Tumour Review

Androgen receptor (AR) positive *vs* negative roles in prostate cancer cell deaths including apoptosis, anoikis, entosis, necrosis and autophagic cell death ☆

Simeng Wen [a,b], Yuanjie Niu [a,*], Soo Ok Lee [b], Chawnshang Chang [b,c,*]

[a] *Chawnshang Chang Sex Hormone Research Center, Tianjin Institute of Urology, Tianjin Medical University, Tianjin 300211, China*
[b] *George Whipple Lab for Cancer Research, Departments of Pathology and Urology, University of Rochester Medical Center, Rochester, NY 14642, USA*
[c] *Sex Hormone Research Center, China Medical University, Taichung 404, Taiwan*

ARTICLE INFO

ABSTRACT

Androgen/androgen receptor (AR) signaling plays pivotal roles in the prostate development and homeostasis as well as in the progression of prostate cancer (PCa). Androgen deprivation therapy (ADT) with anti-androgens remains as the main treatment for later stage PCa, and it has been shown to effectively suppress PCa growth during the first 12–24 months. However, ADT eventually fails and tumors may re-grow and progress into the castration resistant stage. Recent reports revealed that AR might play complicated and even opposite roles in PCa progression that might depend on cell types and tumor stages. Importantly, AR may influence PCa progression *via* differential modulation of various cell deaths including apoptosis, anoikis, entosis, necrosis, and autophagic cell deaths. Targeting AR may induce PCa cell apoptosis, autophagic cell deaths and programmed necrosis, yet targeting AR may suppress cell deaths *via* anoikis and entosis that may potentially lead to increased metastasis. These differential functions of AR in various types of PCa cell death might challenge the current ADT with anti-androgens treatment. Further detailed dissection of molecular mechanisms by which AR modulates different PCa cell deaths will help us to develop a better therapy to battle PCa.

© 2013 Elsevier Ltd. All rights reserved.

Introduction

The abnormal increased cell proliferation and/or decreased cell death in prostate may lead to the development of prostate cancer (PCa), which is the second most leading cause of cancer death in men of North America [1,2]. Importantly, the alteration of cell death signaling may also be involved in PCa resistance to the hormone therapy and chemotherapy [3–6], suggesting both cell death and cell proliferation may play key roles to influence PCa progression.

Androgen receptor (AR), a member of the nuclear receptor superfamily [7–9], can be activated by its ligands, androgens, to regulate its target gene expression. Early studies documented well that AR played complicated yet vital roles in the progression of PCa [10–12]. Importantly, AR could either stimulate or suppress PCa progression *via* modulating cell proliferation or cell death with distinct mechanisms [13–15].

This review will begin with a brief discussion of the differential AR roles in proliferation within individual cells of PCa and then focus on differential AR roles in controlling five types of cell death pathways including apoptosis, anoikis, entosis, necrosis, and autophagic cell deaths.

AR plays differential roles in cell proliferation among various PCa cell populations

Since Huggins and Hodges [12] provided the first *in vivo* evidence that targeting androgen/AR signaling *via* androgen deprivation therapy (ADT) could suppress PCa progression, ADT has become the main therapy for treating later stage PCa [16]. However, most of ADT failed in about 2 years and tumors continued to progress into the castration resistant stage [17–19]. Importantly, more and more studies suggested that AR might not only function

as a stimulator to promote PCa cell growth, AR could also function as a suppressor to negatively control PCa progression [13,20–22]. The differential functions of AR in PCa may depend on various cell types and tumor microenvironments.

PCa is composed of a mixture of cells in various differentiation stages, and might be derived from PCa stem/progenitor cells, which are CK5+, AR− and CK8−. Briefly, in the normal prostate, there are three kinds of epithelial cells: (1) CK5−/CK8+ luminal cells, (2) CK5−/CK8− intermediate cells, and (3) CK5+/CK8− basal cells (Fig 1). Stem/progenitor cells, which are CK5+/CK8−, are able to differentiate into basal intermediate cells (CK5+/CK8+) and finally differentiate into luminal epithelial cells (CK5−/CK8+) [23,24]. Bonkhoff et al. demonstrated that castration could only kill the majority of luminal epithelial cells, but most of the basal cells remained alive [25]. Current ADT for advanced PCa, which targeted androgen/AR signaling, might diminish luminal cells, and increase basal cell and basal intermediate cell populations [13]. These results suggested that androgen/AR signaling might have different roles among different cell types and might partially explain why ADT would finally fail.

This review briefly summarizes the differential roles of AR in the individual cells within tumors that might influence PCa progression.

AR positive roles in PCa CK5−/CK8+ luminal epithelial cell growth

The terminally differentiated CK5−/CK8+ luminal epithelial cells represent the major PCa cell type and they are believed to be differentiated from the CK5+/CK8+ intermediate cells that were derived from CK5+/CK8− stem/progenitor cells [21,26,27]. Niu et al. generated TRAMP mice with deleted AR in PCa epithelial cells (pes-ARKO-TRAMP), and found knocking out AR in PCa epithelial cells led to increasing apoptosis in CK5−/CK8+ luminal epithelial cells (from 2% to 18%) as compared with wild-type TRAMP mice. This result suggested that AR might function with a positive survival role in PCa luminal epithelial cells.

Similar results were also obtained from CK8+/CK18+ LNCaP epithelial cells derived from lymph nodes of metastatic PCa [28,29], showing knocking-down AR with anti-sense oligonucleotides suppressed LNCaP cell growth [30–32]. Furthermore, AR also played positive roles in other CK5−/CK8+ PCa cells, such as CWR22Rv1 cells [33], in which targeting AR with AR-siRNA resulted in suppression of cell growth [34].

Together, results from various human PCa cell lines and TRAMP mouse model with AR deletion in epithelial cells suggested that AR might play positive roles in PCa CK5−/CK8+ luminal epithelial cells.

AR negative roles in PCa CK5+/CK8+ basal intermediate cell growth

During the differentiation from the CK5+/CK8− PCa stem/progenitor cells to CK5−/CK8+ luminal cells, some cells are characterized as CK5+/CK8+ basal intermediate cells. The PC-3 cell line that was derived from a human bone marrow prostate metastatic tumor [35], is AR negative but expresses both CK5 and CK8, and therefore could be regarded as a basal intermediate PCa cell line. Litvinov et al. transfected PC3 cells with a functional AR cDNA under a strong promoter and found overexpression of AR in PC-3 cells might lead to suppression of cell growth [36,37], suggesting AR might play a negative role for basal intermediate-like tumor cell growth. Niu et al. [21] also used an *in vivo* mouse model and confirmed that transfection of a functional AR in PC-3 cells resulted in suppression of orthotopic xenografted tumor growth.

AR negative roles in PCa CK5+/CK8− basal and stem/progenitor cell growth

Lee et al. [38] found that AR might suppress cell proliferation in CK5+ cells that may include basal epithelial cells and stem/progenitor cells. Addition of functional AR in the human CK5+/CK8− basal epithelial cell line (named Lifeline-basal or HPrE) or the mouse CK5+/CK8− stem/progenitor cell line (named mPrE) led to suppressing their growth. Further *in vivo* mouse model study
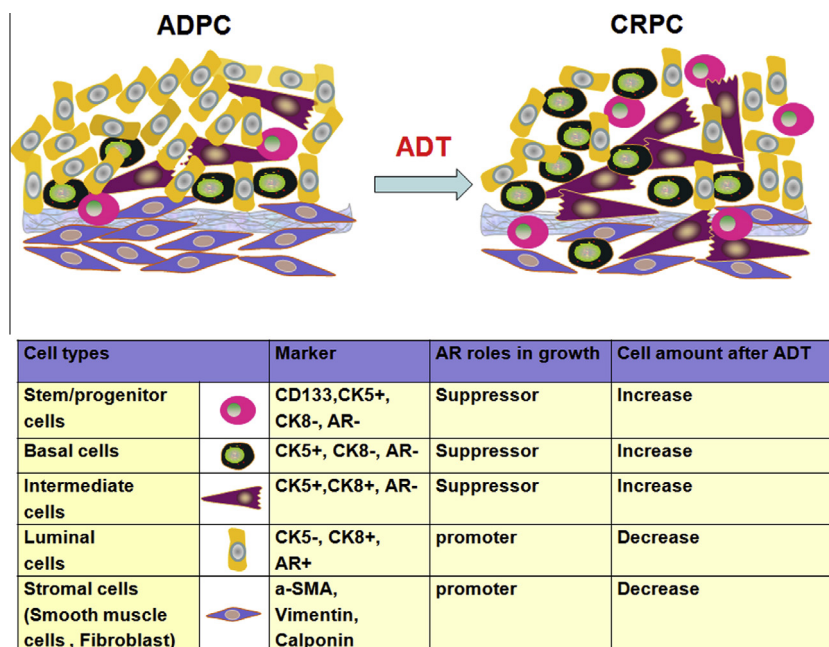

Cell types	Marker	Marker	AR roles in growth	Cell amount after ADT
Stem/progenitor cells		CD133,CK5+, CK8-, AR-	Suppressor	Increase
Basal cells		CK5+, CK8-, AR-	Suppressor	Increase
Intermediate cells		CK5+,CK8+, AR-	Suppressor	Increase
Luminal cells		CK5-, CK8+, AR+	promoter	Decrease
Stromal cells (Smooth muscle cells , Fibroblast)		a-SMA, Vimentin, Calponin	promoter	Decrease

Fig. 1. Androgen/AR signal plays differential roles in prostate cancer progress. Either promoting suppression or promoting PCa growth is dependent on various cell types. So the current ADT, which targets androgen, may lead to different results in individual cell types. After ADT, the androgen-dependent PCa (ADPC) may convert to castration-resistant PCa (CRPC). And the luminal cells and stromal cells will decrease, while the stem/progenitor cells, basal cells and intermediate cells will increase.