Published in final edited form as:

Cancer Treat Rev. 2014 February ; 40(1): . doi:10.1016/j.ctrv.2013.07.008.

Androgen Receptor (AR) Positive vs Negative Roles in Prostate Cancer Cell Deaths including Apoptosis, Anoikis, Entosis, Necrosis and Autophagic Cell Death

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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 of 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 also 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.

Keywords

prostate cancer; androgen receptor; apoptosis; necrosis; autophagy; anoikis; entosis; cell death

1. 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

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also involve 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 brief discussion of the differential AR roles in proliferation within individual cells of PCa and then focus on differential AR roles in controlling 5 types of cell death pathways including apoptosis, anoikis, entosis, necrosis, and autophagic cell deaths.

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

Since Huggins and Hodges¹² 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 treatment of later stage PCa¹⁶. However, most of ADT failed in about two years and tumors continue 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 with mixture of cells in various differentiation stages, and might be derived from PCa stem/progenitor cells, which are CK8–, AR– and CK5+. 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, marked by 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 alive²⁵. Current ADT for advanced PCa, which targeted androgen/AR signaling, might diminish luminal cells, and increase stem/progenitor cell, basal cell and basal intermediate cell populations¹³. These results suggested that androgen/AR signaling might have different roles among different cell types and might partially explain why ADT would finally fail.

Here, we briefly summarize the differential roles of AR in the individual cells within tumors that might influence PCa progression as follows.

2.1. 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 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 node 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 cells³³, in which targeting AR with AR-siRNA resulted in suppression of cell growth³⁴.

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.

2.2. 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 tumor³⁵, is AR negative but expresses both CK5 and CK8, and therefore could be regarded as basal intermediate PCa cells. Litvinov et al transfected PC3 cells with a functional AR cDNA under 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 al²¹ also used *in vivo* mouse model and confirmed that transfection of a functional AR in PC-3 cells resulted in suppression of orthotopic xenografted tumor growth.

2.3. AR negative roles in PCa CK5+/CK8– basal and stem/progenitor cell growth

Lee et al³⁸ 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) all led to suppressing their growth model studies. Further *in vivo* mouse model study confirmed these results and knocking-out AR in basal epithelial cells in the basal epithelium-specific ARKO mouse also led to increased proliferation of CK5+ cells³⁸.

In summary, AR may play either positive or negative roles in PCa epithelial cell growth, depending on in which type of epithelial cell the AR expresses. AR could suppress the growth of CK5+/CK8– basal and stem/progenitor cells and CK5+/CK8+ basal intermediate cells, but promote or support the growth of CK8+ luminal epithelial cells.

2.4. AR positive roles in PCa stromal cells growth

Earlier tissue recombination studies showed that stromal–epithelial interaction is important for PCa progression^{39–41}. Data from stromal-epithelial co-culture approaches also revealed that AR in human stromal WPMY1 cells could play a positive role to promote PCa growth and knocking down AR in WPMY1 cells suppressed PCa epithelial tumor cell proliferation²¹. Similar *in vitro* studies using the co-culture system also demonstrated that rat urogenital mesenchyme or bone marrow fibroblasts promoted LNCaP and other epithelial cells growth^{42, 43}. Importantly, using mice lacking stromal AR, Lai et al found stromal AR could promote prostate tumorigenesis *via* induction of pro-inflammatory cytokines/chemokines expression⁴⁴.

In summary, these findings proved that stromal AR could play a positive role to promote PCa progression and concluded that AR could play either positive or negative roles in individual PCa cells to influence PCa progression.

3. Differential AR roles in 5 types of PCa cell death

In addition to influencing cell proliferation, AR could also modulate cell death to control PCa progression. In the normal prostate, controlling cell death is essential in maintaining tissue homeostasis and is a natural barrier to cancer development^{3, 4}. Loss of this cell death control *via* various mechanisms may then lead to development of cancer. Furthermore, many genes that could regulate the cell death pathways and contribute to “resisting cell death”, which is one of the hallmarks of cancer development⁴⁵, have been documented^{46–51}. Importantly, recent studies also indicated that AR could play key roles to influence the PCa cell death *via* distinct mechanisms^{52–54}, and more and more evidences suggested that targeting androgen/AR-mediated cell death signaling could also alter the PCa progression^{55–58}.

The new classification of cell death established by the Nomenclature Committee on Cell Death (NCCD) was based on molecular feature⁵⁹. According to this classification, cell deaths can be roughly divided into: apoptosis (caspase dependent extrinsic apoptosis and caspase-independent intrinsic apoptosis), necrosis, autophagy cell death, and other tentative definitions of cell death modalities including anoikis, entosis, pyroptosis, netosis and cornification. In PCa, at least 5 types of cell death pathways have been observed and studied, including apoptosis⁶⁰, necrosis^{61, 62}, autophagy⁶³, anoikis⁶⁴, and entosis⁶⁵ that will be discussed in the following sections.

Interestingly, recent studies found that AR might play differential roles in various cell death signaling. AR could either inhibit apoptosis⁶⁶, necrosis⁶² and autophagy^{53, 67}, yet enhance apoptosis, anoikis⁵⁴ and entosis⁶⁵. Furthermore, many studies suggested that apoptosis, necrosis, and autophagy are related to tumor growth, yet both anoikis and entosis are more related to tumor metastasis (see the following sections). These interesting findings support the earlier discussion that AR may play a positive role in PCa tumor growth while it plays a negative role in metastasis⁶⁸.

3.1. AR positive and negative roles in cell apoptosis

Kerr et al first suggested the term “apoptosis” and confirmed it as a general mechanism of controlled cell deletion, which is complementary to mitosis in the regulation of animal cell populations⁶⁹. Deletion of apoptosis might cause uncontrolled cell proliferation and accumulation of cells, and finally result in some serious diseases, such as tumors. Therefore, one main direction of current tumor therapy strategy is targeting apoptosis^{4, 6, 70, 71}. Apoptosis can be histologically determined by formation of small, roughly spherical or ovoid cytoplasmic fragments and can be determined by observing the apoptotic bodies under microscopy^{69, 72}.

Recently, the NCCD divided apoptosis into extrinsic apoptosis and intrinsic apoptosis⁵⁹. Extrinsic apoptosis has been applied to the instances of apoptotic cell death that are induced by extracellular stress signals that are sensed and propagated by specific transmembrane receptors while intrinsic apoptosis is known to be resulted from a bio-energetic and metabolic catastrophes coupled to multiple active execution mechanisms⁵⁹.

Caspase plays a major role in apoptosis⁷³. For example, caspase-3, -6, and -7 are directly responsible for proteolytic cleavages that lead to cell disassembly (act as effectors), and caspase-2, -8, -9, and -10 are involved in upstream regulatory events (act as initiators)⁷⁴. The caspase family-mediated apoptosis^{74, 75} can be mediated *via* both receptor pathway and mitochondrial pathway⁷⁶. Propagation of the cell death signaling ultimately leads to the activation of effector caspase-3, -6, and -7, culminating in the cleavage of various protein substrates that display the typical biochemical and morphological hallmarks of apoptosis⁷¹.

In addition to the caspase family, the Bcl-2 family proteins are also involved in apoptosis and regarded as the second set of apoptotic regulators. This family has been divided into three groups; group I members including Bcl-2, Bcl-X_L, etc possess anti-apoptotic activity, whereas members of groups II (Bax) and III (Bid, Bix, etc) promote cell death⁷⁷. The Bcl-2 family plays a vital role in the regulation of the mitochondrial apoptosis pathway, which plays an important role in most forms of drug-induced apoptosis⁷⁸.

Similar to the above discussed the dual role of AR in PCa proliferation, AR also could modulate apoptosis in both positive and negative ways. AR could either promote⁷⁹ or suppress⁶⁶ apoptosis (Fig. 2) through modulating different signaling pathways⁸⁰, and the AR influences on cell apoptosis would then depend on internal and/or external information the cells received from the tumor microenvironment⁸¹.

3.1.1. AR negative roles in PCa cell apoptosis—Because the pro-proliferating role of AR has been established, the anti-apoptotic role of AR in PCa cells could also be expected, which might be deeply linked to the PCa development and progression⁸². There are many mechanisms by which AR protects cells from apoptosis, among which cyclin-dependent kinase inhibitor p21 (WAF1, CIP1, SDI1, or CAP20) is one of the important contributors. p21 has been proven to be able to protect against p53-mediated apoptosis⁸³. Overexpression of p21 may induce cell cycle arrest and led to an apoptosis-resistant phenotype⁸⁴. Lu et al showed that AR stimulated endogenous p21 mRNA and protein levels and functioned as an apoptosis inhibitor to promote PCa LNCaP cell growth⁸⁵. They also found a functional androgen response element (ARE, AGCACGCGAGGTTCC) located at -200 bp of the p21 gene proximal to the promoter region and showed that androgen could enhance the p21 gene expression at the transcriptional level.

Besides p21, androgen/AR signaling could directly regulate p53 to suppress apoptosis⁵². Rokhlin et al found androgen could suppress the TNFR family (TNF- α /Fas)-induced apoptosis through inhibition of p53 expression and caspase-2 activation, and suppression of the TNFR family-induced apoptosis by androgen could then be enhanced by p53 knockdown⁵². Other studies also showed that androgen could block apoptosis induced by Fas activation and TNF- α ⁸⁶.

Kadowaki et al found that the AR-positive LNCaP cells were resistant to TRAIL-induced apoptosis, while the AR-negative PC-3 cells were sensitive⁸⁷, suggesting AR might play negative roles in this type of apoptosis. Rokhlin et al also revealed that increased AKT might suppress the androgen-inhibited apoptosis⁵². Similar results also obtained from Sun et al showed androgen could activate PI3K and AKT1/AKT2, through AR, and consequently functioned as an anti-apoptosis factor in LNCaP cells^{88, 89}.

Androgen/AR signaling could also suppress apoptosis by inhibiting Bad, the Bcl-2-associated death protein. Androgen activated MAPK and increased the phosphorylation of ERK-1 and ERK-2, and inactivated Bad, which resulted in inhibition of apoptosis^{90, 91}. Brooke et al also found the expression of the RNA-binding protein FUS/TLS (Fused in Ewing's Sarcoma/Translocated in Liposarcoma) was suppressed by androgen that resulted in suppression of PCa cells apoptosis⁹².

Interestingly, AR could also protect PCa cells from apoptosis *via* an androgen-independent manner. Diallo et al found that AR-negative PC-3 cells were more sensitive to the anti-cancer drug effect *via* inducing caspase-dependent apoptosis⁹³ than PC-3 cells stably transfected with AR in the absence of androgen.

Other published papers showed that the down-regulation of AR induced PCa apoptotic death upon addition of proteasome inhibitor⁶⁶ and docetaxel⁹⁴. Liao et al showed that knockdown of AR *via* siRNA led to apoptotic death in PCa cells³². They further found both the cisplatin and the proteasome inhibitor induced caspase-3-associated cell death in AR-negative PC-3 cells while non-caspase-3 associated cell death was observed in AR-positive PC-3AR and LNCaP cells. In addition, they found that co-treatment with Bortezomib and the AR antagonist Casodex caused significant decrease in AR expression and led to caspase-3 activity increase in LNCaP and PC-3AR cells, suggesting AR might suppress caspase-3 expression⁶⁶.

In summary, results from above suggested that androgen/AR signaling could play negative roles in PCa cell apoptosis (Fig. 2.).

3.1.2. AR positive roles in PCa cell apoptosis—In contrast to the main negative roles of AR in apoptosis, its positive roles have also been suggested⁴⁷. Godfrey and his colleagues reported that AR could promote stress-induced cell death independent of its transcription activity in the androgen-independent PCa cells⁷⁹. They showed that, upon exposure to stress (ultraviolet light and staurosporine), the N-terminal domain of AR (AR-N) would undergo proteasomal degradation which might lead to stress-induced apoptosis mediated by Bax⁴⁷ and caspases⁷⁹. Blockade of AR degradation, ectopic expression of Bcl-2 or selected caspase inhibitors can suppress this pro-apoptotic activity of AR⁷⁹. This conclusion was confirmed by their further study⁹⁵. In 2012, Lin et al demonstrated that UV might induce DNA damage and AR proteasomal degradation. This AR degradation produces the N-terminal domain that might then induce up-regulation of PIRH₂ and p53 and down-regulation of p21, and finally resulted in cell apoptotic death⁹⁵. This conclusion may suggest that AR can promote radiotherapy through PIRH₂-p53-p21 axis. However, opposite results have also been reported, showing that AR could protect PCa from irradiation-induced apoptosis⁸⁶. AR was also proven to improve photodynamic therapy (PDT)⁹⁶ that might result in cell oxidative DNA damage and apoptosis. So, the exact role of AR in radiotherapy is complicated and still unclear. Other studies demonstrated that truncated PolyQ expression of AR gene promoted apoptosis through up-regulation of Bax and JNK^{97, 98}, suggesting that the pro-survival/pro-death function of AR is mediated mainly by transcriptional regulation of apoptosis associated genes⁹⁵.

In addition to intracellular AR functions in apoptosis, it was suggested that membrane AR could induce apoptosis in PCa cells as well^{99, 100}. Mechanism study showed that membrane AR activation triggers down-regulation of PI-3K/Akt/NF-kappaB activity and induces apoptotic responses via Bad, FasL and caspase-3 in PCa¹⁰⁰.

Together, results from above suggested that androgen/AR signaling could play positive roles in PCa cell apoptosis.

Since both positive and negative roles of AR in PCa cell apoptosis have been reported, it is still arguable when and under what circumstances AR selectively plays its roles. To our knowledge, AR function is regulated by multiple signaling pathways and depending on different AR associate protein complexes, which indicates AR may induce or suppress cell apoptosis according to cell microenvironments and cell types. Besides, the anti-apoptosis and pro-survival function of AR (intracellular AR) is mediated mainly by transcriptional regulation of its target genes. In contrast, the pro-apoptosis function of AR (intracellular AR) is mainly transcription-independent, or mediated by membrane AR.

3.2. AR positive roles in promoting PCa cell anoikis

The interactions between cells and the extra-cellular matrix (ECM) play very important roles in the cell growth and cell death^{101–103}. Aside from attachment to ECM, epithelial cells and/or endothelial cells could be induced by another type of cell death¹⁰⁴, named as anoikis¹⁰⁵, that resulted from insufficient cell-matrix interactions. Normal cells might use anoikis to prevent cell proliferation at inappropriate locations¹⁰⁶ and cancer cells could also adapt to overcome anoikis and result in tumor growth and metastasis. Therefore, targeting anoikis might lead to suppressed tumor growth and metastasis^{106–108}.

Based on several discovered mechanisms involving in anoikis^{109–112}, the NCCD defined anoikis as an adherent cell-restricted lethal cascade that is ignited by detachment from the surrounding matrix with the following characteristics: (i) lack of α 5 β 1-integrin engagement; (ii) down-regulation of EGFR expression; (iii) inhibition of ERK1 signaling and (iv) overexpression of the BCL-2 family member BIM⁵⁹.

Anoikis has been linked to the epithelial-mesenchymal transition (EMT) process¹⁰⁶ that involves the PCa metastasis. The strategy of combination therapy with targeting tumor vascularity (*via* anoikis) and impairing tumor initiation (*via* classic apoptosis) resulted in the significant therapeutic promise to battle metastatic PCa¹¹³.

Ma et al first found that hepatic AR might play dual yet opposite roles to promote hepatocellular carcinoma (HCC) initiation yet suppress HCC metastasis that involved the suppression of the phosphorylation/activation of p38 at later HCC stages⁵⁴. Since p38 is a member of the MAP kinase family that might play important roles in anoikis^{114, 115}, their results suggested that down-regulation of p38 by AR might result in increased anoikis (Fig. 3) that led to suppression of tumor metastasis⁵⁴. Furthermore, they also found androgen/AR signaling could increase anoikis in LNCaP cells, suggesting that androgen/AR signaling could also regulate anoikis in some selective PCa cells, and provided another explanation why AR could suppress PCa metastasis (Ma et al, unpublished results).

3.3. AR positive roles in enhancing PCa cell entosis

Overholtzer and his colleagues first introduced the term entosis to describe a non-apoptosis cell death mechanism linked to the way of clearing detached cells that might be accompanied with the cell-in-cell phenotype¹¹⁶. Entosis is defined as only a homogeneous live cell invasion phenomenon and only happens within the living cells and their neighborhood^{117–119}. Furthermore, entosis is an active process that is formed by the invasion of one cell into another, rather than by engulfment¹¹⁶.

Even though both entosis and anoikis could be provoked by the loss of ECM interaction, entosis would not entail the activation of apoptotic executioners and is a non-apoptosis pathway, so is distinct from anoikis¹⁰⁹. Entosis is also distinct from autophagy (see later section).

There are many fates for the internalized cells during entosis, such as undergoing the lysosome-mediated degradation process or undergoing cell division within the host cells^{116, 120}. Entosis could also disturb the host cell cytokinesis resulting in aneuploidy and could be regarded as a non-genetic route to aneuploidy in human cancers^{121, 122}. Overall, as the main outcome of entosis is the death of the internalized cells, it might represent a novel pathway to eliminate detached cancer cells, and thus its stimulation may offer a better outcome in clinical oncology^{116, 120}.

Entosis was reported as a process that is independent of both caspase and Bcl-2 related cell death pathways, but it might depend on the activation of the small GTPase-RhoA, the

ROCK1/ROCK2 in the engulfing cells^{116, 123}. Other reports also suggested that Metallothionein 2A¹²⁴ and Par3-Lgl¹²⁵ could regulate entosis through the RhoA-ROCK pathway.

Wen et al⁶⁵ found that androgen/AR signaling could enhance entosis through modulation of the RhoA/ROCK pathway (Fig. 3), as 10 nM DHT treatment exhibiting better effects to promote entosis compared to 1 nM DHT. Knocking-down AR suppressed entosis in PCa cells in the presence of both 1 and 10 nM DHT. Suppression of the RhoA-ROCK pathway with the inhibitor (Y-67236) or siRNA then resulted in blocking the androgen/AR-enhanced entosis. Importantly, clinical sample surveys found entosis phenomenon in the late castration resistant stage of PCa, compared to its absence in the early androgen dependent stage of PCa and non-tumor area including benign prostatic hyperplasia (BPH). These contrasting clinical data suggested that entosis might occur mainly at the late stage of PCa with increased invasion ability. Under this circumstance, the connection between PCa cells and ECM become weak (especially when the PCa cells invade into blood or lymph nodes). The diminished connection suggested that the actin polymerization and myosin II activity, regulated by RhoA/ROCK signaling pathway, might involve in the entosis-related PCa cell invasion. AR roles in entosis could be another reason to explain why AR could suppress PCa cells invasion.

3.4. AR negative roles in suppressing PCa cell necrosis

Laster et al first found both apoptosis and necrosis was responsive to the same trigger of TNF-¹²⁶. Accumulating evidences revealed that necrosis could also occur in a regulated manner^{127–129}, and then a new term “necroptosis” was introduced to describe the programmed necrosis¹³⁰. According to the suggestion from NCCD we here use “programmed necrosis” term. Programmed necrosis has been reported to be induced by several stimulations, such as alkylating DNA damage¹³¹, excitotoxicity¹³², and the activation of death receptors¹²⁶. Other reports also suggested that proteins/kinases, such as death receptors of CD95, also known as Fas¹³³, TNFR1 and TNFR2¹²⁶, TRAILR1 and TRAILR2¹³⁴ were involved in the initiation of progression of necrosis and RIP1/RIPK1, RIP3/RIPK3¹²⁷, LMP and lysosomal¹³⁵, mitochondrial and cytosolic hydrolases¹³⁶ are all involved in the action of programmed necrosis. In addition, reactive oxygen species (ROS) generated by mitochondria can also contribute to the programmed necrosis^{137–139}.

An early report indicated that androgen could protect renal cortical cells from programmed necrosis induced by vasopressin administration and suppression of androgen binding to AR via anti-androgen of cyproterone acetate increased programmed necrosis¹⁴⁰, suggesting androgen/AR signaling might play a negative role in programmed necrosis.

Frezza et al reported that cisplatin and the proteasome inhibitor bortezomib might induce caspase-3-associated apoptotic cell death in parental PC-3 cells. In contrast, they could not induce necrosis cell death in LNCaP and PC-3AR cells⁶⁶. Blocking androgen binding to AR *via* the anti-androgen Casodex in these two AR+ PCa cell lines might then lead to cell death *via* the caspase-associated apoptotic pathway after treatment with cisplatin and bortezomib, suggesting that blockade of androgen/AR signaling might be able to switch programmed necrosis to apoptosis in these PCa AR+ cell line⁶⁶ and indicated that AR might play a negative role in programmed necrosis.

Liu et al found that 10 nM DHT could protect AR+ PCa cell lines including PC-3AR9 and C4-2 from the programmed necrosis induced by H₂O₂ or heat⁶². Knocking-down AR *via* siRNA in these PCa cell lines led to increase programmed necrosis, suggesting AR might play negative roles in programmed necrosis. Whether AR might go through modulation of

the NF- κ B pathway¹⁴¹ or death receptor pathway (such as Fas activation and TNF- α)⁸⁶ to suppress the programmed necrosis might need further studies in the future.

3.5. AR negative roles in decreasing PCa autophagic cell death

In 1963, de Duve first suggested the term autophagy to describe the presence of single- or double-membrane vesicles that contain parts of the cytoplasm and organelles in various states of disintegration and called these sequestering vesicles autophagosomes¹⁴². Recently, autophagy was described as a process in eukaryotes by which cytoplasmic cargo sequestered inside double-membrane vesicles (known as autophagosomes) would be delivered to the lysosome for degradation¹⁴³. The NCCD suggested the term autophagic cell death (ACD) as a cell death instance that is mediated by autophagy, and could be suppressed by the inhibition of the autophagic pathway with chemicals (VPS34 inhibitor) and/or genetic means (down-regulation of essential autophagic modulators like AMBRA1, ATG5, ATG12 or beclin1)⁵⁹.

Autophagy has essential roles in survival, development, and homeostasis processes^{143–147}. In eukaryotic cells, autophagy, which is induced by stress and development, has double functions. Stress-induced autophagy can often exert cyto-protective functions to support the re-establishment of cell status, and inhibition of autophagy may induce cell death. On the other hand, the inhibition of autophagy may also result in inhibition of the developmental cell death⁵⁹. There is a hypothesis that excessive autophagy may lead to suppression of cell growth. Most of the anti-cancer therapies that target ACD are based on this hypothesis^{148, 149} and some selective PCa therapies also target ACD^{53, 150–152}.

Bennett et al found reduced androgen might result in increased autophagy⁵¹ and detailed mechanistic studies indicated that this suppression might be due to alteration of AR-mediated up-regulation of the endoplasmic reticulum (ER) chaperone Grp78/BiP⁶⁷. They also found addition of the anti-androgen of Casodex to block androgen/AR signaling in LNCaP led to increased autophagy. Interestingly, combining 3-methyladenine to inhibit autophagy with ADT, with or without docetaxel treatment, resulted in better efficacy to suppress PCa progression⁶⁷.

Jiang et al found knockdown of AR in AR positive cell lines, such as LNCaP or CWR22R human PCa cells led to increased autophagy, and addition of functional AR in AR negative cell lines, such as PC-3 cells, resulted in decreased autophagy, suggesting AR could play a negative role in regulating autophagy. Mechanism dissection indicated that AR might repress autophagy *via* modulation of p62 expression. Importantly, the therapeutic approach *via* targeting AR to increase autophagy with AR degradation enhancer ASC-J9[®] resulted in the suppression of PCa growth⁵³.

Interestingly, Kung et al found that AR activation *via* non-androgens could also inhibit autophagy and the autophagy blockade might sensitize PCa cells to the Src tyrosine kinase inhibitor. So they suggested a therapy combining Src tyrosine kinase inhibitor with autophagy modulator might deserve further attention as a potential treatment for relapsed PCa¹⁵³.

Taken together, results from above suggested that AR could play a negative role in autophagy to promote PCa cells growth.

4. AR differential effects in PCa progression based on its positive or negative roles in cell deaths

None of above described cell deaths contributes to PCa growth and metastasis equally, and PCa progression is not dependent entirely on any single cell death pathway. Generally, apoptosis, ACD, and programmed necrosis are closely related to tumor growth, while anoikis and entosis are mainly correlated to tumor metastasis. As reviewed by Niu et al¹³, AR might function as a stimulator and as a suppressor in PCa cell growth and metastasis, respectively. Based on differential AR roles in tumor progression and metastasis, we summarized all 5 types of cell death mediated by AR as either beneficial or harmful in PCa progression.

Three types of cell death (apoptosis, ACD, and programmed necrosis), especially apoptosis, might play predominant roles in controlling the amount of PCa cell numbers. In PCa, AR could protect cells from apoptosis, ACD and programmed necrosis in most androgen sensitive PCa cells that would result in promotion of PCa growth. However, in some androgen-insensitive PCa cell lines¹⁵⁴, AR might function as an apoptosis promoter instead of survival protector. This phenomenon could partly explain why ADT does not work well in castration-resistant PCa. After an early success to suppress PCa growth, ADT eventually fails, and might lead to tumor re-growth during the castration resistant stage, due to AR signaling blockage that may not be sufficient to lead to all types of PCa cell deaths.

Interestingly, two other kinds of cell death (anoikis and entosis), which were induced by detachment from ECM, are closely related to tumor metastasis. AR enhanced anoikis and entosis through different pathways, but both might lead to metastasis inhibition, consistent with AR suppressor roles in PCa metastasis¹³.

In summary, in PCa, androgen/AR signaling is one of the most important mechanisms that could regulate death induction and death resistance at the same time. Clear dissection of how AR modulates each type of cell death will help us to fight PCa more effectively.

5. New PCa therapies based on the opposite AR roles in different types of cell deaths

5.1 Challenge to current ADT

As mentioned above, androgen/AR signaling not only protected PCa cells from cell deaths including apoptosis, ACD and programmed necrosis, it also differentially modulated cell proliferation in PCa, suggesting it will be extremely difficult to apply a simple therapy, for example the current ADT, to systematically reduce androgen or prevent androgens binding to AR in every cell to suppress PCa progression. Furthermore, considering anoikis was closely linked to the progression of EMT¹⁰⁶, which plays important roles in PCa metastasis, targeting anoikis has been indeed regarded as a strong therapeutic approach to battle metastatic PCa¹¹³. One may speculate that blocking of anoikis by ADT may then lead to the undesirable increase of metastases. Similar concerns also occurred in the entosis that was induced under the same condition as anoikis¹¹⁶ and it may also be speculated that ADT increased entosis might lead to enhanced PCa metastases.

Taken together, because of dual and opposite roles of AR in PCa proliferation, cell death and metastasis, it is necessary to re-consider whether the ADT that is currently used to treat PCa is safe and effective.

5.2 Combination therapy of ADT with inhibitor(s) of or interruption of AR-mediated cell death signaling pathways

The traditional ADT will block androgen/AR signaling and results in enhancement of cell deaths including apoptosis, ACD and programmed necrosis of PCa. However, it may also suppress other types of cell deaths, including anoikis and entosis, and might lead to increased metastases. This could be one of the reasons why the current ADT fails. Therefore, we need to develop a therapy combining the current ADT using the anti-androgen/AR drugs with a strategy that can block metastases that might be caused by these drugs-induced anoikis and entosis.

For the strategy to block the ADT drugs induced-anoikis, Platycodin D can be considered as a potential new therapy to battle PCa. AR could increase anoikis through suppression of the phosphorylation/activation of p38⁵⁴. Platycodin D, which activates p38 MAPK signaling, has been used to induce anoikis in different human cancer cells^{115, 155}. Therefore, ADT with Platycodin D to activate p38 could be a potential approach to block the ADT drugs induced-anoikis. Meanwhile, for the strategy to block the ADT with anti-androgen treatment induced-entosis, blocking with the RhoA/ROCK activator (such as RhoGEF2) could be considered since it was demonstrated that AR could enhance the RhoA/ROCK pathway that resulted in increased entosis⁶⁵.

6. Conclusion and future prospects

The main current therapy for PCa (ADT with anti-androgens treatment) to reduce or prevent androgens binding to AR has been proven successful in some ways. However, these efforts eventually fail leading to a more advanced stage of PCa and this may be partially due to the dual yet opposite roles of AR in different types of cell death. Therefore, we may need to develop a therapy combining the current ADT treatment with the anti-anoikis and/or anti-entosis agents to fight the PCa. Alternatively, the recently developed AR degradation enhancer, ASC-J9[®] has been proven to suppress PCa in selective cells effectively^{156, 157}. These types of combination therapies may be developed to better battle PCa in the future.

Acknowledgments

Grant support: NIH Grants (CA127300 and CA156700), Taiwan Department of Health Clinical Trial and Research Center of Excellence Grant DOH99-TD-B-111-004 (China Medical University, Taichung, Taiwan), and National Basic Research Program of China (2012CB518304).

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Cell types		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)		α-SMA, Vimentin, Calponin	promoter	Decrease

Fig. 1.

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

Fig. 2.

The major role of AR in apoptosis is a suppressor. However, in contrast to the main negative roles of AR in apoptosis, in some specific environment(exposing in UV), AR may induce apoptosis. Meanwhile, some specific AR(membrane AR or polyQ AR) may also promote apoptosis. **A**, AR can go through ①p53; ②p21; ③JNK; ④PI3K/AKT; ⑤FLIP; ⑥ FUS/ TLS; ⑦MAPK; ⑧Caspase family; ⑨Bcl-2 family to suppress Apoptosis. **B**, AR could also promote apoptosis *via*: ①PIRH2-p21 axis; ②JNK, Bax; ③PI3K/AKT and NF-κB.

Fig. 3.

In addition to apoptosis, AR may also regulate other kinds of cell death. Such as: ①AR enhances entosis through Rho/ROCK pathway; ②AR promotes anoikis through MAPK/ERK pathway; ③AR suppresses necrosis through TNF α /FasL and NF- κ B pathway; ④ AR suppresses ACD *via* p62 and Grp78/Bip.