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Review

Progesterone receptor in the prostate: A potential suppressor for benign prostatic hyperplasia and prostate cancer

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ABSTRACT

Advanced prostate cancer undergoing androgen receptor pathway inhibition (ARPI) eventually progresses to castrate-resistant prostate cancer (CRPC), suggesting that (i) androgen receptor (AR) blockage is incomplete, and (ii) there are other critical molecular pathways contributing to prostate cancer (PCa) progression. Although most PCa occurs in the epithelium, prostate stroma is increasingly believed to play a crucial role in promoting tumorigenesis and facilitating tumor progression. In the stroma, sex steroid hormone receptors such as AR and estrogen receptor-α are implicated to have important functions, whereas the progesterone receptor (PR) remains largely under-investigated despite the high sequence and structural similarities between PR and AR. Stromal progesterone/PR signaling may play a critical role in PCa development and progression because not only progesterone is a critical precursor for *de novo* androgen steroidogenesis and an activator of mutant androgen receptors, but also PR functions in a ligand-independent manner in various important pathways. In fact, recent progress in our understanding of stromal PR function suggests that this receptor may exert an inhibitory effect on benign prostatic hyperplasia (BPH), reactive stroma development, and PCa progression. These early findings of stromal PR warrant further investigations as this receptor could be a potential biomarker and therapeutic target in PCa management.

Contents

Abbreviations: AR, androgen receptor; ARPI, androgen receptor pathway inhibition; CRPC, castrate-resistant prostate cancer; PCa, prostate cancer; BPH, benign prostate hyperplasia; ERα, estrogen receptor-α; PR, progesterone receptor; PRA, PR isoform A; PRB, PRB isoform B; PRC, PR isoform C; CAF, cancer-associated fibroblast.

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1. Introduction

The prostate is a tubule-alveolar gland consisting of epithelial and stromal tissues. Since most prostate cancer (PCa) occurs in the epithelium, the epithelial cells have been receiving the most attention by investigators. However, increasing focus is brought to the stroma as it plays an essential role in prostate development, tumorigenesis, and tumor progression [1]. The main components of prostate stroma include fibroblasts, myofibroblasts, and smooth muscle cells. During prostate development, the urogenital sinus mesenchyme (UGM) and the urogenital sinus epithelium (UGE) interact with each other for prostate differentiation, indicating a reciprocal developmental interaction [2,3]. In a normal prostate, stromal tissues interact with the epithelium dynamically to maintain homeostasis, whereas disruption of the epithelium-stromal crosstalk is observed in adenocarcinoma oncogenesis [4]. The crosstalk between cancer promoting stroma and epithelial carcinoma resembles the "seed and soil" concept introduced by Stephen Paget in 1889 as the soil (tumor stroma) provides the proper environment for the seeds (tumor cells) to grow [5]. Indeed, the cancer promoting stroma, also called the reactive stroma, has been reported to secrete cytokines, growth factors, and extracellular matrices that support cancer cell migration, invasion, angiogenesis, as well as distal metastasis [6], making the stroma an important target for further investigations. In addition, prostate stroma expresses androgen receptor (AR) and estrogen receptor-α (ERα), which have been implicated in benign prostatic hyperplasia (BPH) and PCa development by influencing the stromal cell proliferation and differentiation [7,8]. Although progesterone receptor (PR) is also expressed in prostate stroma [9–16] and belongs to the same receptor family as AR and ER, the function of this receptor is poorly understood. Recent findings from our lab suggest some critical roles of stromal PR in the prostate including: (1) PR regulates stromal cell proliferation by interfering with cell cycles [17]; (2) PR suppresses the transdifferentiation of stromal cells to prevent a "reactive stroma"-like phenotype [18]; and (3) PR inhibits the stromal secretion of tumor-favorable cytokines into the prostate microenvironment [19]. This manuscript will provide an overview of the recent progress of our understanding in this receptor's expression and function in the context of PCa.

2. Progesterone

The ligand of PR is the steroid hormone progesterone. Progesterone plays multiple key physiological roles in mammals, especially in female reproductive functions. This 21-carbon hormone synthesized from steroid precursors is not only essential for regulating the establishment and maintenance of ovulation, the uterine, and the mammary gland, but also important in non-reproductive organs such as the heart, bone, and brain [20,21]. In females, the primary site of progesterone synthesis is the ovary and the principal site of progesterone secretion is the corpus luteum. The plasma progesterone concentration is approximately 5 nmol/L in the follicular phase of the menstrual cycle and rises after ovulation until menstruation [22]. In males, progesterone is synthesized by the testes and adrenal glands [16]. Males typically have a similar plasma progesterone level as females in their follicular phase [23]. In addition to the non-reproductive roles discussed above, progesterone in males is also an important precursor for androgen synthesis [24].

Androgen synthesis begins as cholesterol is converted to pregnenolone/progesterone and then followed by three proposed pathways [24]. In the classical pathway, the 21-carbon progesterone is converted to the 19-carbon dehydroepiandrosterone (DHEA) and androstenedione (AED) via the sequential hydroxylase and lyase activities of cytochrome P450 17A (CYP17A). DHEA and AED are then catalyzed to testosterone by enzymes such as hydroxysteroid dehydrogenase −3B (HSD3B), −17B3 (HSD17B3), and aldo-keto reductase 1C3 (AKR1C3). Finally, 5α-reductase (SRD5A) converts testosterone to dihydrotestosterone (DHT). In the backdoor pathway, progestin intermediates can be initially catalyzed by SRD5A and aldo-keto reductase 1C2 (AKR1C2) before undergoing the lyase activity of CYP17A. The resultant product androsterone can form DHT via the catalytic activities of HSD17B3 and oxidative 3α-HSDs [25]. In the third pathway, DHEA and AED are produced in the same way as the classical pathway, but they are converted to testosterone by the action of SRD5A1 first and then AKR1C3 [24,25]. Since increased *de novo* androgen synthesis is a major contributor to androgen receptor pathway inhibition (ARPI) resistance in PCa, targeting progesterone may effectively block the *de novo* androgen synthesis, thus providing additional therapeutic benefits for PCa patients.

In addition, progesterone may contribute to the progression of castrate-resistant prostate cancer (CRPC) by acting on progesterone responsive mutant AR. Chen and colleagues recently reported that treatment of the CYP17A1 inhibitor Abiraterone resulted in the selection of a progesterone responsive AR mutant (T878A), discovering an effective way for progesterone to facilitate PCa resistance to androgen inhibition [26].

3. Progesterone receptor

3.1. Structure and isoforms

PR is a member of a large ligand-activated nuclear hormone superfamily. Like other members of the family, PR is a modular protein composed of an N-terminal domain, central DNA binding domain, hinge region, and C-terminal ligand-binding domain [27] (Fig. 1). In humans, there are three PR isoforms (PRA, PRB, and PRC) with PRA and PRB being the major functional isoforms. PRA and PRB are transcribed from the same gene, but regulated by two different promoters [28]. Structurally, both PRA and PRB contain a centrally located DNA binding domain flanked at the N-terminus by an activation function-1 (AF-1) domain and at the C-terminus by a hinge region containing nuclear localization signals. Both isoforms have a ligand-binding domain that includes a second

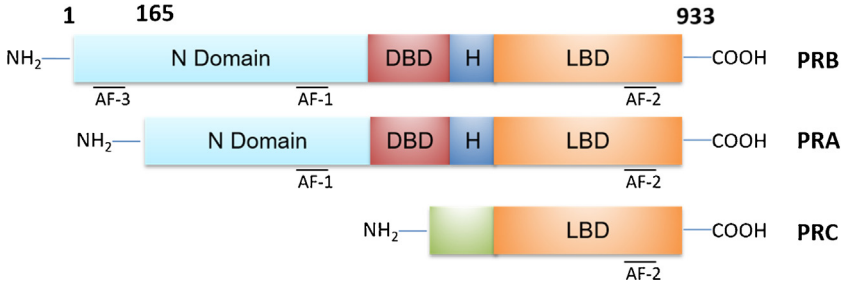

Fig. 1. A summary of PR isoforms. DBD stands for DNA binding domain; H stands for hinge region; LBD stands for ligand binding domain.

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