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Prostate Cancer: A Continuous Evolutionary Search for Molecular Therapy Targets

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Abstract

Prostate Cancer (PCa) is the most frequently diagnosed carcinoma in males and one of the leading causes of death in men around the globe [1]. Recent studies estimate that over a million males are diagnosed with prostate cancer on an annual basis, with approximately 0.3 million prostate cancer-related deaths per annum. Development of Castration-Resistant Prostate Cancer (CRPC) culminates from over-expression of the Androgen Receptor (AR) gene; mostly through amplification of the AR gene, AR gene mutations and elevated synthesis of androgens in prostate cancer tumors. Advanced CRPC eventually develops to metastatic Castration-Resistant Prostate Cancer (mCRPC) in all patients. On the other hand, TP53 gene has the highest frequency of mutations across all variations of human cancer, with well over 50% of alterations found on various regions of the protein. Missense mutations of p53 frequently result in the loss of wild-type p53 (wtp53) which plays a very vital role in tumour suppression. In prostate cancer, Tp53 is one of the most common mutated or in activated protein which results in cancer development and progression. This review aims to look at progress made to date on both Tp53 targeted therapy in relation to all existing therapy both in clinical trials and those that still at initial phases.

Keywords: Prostate cancer; Cisplatin; RGX-104; p53; Nutlin-3

Introduction

Prostate Cancer (PCa) is the malignant neoplasia that develops in the prostate gland of a male reproductive system. It's clear causes are unknown, but it usually results from alterations in cellular growth in the epithelial cells of the prostate glands, thus undergoing several mutational changes that ultimately develop into cancerous cells [2]. Most prevalent cases of the tumors are usually slow progressing but relapse to more aggressive metastatic tumors that are lethal and can result in death. PCa prevalence is estimated by the Prostate Specific Antigen (PSA) produced by the prostatic epithelial cells [3,4]. Its progression has been related to several genetic abnormalities that affect the Androgen Receptor (AR) and cellular mechanism involved in the regulation of cell survival and apoptosis [5]. According to, androgens are involved in the normal prostate development, growth, and the maintenance of physiologic functions and progression of PCa, and alterations in AR leads to changes in androgen-responsive genes, hence AR signaling remains the most sort after an attractive target for intervention in PCa [1]. Androgens are nuclear receptors that functions as a transcriptional factor involved in the growth functioning and differentiation of the prostate; thus they are also involved in the development and progression of PCa where AR is the primary target for PCa ablation therapy.

Like many other carcinomas, PCa also develop similarly in a process that involves multiple steps including tumour initiation, and ultimately its progression, factored by abnormalities or mutations such as chromosomal instability, mutations, and genetic and epigenetic changes. Evidently most prostate tumors have shown to be adenocarcinomas, sharing similar features with other prevalent epithelial cancers, including breast cancer. Prostate carcinogenesis is usually characterized by indolent phenotype and its consistent slow rate of progression of most tumors. If the cancer is not detected early, it can result in a more aggressive form which is commonly characterized by the transition from androgen-dependent to androgen-independent form which is more challenging for treating as it results in invasion and metastasis of the surrounding local organs such as seminal vesicles, eventually metastasizing to the bones resulting in fatality. Though widely investigated novel therapeutic strategies that can completely cure this aggressive malignancy are have not been fully elucidated, altogether with underlying molecular mechanisms of its progression and proliferation. Hence, new improved treatment strategies that will effectively target specific genes expressed

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in PCa development and progression are needed. Therefore, treatments utilizing photochemical have been widely used globally as traditional medicine and associated with inhibition of various cancers. Cannabinoid derived compounds are among those shown to exhibit anti-cancer effects. Cannabidiol (CBD) is one of the most active cannabinoids found in the Cannabis Sativa with less toxic properties and massively proven to inhibit cancer related cellular or molecular aberrations. Molecularly and structurally, it consists of twenty-one atoms of carbon, thirty hydrogen and two oxygen molecules. Considering present PCa related therapeutic data, CBD has effect on several cellular signaling inhibiting cancer development and progression. However its effect on PCa has not yet been fully characterized thus potentiating this novel agent as a candidate for unraveling apoptotic induced cell death. In the following study, we have examined the potential therapeutic properties of CBD and its underlying molecular mechanisms in human prostate cancer PC3 cells.

Prostate Cancer Epidemiology

PCa is one of the most commonly diagnosed carcinomas affecting the male urogenital system, and cancer-causing death among men globally, with approximately 1.6 million deaths reported in 2015. (Global Burden of Disease Cancer Collaboration 2016). It is documented to be the fifth most common cause of cancer death globally, accounting for approximately 366,000 deaths and 6.3 million disability adjusted life years [6], furthermore ranking it the second most frequently diagnosed cancer and the fifth leading cause of cancer death amongst men. Prostate cancer is mostly common in developed countries (Global Burden of Disease Cancer Collaboration 2016), and according to GLOBOCAN 2018, the most recorded incidence rates are mostly seen in western countries such as Australia, United States and Sweden (GLOBOCAN, 2018). However, highest mortality cases are recorded in underdeveloped or developing countries such as Sub-Saharan African regions (including South Africa, Zimbabwe and Zambia) and the Caribbean regions (such as Haiti, Barbados and Jamaica). It is estimated that by 2030 the incidence rate will be approximately 1.7 million cases with 500.000 deaths yearly [7]. The GLOBOCAN 2018 estimates also 18.1 million new cases of cancer and 9.6 million deaths from cancer in 2018.

According to [8], the prevalence or incidences of PCa increases with host age, it is a slow progressing malignancy and it undergoes a series of stages [8]. Pan American Health Organization, WHO, 2006 as cited in their 2010 review, mentioned PCa among the most common cancers worldwide. PCa is the most prevalent diagnosed malignancy and the second leading cause of mortality from cancer among men globally, with dominant susceptibility genes responsible for 5% to 10% of all the incidence cases [9]. In South Africa, PCa is the most common cancer affecting man followed by skin and lung cancer respectively (NCR, 2011). Prostate cancer forms from alterations in cellular growth in the epithelial cells of the prostate glands, thus undergoing several mutational changes resulting cancerous cells developing and proliferating [2]. Prostate cancer prevalence is estimated by the Prostate Specific Antigen (PSA) produced by the prostatic epithelial cells [3,4]. According to Bostwick et al. [8] prostate cancer prevalence or incidences increase with host age, it is a slow progressing malignancy and it undergoes a series of stages [8]. Its progression has been related to several genetic abnormalities that affect the Androgen Receptor (AR) and cellular mechanism involved in the regulation of cell survival and apoptosis [5].

Risk Factors Associated with Prostate Carcinoma

The a etiology of prostate cancer is yet to be discovered, but there are numerous risk factors that can increase a man's chances of developing PCa, and they include aging, familial inheritance due to genetic variances, poor diet or diet high in fats, ethnicity, hormones, lifestyle and environmental carcinogenic agents [8,10,11]. However, these risk factors involvement in the aggravating the cancer to advanced stage is still unclear. PCa has always been closely correlated with aging, as it is one of the most slowly progressing cancers and can only be clinically detected at an older age normally ranging from 60 or 70 year old men [6,12]. Elevated concentrations of testosterone and its metabolite, di hydro testosterone have also shown to increase PCa risk. The genomic effects androgens which have shown to have oncogenic potential are mediated by the Androgen Receptors (AR), mediating transcriptional responses by targeting sequence-specific DNA regulatory elements [13].

Familial inheritance has been proven to account for small percentage (~10%) of PCa in its initiation phase, studies have correlated males with first degree relatives to have high chances of developing PCa due to inheritance of genes such as BRCA1 and BRCA2 [14]. Genetic mutations such as inactivation or loss of tumour suppressor genes such as RB, p53, apoptotic genes such as bcl-2, bax, bad and back have been implicated in its development [15]. Prostate cancer progression has been related to several genetic abnormalities that affect the Androgen Receptor (AR) and other molecules that are involved in the regulation of cell survival and apoptosis [5], and its tumour development is driven by the expression of a mutant AR. In prostate cancer, the retinoblastoma tumour suppressor protein has been shown to be lost, rendering its pathway dysfunctional [16]. Its inactivation induces cell cycle progression and since RB controls Androgen Receptor (AR) levels through E2F transcriptional factors RB-E2F pathway. Most human cancers show changes in this pathway which affects the AR responsible for stimulating cell growth and proliferation in cancer cells [17]. It has been proven that a decrease in growth factors such as IGFBP down-regulate the expression of RB, p53 and p21 proteins, which as a result inhibit apoptosis and lead to proliferation of prostate cancer cell lines [18].

Histopathological of Prostate Cancer

In general morphology, normal prostate composes of glands and stroma. The glands are seen in cross section to be rounded to irregularly branching and represent the terminal tubular portions of long tubuloalveolar glands that radiate from the urethra. There are two layers of the outer low cuboidal and inner columnar mucin-secreting epithelium that that make up the gland. Prostate cancer is a heterogeneous group of malignant tumors that are classified according to the World Health Organization (2004). Ninety-five percent of these tumors are adenocarcinoma originating from the glands and ducts in the prostate. Microscopically, nodular prostatic hyperplasia consists of nodules of glands and intervening stroma. Most of the hyperplasia is contributed by glandular proliferation, but the stroma is also increased, and in rare cases may predominate [19]. MDM2 and RBBP6 which are classified as proliferative genes since they promote cancer proliferation, have been found to be highly expressed around glandular tissues of prostate cancer which on their morphological appearance have increased cell proliferation [19,20] (Figure 1). This kind of evidence suggests that the two genes as reported they interact with each other leading to the degradation

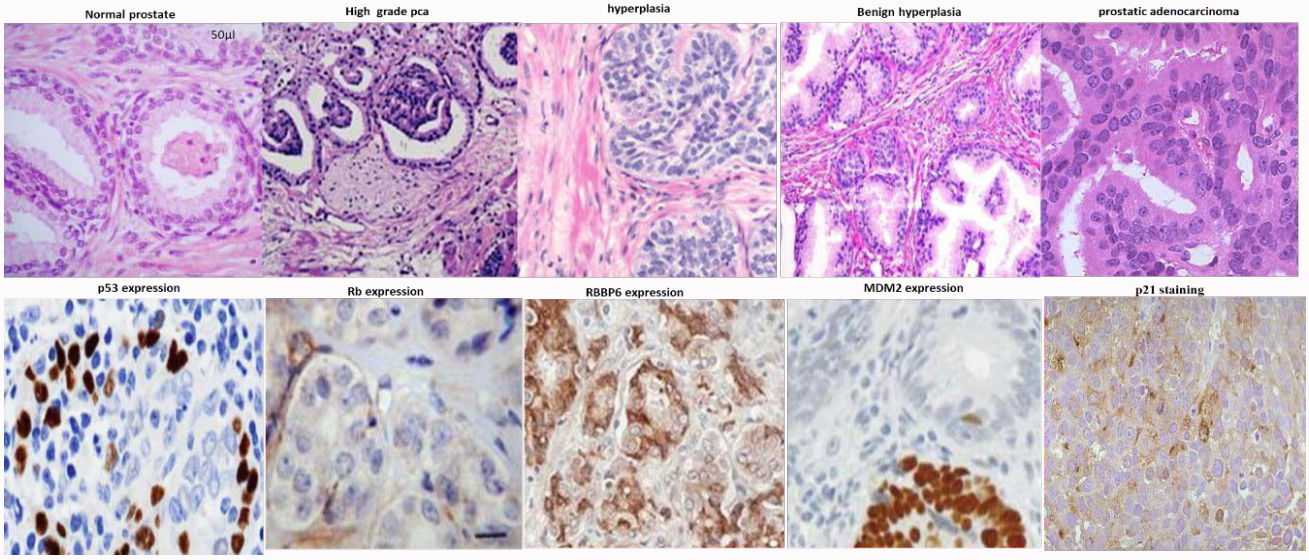

Figure 1: Histopathological and immune histochemistry of prostate cancer. Expression of p53, Rb, RBBP6, MDM2 and p21 as show in the figure predominantly around the glandular regions.

of p53 and to some extend Rb. Similarly looking at the expression of p53 and Rb proteins in prostate cancer across all types and stages over expression of p53 and Rb are seen around the glandular region of the cancer [20] (Figure 1). This result is a clear indication that a targeted therapy as suggested widely by medical science research would need to look at overcoming RBBP6 and MDM2 over expression in cancers like prostate cancer.

Expression of Cell Cycle Regulatory Genes in Prostate Cancer

PCa results from mutations or gene expression alterations which may lead to overgrowth of cells surrounding the prostate gland, angiogenesis, inhibition of apoptosis of the prostate gland cells, and invasion [21]. Cell cycle regulation is an integral component in cancer treatment. Normal cell growth is regulated by various signaling pathways; and sequential activation and subsequent inactivation of a series of protein kinases (Cdks) and cyclins [22]. Activated Cdks phosphorylate specific proteins at precisely timed intervals to regulate the cells metabolic activities to ensure orderly cell division. G1-phase of the cell cycle, individual D-type cyclins induced in a cell assemble into with one or two Cdks 4/6, cyclin E and A to activate a cascade of cell regulatory processes [23-25]. Cell proliferation is controlled by the activation of G1 Cdks regulated by Cdk inhibitors such as p16, p21 and p27, and subsequent phosphorylation of the RB protein, thus repressing its inhibitory activity by binding to the E2F transcription factor. The RB protein transcriptionally inhibits expression of the p16 gene. Because RB normally prevents apoptosis [24].

The loss of cell cycle regulatory control in G1 has been shown to cause tumour development, cell proliferation and inhibition of apoptosis of many cancers. These tumour suppressor genes such as RB and p53 are known to massively regulate the cell cycle by acting as mediators in several mechanisms; several studies have proven that they are functionally inactivated in most human cancers [17]. The genes are altered in many cancers either through direct mutations or indirectly through alterations in the expression of their upstream regulators. Studies on Androgen Receptor (AR) have shown enhance prostate cancer cell survival through the accumulation of cyclin D1 and activation of CDK4 which promote phosphorylation of Rb tumour suppressor resulting in prostate cancer progression [26]. Targeting the cell cycle using compounds in prostate cancer Zhang et al. [27] found that Honokiol which is a pure compound isolated from Magnolia officinal is extracts decreased the viability of PC-3 and LNCaP human prostate cancer cells through mediated cell cycle arrest associated with a decrease in protein levels of cyclin D1, cyclin-dependent kinase 4 (Cdk4), Cdk6, and/or cyclin E and suppression of complex formation between cyclin D1 and Cdk4. In another study Docetaxel and paclitaxel were found to bind to and stabilize microtubules, causing G2/M cell-cycle arrest and apoptosis through p21 activation [28].

p53 Expression in PCa

The p53 protein is a TSG known as genomic "gate keeper" which plays a pivotal role of ensuring that balanced is maintained between cell growth and cell death in the living system. It is known to have a powerful antitumor activity that is controlled by MDM2 which negatively regulates it [29,30]. P53 normally responds to stress signals that can disrupt the fidelity of DNA replication and cell division [31]. The p53 protein has shown to be induced in response to DNA damage in normal cells, by activating the expression of specific genes whose proteins are responsible for cellular growth inhibition such as bax which is involved in the cascade of regulatory events promoting the stimulation of apoptosis which is a programmed cell death or suicide of cells that are abnormal or are longer capable of dividing normally [31,32]. The activation of p53 results in growth arrest, apoptosis, cell death and/or cell repair which ultimately reduces proliferation of damaged cells or tumour progression and chemo-resistance [33].

It represents a checkpoint that halts the cell cycle upon DNA damage in the G1-phase [34]. Its inactivation or its absence as a result of mutations, damaged cells tend to activate specific oncogenes, which proliferate resulting in tumorigenesis, which has been implicated in many cancers including PCa. It is, therefore, important to study the role of all regulatory genes underpinning for tumour growth inhibition and induction of apoptosis. Like RB, p53 is modulated by methylation, phosphorylation, and acetylation. The

phosphorylation of p53 prevents its interaction with MDM2 [29,34]. p53 transcriptionally induces the expression of p21 which inhibits and prevents CDKs from phosphorylating RB at G1-S transition, thus inhibiting E2F transcriptional activity and cell cycle progression . The p53-p21 response pathway involves p21 being induced by p53 thereby maintaining RB in its non-phosphorylated [24].

MDM2 Inhibitors Nutlin-3 in Prostate Cancer as Possible Therapeutic Target

For years medical science has established that MDM2 negatively regulate p53 in cancer thereby preventing cellular machinery to arrest cell proliferation. One of the hallmarks of prostate cancer is mutation or inactivation of p53 which might be as a result of MDM2 activity. For a successful future target it should be in inhibit MDM2. In this regard small molecule MDM2 antagonists might be useful in the treatment of human prostate cancers that retain functional p53 also their androgen receptor signaling. One of the identified molecules is Nutlin-3 which is a small-molecule inhibitor that acts to inhibit MDM2 binding to p53 and subsequent p53-dependent DNA damage signaling. Nutlin-3 bind in the p53- binding pocket of MDM2 to displace p53 from the complex and induce p53 stabilization. p53 then activates downstream targets leading to p21WAF induction, cell cycle arrest, and apoptosis. Several studies have since been carried out to assess the potential of Nutlin-3 in inhibiting MDM2 in cancer cells that had functioning p53 and one study by Supiot et al. [35] has found that Nutlin-3 in combination with radiation under toxic conditions decreased clonogenic survival of prostate cancer cells. In anoxia, Nutlin-3 induced p53 protein expression. Furthermore, Nutlin-3 was more effective as a radio sensitizer under hypoxic conditions particularly in WTp53-expressing cells. They concluded that Nutlin-3 can act as a radio sensitizer via p53-independent mechanisms under low O_2 levels. In another study by Zhu et al. [36], Nutlin-3a, the active enantiomer of Nutlin-3, increased the sensitivity to cisplatin by inhibiting MDM2 binding to E2F-1 in a chemo sensitization. The Increased sensitivity was linked to the induction of proapoptotic proteins. Nutlin-3 was also reported to have prevented the association between MDM2 and HIF-1a resulting in inhibition of vascular endothelial growth factor production which led to reduced tumour angiogenesis. Prostate cancer colony growth was more prevalent when p53 transcriptional activity was decreased, whereas growth was more limited in the presence of functional p53. These results demonstrate that the functional status of the tumour suppressor p53 is important in the progression of prostate cancer and dictates the overall effectiveness a given drug would have on disease treatment. Nutlin-3 may radio sensitize WTp53-expressing cells, such as 22RV1, via multiple factors, including p21WAF activation and increased apoptosis [37]. However, the mechanism of the radio sensitization of mutated p53 –expressing or p53-null cells remains unclear. This enhanced radio sensitivity mediated by Nutlin-3 might improve outcome at currently used radiation doses. The phosphatidylinositol 3-kinase (PI3K)/Akt and p53 pathways play anti apoptotic and proapoptotic roles in cell death.

Cancer cell growth and progression are associated with high levels of PI3K/Akt activation by loss of PTEN expression and the inactivation of p53 by MDM2 over expression. Zhu et al. [36] reported that inhibition of PI3K/Akt, either by the PI3K inhibitor Ly294002 or by expression of PTEN, synergized the ability of the MDM2 antagonist nutlin-3 to induce apoptosis in acute lymphoblastic leukemia. While another study showed that Nutlin-3 effected cell cycle in gastric cancer cell lines by inducing G1 arrest in MKN-45 and SNU-1 cell lines. p53 can induce HO-1 by directly binding to the putative p53 responsive element in the HO-1 promoter in a study by Arya et al. [37] Nutlin-3 induced HO-1 expression at the level of transcription in human cancer cells in a transcription-independent manner of p53 with a knockout of HO-1 resulting in Nutlin-3-inducing apoptosis. So from this study it is clear that nutlin-3 induces HO-1 expression via the activation of both JNK which is dependent on ROS generated by p53 Trans located to the mitochondria and p38 MAPK which appears to be stimulated by a ROS-independent mechanism. Combination of radiotherapy or Chemotherapy with Nutlin in inactivated p53 prostate cancer remains a useful strategy in combating the disease and also preventing its angiogenesis.

Mitoxantrone as Prostate Cancer Apoptosis and Cell Cycle Arrest Inducer

The cell machinery especially p53 which guards the genome of the cell activate apoptosis or cell cycle arrest in respond to any DNA damage thereby leading to cell cycle arrest until the cell is repaired of apoptosis if the cell can't be repaired. It is common knowledge that many cancers especially prostate cancer is as a result of mutation however, the cell machinery is not activated to arrest proliferation of damaged cells. One possible strategy to combat cancer cells would be to damage DNA in a normal functioning p53 with the hope that this will trigger cell cycle arrest or apoptosis. One molecule that was identified is Mitoxantrone which is a small molecule that intercalate into DNA and inhibiting topoisomerase II resulting in DNA damage during replication. Mitoxantrone mechanism of action focuses on reducing disease progression and through a variety of different ways by suppressing the proliferation of T cells, B cells, and macrophages that's why it is said to be antibiotic of cancer.

Mitoxantrone treatment produces single and double strand breaks in DNA. Some of the protein-associated DNA strand breaks result from a cleavable complex with topoisomerase. Mitoxantrone induce cell-cycle arrest and accumulation of the cells in late S and G2/M phase. Inhibition of ATM, but not of MEK1/2, abrogated mitoxantrone-induced cell-cycle arrest. Inhibition of MEK1/2 did not change mitoxantrone induced up-regulation of p53 and p21, but inhibition of ATM markedly decreased up-regulation of p53 and p21, and p53 phosphorylation on serine 15 and serine 392 [38,39]. In another study by Senbabaoglu et al. [40], co-delivery of the anticancer drug, Mitoxantrone (MTO) and the gene encoding tumour suppressor protein p53 was evaluated towards anticancer combinatorial therapy. Combined drug and gene loaded nanoplexes was reported to have more apoptotic effect than either the drug or gene individually. Mitoxantrone-induced PCD was associated with a marked induction of c-jun and significant repression of c-myc and BCL-2 oncogenes. Cervical cancer cells are characterized by Wt p53 which is inactivated by E6 through degradation. In a study to test the effectiveness of mitoxantrone, Alpay et al. [41], reported activation of caspase and apoptosis in a combinational therapy which was independent of either p53 or p73 despite increased p53 activity in Hela cells. Mitoxantrone activate DR4 and 5 that also sensitized cells to TRAIL and increased cells into apoptosis that is independent of p53 [40]. Mitoxantrone as it is carried fourth through clinical trials it shows both potential in tumour treatment and apoptosis restoration either through p53 dependent and independent manner.

Molecular Effect of Cisplatin in Prostate Cancer

Cisplatin is a chemotherapy anticancer drug which is used to treat several cancers. It is administered intravenously as short-term infusion in normal saline for treatment of solid and hematological malignancies. In testicular cancer it increased the cure rate from 10% to 85% is particularly effective against testicular cancer; its adoption has increased the cure rate from 10% to 85%. The mechanism of action of the drug involves interfering with DNA replication by preventing its repair which results in the killing of the fastest proliferating cells, which in theory are carcinogenic. Even though cisplatin has been effective in many cancers, prostate cancer cells exhibit intrinsic and acquired resistance to cisplatin. In order to improve its sensitivity to cisplatin, combinational therapy with either agents that reduces side effects or increases it cytotoxicity is necessary. One such example of combinational therapy successful in prostate cancer is cisplatin-β-Elemene which markedly promoted cisplatin-induced apoptotic cell death in prostate cancer cells by activating caspase-3/7/10 and caspase-9, cleavage of caspase-3 and -9, suppression of Bcl-2 and Bcl-XL expression, and release of cytochrome c from mitochondria in these cells [42]. Apoptosis-Inducing Factor (AIF) is a small protein that resides normally within the inter membrane space of mitochondria, and upon certain death stimuli Trans locate into the cytosol and ultimately the nucleus where it contributes to DNA fragmentation and chromatin condensation. With cisplatin playing a role in DNA repair as part of its cytotoxic mechanism in cancer, in order to sensitize prostate cancer cells to cisplatin an inhibition of AIF by its inhibitor molecule N-acetyl-L-cysteine thereby preventing it from translocating into the nucleus and resulting in cisplatin-induced apoptosis in LNCaP cells [27]. In a study by Zhang et al. [43] they reported that KLF4 was induced by cisplatin in prostate cancer cells and that the increase in KLF4 promoted cell apoptosis through the binding of KLF4 directly to the promoter of BIK facilitating its transcription. This mechanism was facilitated by the down regulation of miR-32-5p in response to cisplatin treatment which promoted KLF4 expression, resulting in increase in the chemo sensitivity of prostate cancer. In another combination study Resveratrol in combination with cisplatin was found to up-regulate DUSP1 which resulted in increased apoptosis in androgen-independent prostate cancer cells through the inhibition of the NF-κB pathway and Cox-2 expression [44]. Anti apoptotic Bcl-2 is frequently over expressed in refractory prostate cancer and increased following standard hormonal therapy and chemotherapy. Its designed antagonist, ABT-737, has not shown single agent apoptosis-promoting activity against human prostate cancer. In a combinational study using mice models infused with prostate cancer cells, Bray et al. reported increased apoptosis induction by cisplatin, ABT-737 alone or in combination with the combination producing an increased activation of caspase-3 and cell death. Further studies showed that Calcitriol enhances both carboplatin and cisplatin-mediated growth inhibition in prostate cancer LNCaP and DU145 cells [45]. From extrinsic pathway Cisplatin/LA-12 and TRAIL combinational therapy was reported to promote stimulation of mitochondrial apoptotic pathway associated with activation of Bid and Bak proteins in prostate cancer [46]. From all this information it is clear that the new effective strategy to overcoming prostate cancer resistant to cisplatin is through targeted combinational therapy.

Estramustine in Prostate Cancer and Its Molecular Impact

Estramustine is a combination of oestrogen and nitrogen mustard used to treat prostate cancer that no longer responding to hormone treatment. The mechanism of the drug is to stop the cancerous cells from dividing into two new cells, by inhibiting mitosis through binding to tubulin, causing its depolymerization and preventing the formation of microtubules, or decreasing the kinetic ability of the microtubules, which are necessary to complete cell division [47,48]. Mitosis is arrested in the G2/M-phase. Which results in a blockage of tumour growth as well as of other hormones in the body that promote cancer growth. Estramustine phosphate has been reported in many studies to induce apoptosis in prostate cancer cells [49]. Even though the mechanism of apoptosis induction is still not clear, [50] reported that MiR-31 Knockdown Enhanced EP induced PC3 Cell Apoptosis by increasing expression of proapoptotic genes such as p53. In another study by Ståhlberg et al. [51] showed that combinational therapy with Radiation resulted in DNA damage in mice which initiated apoptosis in cancer. In another study using Taxol and Estramustine, the combination resulted in total down-regulation of bcl-xL protein in the absence of alteration of bax, bak, or bcl-2 levels. Which resulted in an increased ratio of Bax/Bcl2 expression and leading to apoptosis activation. Estramustine continue to be recommended for certain individuals with prostate cancer, however continuing improvement of the treatment might be important for future effectiveness use.

Androgen Targeted Therapy in Prostate Cancer

Abiraterone acetate is a novel steroidal inhibitor of CYP17A1 a cytochrome P450 complex, a rate-limiting enzyme in androgen biosynthesis resulting in inhibition of testosterone production in both the adrenals and the testes. It improves overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy by blocking the remaining or residual male hormones in the body that may be helping prostate cancer to grow. Abiraterone was found to improve radiographic progression-free survival which showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer [52]. In 2011, its combination with prednisone was approved for patients with metastatic high-risk castration-sensitive prostate cancer, based on findings from the phase III latitude clinical study. In other findings by Maughan et al. [53] that compared treatment of castration-sensitive prostate cancer patient with or without p53 reported that inp53 inactivation in the primary tumour, the co-treatment may be predictive of inferior outcomes to novel hormonal therapies. Suggesting that patient with p53 survived and coped well with treatment as compared to those without. On the other hand over expression of MDM2 showed poor prognosis and when inhibitors of MDM2 were added the cells showed improved sensitivity of castration-resistant prostate cancer to Abiraterone [54,55]. In male patient metastatic Castration Resistant prostate cancer, administration of CPI-1205 in combination with enzalutamide or abiraterone/prednisone has passed label Phase 1b/2 clinical trials and is available orally for selective inhibitor of the histone lysine methyl transferase which causes apoptosis in cancer [53].

Immunotherapy Process in Prostate Cancer

Like any other disease or infection the body's immune system must

respond to cancer and assist the body in removing the cancer from the system. However, in cancer patients the immune system is unable to detect the cancerous cells probably because they might be recognized as self-tissue. Immunotherapy, also known as biologic therapy is a type of cancer treatment that boosts the body's natural defenses to fight cancer. This type of therapy uses a substance produced by the body or in the laboratory to improve or restore immune system function to stop or slow growth of cancer cells. In recent years, medical science has identified several antibodies that are produced by cancer cells in their fight against the disease. One such molecule is RGX-019 which is a humanized monoclonal antibody that selectively targets MERTK, a receptor tyrosine kinase of the TYRO3/AXL/MERTK (TAM) family which is expressed in immune cells such as macrophages and NK cells, and is over expressed in a wide variety of liquid and solid cancers. MERTK once activated through binding to a ligand on cancer cells promote tumour-promoting signaling pathways, proliferation of cancer cells and angiogenesis while decreasing apoptosis and chemo sensitivity [56,57]. MERTK inhibition increased apoptosis, decreased colony formation, increased chemo sensitivity, and decreased tumour formation in a mouse model [58]. RGX-019 bind to MERTK with high affinity preventing the binding of a ligand leading to degradation of MERTK [56,59].

A small molecule immunotherapy (RGX-104) against solid tumors, including drug-resistant malignancies was also synthesized which reverses the immunosuppressive effects of cancer by targeting the LXR/ApoE pathway that regulates the innate immune response to cancer. RGX-104 depletes myeloid-derived suppressor cells which blocks the ability of T cell activation and stimulates dendritic cells which are required to activate T cells [57,60-62]. RGX-104 is an oral first-in-class LXR agonist that robustly induces ApoE expression resulting in innate-immune mediated anti-tumour activity. In recent clinical trials, 26 patients with a variety of refractory solid tumors were treated at doses ranging from 120 mg QD to 200 mg BID of RGX-104 and was found to be effective in restoring immune system and decreased cancer growth [57,63]. p53 is well documented as mutated in over 50% of all prostate cancer cells and restoring the functioning of p53 would result in improved prognosis in cancer cells. Advexin which is a replication-impaired adenoviral vector that carries the p53 gene, has been evaluated in both preclinical and clinical trials since 2006 and has shown a well-tolerated and efficacious treatment for numerous cancers in combination with radiation and/or chemotherapy agents [64-66]. During most clinical trials some patients with MDM2 family amplification had poor clinical outcome and significantly increased rate of tumour growth after single-agent checkpoint (PD-1/PD-L1) inhibitors which continue to indicate that even with restored p53 you will need it to be phosphorylated and MDM2 degraded for the protein to be able to perform its function. Immune system restoration and target as possible therapeutic agents and would play a huge role in overcoming cancer. Another molecule on the market is Nivolumab, which is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PDL1 and PD-L2. Programmed cell death protein 1 (PD-1) is a protein on the surface of cells that has a role in regulating the immune system's response to the cells of the human body by down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity [67,68]. In prostate cancer, previous studies had shown that the anti-PD1 agent nivolumab (Opdivo) did not enhance anti-tumour responses of CRPC patients. But two CRPC patients were reported to have exceptional responses to immunotherapy [67,68].

Medicinal Plants Target in Prostate Cancer

Many methods are used currently in the treatment of cancer and in particular, prostate cancer such as Radiotherapy and Chemotherapy. However, their unspecific target and the resultant increased healthy cell killing remains the setback in all this treatment. Event through improved combinational therapy the combined treatment is still ineffective and not specific and there arise the more effective naturally produced products or molecules. Plants produce a wide range of chemical compounds that have no direct role in the plants' growth. These compounds are called secondary metabolite such as Alkaloids, terpenoids, flavonoids, pigments, and tannins are important constituents the compounds. Secondary metabolites have biologic effects such as anti-inflammatory, anticancer, contraceptive, and different effects on hematopoietic cells [69-71]. One of the plants that have recently got attraction of many researchers working on cancer is Cannabis Sativa which is an ancient plant that has been cultivated in the Neolithic times, and it contains at least phytochemicals with almost 66 of them belonging to a class of cannabinoids [72-74]. According to [72] the plant is composed of phyto-cannabinoids, flavonoids, enzymes, steroids and terpenoids [72]. Plant-derived cannabinoids have shown to be potent inhibitors of various cancers including prostate carcinoma both *in vitro* and *in vivo* [75-77]. Cannabinoids can either have toxic or none-toxic properties, and they work by interacting and activating specific G-proteins coupled receptors (CB1 and CB2) usually located in different parts of the Central Nervous System and Immune system respectively [74,77-80]. In recent studies using PC3 and WIN-55,212-2 cell lines treated with cannabinoid there was a sustained up-regulation of ERK1/2 and inhibition of PI3k/Akt pathways in WIN-55,212-2-treated cells. Inhibition of ERK1/2 abrogated WIN-55,212-2-indued cell death suggesting that sustained activation of ERK1/2 led to cell cycle dysregulation and arrest of cells in G0/G1 phase subsequently leading to an induction of apoptosis through Bax/BCl2 activation [81]. However, further studies on prostate cancer and cannabinoid and cannabis sativa need to continue and more information could be collected especially since most of the compounds in the plant have been reported to be involved in p53 induced apoptosis. Another plant product which has been thoroughly studied and in phase II clinical trials is Curcumin which is a polyphenolic molecule extracted from the rhizome of the plant Curcuma longa. Curcumin target the nuclear factor kappa-B (NF-kB) pathway thereby reducing fatigue in patient that was treated with either chemotherapy or Radiotherapy. In prostate cancer Curcumin is suggested to stop the growth of tumour cells by blocking protein kinases such as AKt and mitogen-activated protein kinases which are growth enzymes needed for cell growth thereby prevent prostate cancer from returning after surgery [82-84]. In many other cancers Curcumin induces apoptosis independent of p53 by targeting caspase 8 which induces apoptosis through the extrinsic pathway [82,83].

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