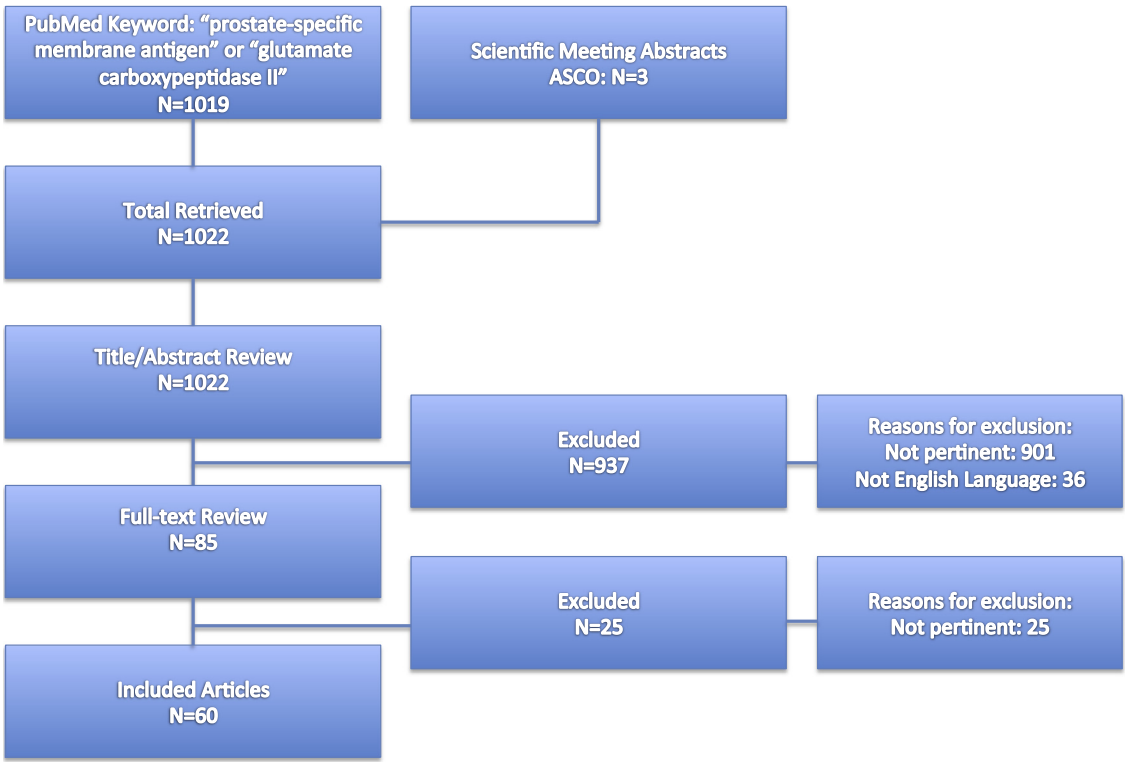

Fig. 1. Article selection for review. (Color version of figure is available online.)