RAGE as a Novel Biomarker for Prostate Cancer

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Prostate cancer (PCa) is a commonly diagnosed cancer among men worldwide. The receptor for advanced glycation end-products (RAGE) has been implicated in driving PCa growth, aggression, and metastasis through the fueling of chronic inflammation in the tumor microenvironment. RAGE expression is strongly tied to PCa progression and can serve as an effective diagnostic target to differentiate between healthy prostate, low-grade PCa, and high-grade PCa, with potential theragnostic applications.

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1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among men in the United States [1]. The current screening and diagnostic pathway for PCa consists of testing the serum levels of prostate-specific antigen (PSA) and performing a transrectal ultrasound-guided biopsy to histologically confirm PCa and rule out benign prostatic hyperplasia (BPH). This current standard of care has been shown to carry significant disadvantages: potential for sepsis and post-operational complications; omission of parts of the prostate due to patient pain; significant false-negative risk; and overdiagnosis due to the inability to differentiate between clinically significant and insignificant cancer cells effectively [2]. Perhaps as a result of new, more limited screening recommendations and more intensive initial treatments, diagnoses of localized disease are trending downward while the incidence of metastatic PCa is increasing [3]. To address these issues, new biomarkers, such as prostate-specific membrane antigen (PSMA), are being sought out as alternatives to PSA screening, which may provide additional information that will enable clinicians to differentiate between benign tissue, low-grade PCa, and high-grade PCa [4][5][6].

Chronic inflammation associated with increased body adiposity is a critical part of the initiation and development of PCa and other solid cancers [7]. The Western diet has been demonstrated to play a prominent role in the development of obesity and obesity-associated carcinogenesis [8]. In fact, the Western diet has been shown to exacerbate PCa tumorigenesis [9][10] and has been associated with increased mortality following PCa diagnosis [11]. Comprised largely of animal protein and high-carbohydrate and high-fat processed foods, the Western diet is also rich in dietary advanced glycation end-products (AGEs) [12]. AGEs are stable end-products formed endogenously and exogenously through the nonenzymatic glycation of proteins, lipids, and nucleic acids, which can form toxic

crosslinks with other molecules and bind to specific inflammatory receptors [13]. High levels of dietary AGEs are associated with the development of inflammation-related chronic pathologies, including cancer [14][15].

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin protein family of cell surface proteins found in a wide range of tissue types [16]. RAGE activation by AGEs stimulates the PI3K-mediated activation of NF-κB, which leads to a positive feed-forward cascade of pro-inflammatory responses, including an increased expression of RAGE [17][18][19][20][21][22]. The activation of RAGE can also be induced by a wide range of ligands, such as the S100 protein family and high mobility group box 1 protein (HMGB1), a damage-associated molecular pattern (DAMP) molecule released by damaged cells [20]. The activation of RAGE by proteins such as HMGB1, which is released by cells that die during PCa treatment as a result of therapy such as radiation, suggests that RAGE may play a role in PCa treatment resistance. In fact, inflammation in the PCa tissue microenvironment has been linked to proliferation, apoptosis inhibition, treatment and immune resistance, angiogenesis, and epithelial–mesenchymal transition (EMT) [23].

2. RAGE as a Novel Biomarker for Prostate Cancer

RAGE, the physiologic receptor for AGEs, has attracted significant attention since its discovery [24] due to its diverse ligand repertoire and involvement in several pathophysiological processes linked to inflammation, including cancer [25][26]. It was demonstrated that RAGE expression is directly tied to the malignant potential of PCa through different signaling mechanisms [27][28], including the activation of critical processes that promote drug resistance, stimulate angiogenesis, and enhance invasiveness [29][30][31]. Moreover, recent studies provided a positive association between RAGE, its ligands, such as AGEs and DAMPs, and neuroendocrine differentiation of PCa, which correlates with tumor grade, loss of androgen sensitivity, auto/paracrine activity, and poorer prognosis [32].

Results demonstrate that RAGE expression is elevated in PCa, with an overall OR of 11.3 when compared to benign prostate tissue. Importantly, many studies have evaluated PCa in comparison to prostate tissues with BPH rather than normal prostate tissue. This may be highly significant, as BPH has been shown to be a strong predictor for developing PCa [33]. No current biomarkers exist to differentiate BPH from PCa [34], but increased RAGE expression in high- vs. low-grade PCa suggest there may be an association with RAGE in BPH as well as PCa. Results show that high-grade PCa was found to be much more likely to express RAGE compared to low-grade cancers, suggesting that RAGE could be used as a biomarker to differentiate among different gradations of PCa.

Importantly, RAGE expression may be used for assessment when indolent cancers undergo a phenotypic switch to more aggressive, high-grade cancers. Cell culture studies consistently demonstrated that the expression and activation of RAGE is directly linked to PCa cell proliferative and migratory abilities, shown to occur mainly through the stimulation of the PI3K/Akt pathway and ultimately leading to the activation of oncoprotein NF-κB. HMGB1 expression in PCa was also investigated in several of the included studies, and HMGB1-specific activation of the RAGE axis was found to play a prominent role in the measured outcomes of PCa [21][28][35][36]. Because only two studies [28][36] compared the co-expression of RAGE and HMGB1, a meta-analysis was not conducted. As a DAMP, HMGB1 release by necrotic cells plays a role in priming immune cells to recognize dead or damaged tumor cells;

however, this acute inflammatory effect by HMGB1 also results in sustained inflammation in the PCa microenvironment by RAGE ligand activity, ultimately promoting treatment resistance and tumor growth through RAGE activation [37][38].

Due to the high association identified between RAGE and PCa, RAGE expression could be used as a prognostic tool to monitor BPH and localized PCa. However, the risks and side effects associated with repeated biopsies to longitudinally monitor RAGE expression are numerous [2], and, as such, are not clinically feasible. To this end, a research group has developed a multimodal imaging platform to non-invasively quantify RAGE expression in tissues, with the probe having demonstrated consistent utility in imaging RAGE in PCa [39][40]. This platform has the potential to transform current diagnostic and therapeutic paradigms of PCa treatment by enabling clinicians to use medical imaging tools to non-invasively and longitudinally monitor BPH or localized PCa. Increases in RAGE expression over time would indicate PCa progression, providing a necessary criterion that will help determine clinical therapeutic response.

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