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Review Article

Oncogenic activation in prostate cancer progression and metastasis: Molecular insights and future challenges

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Abstract

Prostate cancer is a leading cause of death among men in the United States, and currently early diagnosis and appropriate treatment remain key approaches for patient care. Molecularly prostate cancer cells carry multiple perturbations that generate malignant phenotype capable of uncontrolled growth, survival, and invasion-metastasis to other organs. These alterations are acquired both by genetic and epigenetic changes in tumor cells resulting in the activation of growth factor receptors, signaling proteins, kinases, transcription factors and coregulators, and multiple proteases required for the progression of the disease. Recent advances provide novel insights into the molecular functions of these oncogenic activators, implicating potential therapeutic targeting opportunities for the treatment of prostate cancer.

Keywords: Prostate cancer, oncogene, PI3K-Akt, proteases, signaling pathways, growth factor receptors

INTRODUCTION

Prostate cancer is a highly prevalent disease and leading cause of cancer related deaths in the Western World. National Cancer Institute (NCI) estimates that about ~240 890 American men will be diagnosed with prostate cancer in 2011 and approximately ~33 720 will die of the disease. It is the most prevalent tumor in men and despite increasing efforts at early detection, 10–20% of the cases present bone metastasis at diagnosis. Most men diagnosed with prostate cancer can survive the primary localized tumor; however, because of the widespread metastasis that are resistant to conventional treatment including improved surgical techniques, mortality rates remain extremely high. Development of prostate cancer is prevalently asymptomatic, and once symptoms are noticed, it usually implies an advanced disease stage. Metastatic dissemination of cancer cells consists of series of sequential interrelated steps that lead to spread of the disease to distant organs such as bone, lymph nodes, rectum, urinary bladder, and brain, which ultimately leads to death. So, it is critical to understand the mechanisms that drive prostate cells to become metastatic. Moreover, it is also important to diagnose the disease at an early stage so that proper therapy can be administered, for which we need a predictable biomarker. Thus, by understanding the molecular events in the pathogenesis of prostate cancer and detecting a reliable biomarker will offer improved diagnosis, prognosis, and therapy of the disease that will ultimately help us to eliminate prostate cancer.

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Tumorous growth in prostate can either be benign or malignant. Benign, nodular, paraurethral hyperplasia of the prostate (BPH) is one of the most prevalent disease of elderly American men. BPH can develop due to hormonal imbalance due to altered testosterone level, or may be stimulated by testosterone or dihydrotestosterone. Several growth factors may play important role in regulating epithelial and stromal cells in BPH.[1] In the presence of hormonal imbalance, the expression of the growth factor receptors are altered, which leads to increased cellular signaling and stromal cell proliferation. Nodular hyperplasia of the prostate is due to increased proliferation of glandular-epithelial compartment, with simultaneous mesenchymal stromal cell proliferation. This may lead to the alteration of the stromal unit, with inversion of the proliferation compartment, shift of luminal cells, thereby development of adenomatous hyperplasia. If this develops in the peripheral part of the prostate gland, it is termed as prostatic intraepithelial neoplasia (PIN).[1] Histopathologically PIN is regarded as the precursor of prostatic adenocarcinoma. PIN exists with more than 85% of cancer, and clinically it has a strong association with prostatic carcinoma.[2,3] A number of studies have identified differentially regulated genes that are expressed in neoplastic progression of prostatic progression. Differentially expressed genes are predicted to play key roles in prostate cancer development and may also serve as clinically useful biomarker for early detection and diagnosis. Although large sets of genes have been identified, few have been characterized in the molecular progression of the disease. In this review, we will focus on the advancements of crucial prostate cancer oncogenes, which have been established as potential target for therapy.

Growth factor receptors

Insulin growth factor

A number of growth factors have been shown to be implicated in the development of prostate cancer. One of the most studied growth factors in the process of promoting oncogenesis in prostate cancer is insulin-like growth factor (IGF). Although the IGF functions as an endocrine hormone, being predominantly secreted by the liver,[4] it can also act as an autocrine and paracrine hormone, whose local secretion may be a possible stimulus for cell growth in neoplasms.

IGF1 and IGF2 work via the same receptor, a transmembrane glycoprotein[5] with tyrosine kinase activity, IGF1R. Increased expression of IGF1 and IGF2 has been shown via immunohistochemistry to be a positive correlation with serum PSA over 10. Additionally, the same study discovered that IGF2 has a positive statistically significant correlation with Gleason's score.[6]

Epidemiologically, there is a significantly higher elevation serum concentration of IGF levels in patients with prostate cancer compared to normal.[7] The role of IGF in oncogenesis is evident through a number of different studies correlating decreased invasiveness with an inhibition of IGF. Remarkably, even the growth of metastatic prostate cancer tumor in the bone is inhibited by the administration of an IGF1 antibody, KM1468.[8] Reducing the hepatic production and secretion of IGF1 via disruption of growth hormone receptors significantly reduces the early carcinogenesis of prostate.[9]

IGF availability in the serum is regulated *in vivo* by IGF binding protein 3 (IGFBP3).[10] Several cell lines of prostate adenocarcinoma (22Rv1, PC-3, and DU-145) display increases concentrations of IGFBP3 in a dose-dependent manner via treatment with 5-FU; however, a significant decrease in the growth of PC3 was found attributable to a decreased bioavailability of IGF1[11] although IGFBP3 may play a role later in prostate adenocarcinoma migration, and cell-matrix adhesion in an IGF-1 independent mechanism.[12] It can also promote apoptosis in a poorly understood mechanism independent of IGF-1[13] making it debatable if the change in IGFBP3 levels really affected the cells in a IGF-1 independent or dependent manner. The significance of the role of IGFBP3 in regulating active IGF1 can be seen epidemiologically in Korean men revealing that prostate cancer sufferers more likely had lower serum levels of IGFBP3. The epidemiology remains controversial however with a different study suggesting that increased serum levels of IGFBP3 or IGF1 to IGFBP3 ratio are not correlated with likelihood of prostate cancer.[14]

IGF1 interacts with its respective intranuclear receptor, IGFR1. Through the receptor's tyrosine kinase activity[15] several downstream signaling pathways are activated, including the phosphatidylinositol 3-kinase (PI3K), AKT, TOR, S6 kinase, and mitogen-activated protein kinase (MAPK) pathways, by which the antiapoptotic and proneoplastic effects of insulin like growth factor 1 function.

IGF1R has been spotlighted as a major player in prostate carcinogenesis and a major player in possible pharmacologic interventions in prostate cancer. There is a plethora of data suggesting a significant relationship between the increased IGF1R activity and increased prostate carcinogenesis, while at the same time illustrating that inhibition of the pathway will result in the diminished tumor growth. Additionally, it has been shown that both IGF1R protein and mRNA is upregulated in primary prostate cancer, as opposed to benign prostatic hyperplasia.[16]

Reducing the expression of IGF1R via antisense RNA retards

tumor growth of prostate cancer cells.[17] IGF1R may be an essential player in facilitating the continued activity of the androgen receptor, well after castration has occurred. It has been shown that the IGF pathway is capable of inducing the activation of the androgen receptor in the absence of androgens,[18] or in facilitating its translocation into the nucleus, without androgens, although this activation of androgen receptor may rely on the assistance of several other proteins such as beta catenin.[19] The IGFR pathway via its actions on the PI3K/AKT pathway phosphorylates the androgen receptor inhibitor Foxo1.[20] In addition to the direct stimulation of the androgen receptor in an androgen independent pathway, it is apparent that IGF1 pathway may also up regulate proteins that are also up regulated by the androgen receptor. One possible candidate protein is survivin, which is an antiapoptotic caspase inhibitor, which has been shown to be androgen dependent, but can be up regulated in the absence of androgens by the presence of insulin growth factor.[21]

Although androgenic stimulation of the androgen receptor remains essential in stimulating growth of the prostate cells, it is important to note that it is possible for the prostate to continue having an activated androgen receptor, and tumor growth even following the lack of androgenic stimulation via castration. It has therefore been hypothesized that there must be some sort of androgen independent stimulation of the androgen receptor that may be at work in causing the prostate tumor growth. The IGF signaling pathway is a candidate pathway for this functionality. The inhibition of IGF1 signaling by antibody to IGF1R following castration reduced prostate tumor growth much more in androgen-dependent cells than it did mice that underwent castration alone.[22] Although there may be a drop in IGF signaling immediately after castration, the IGF1 signaling pathway remains active throughout the course of the disease.[23] Additionally, IGF1 signaling may also play an important role in migration and invasion in addition to encouraging proliferation and resistance against apoptosis through the possible stimulation of the metalloprotease MT1-MMP[24] and encouraging actin rearrangements in the cytoskeleton that may activate integrins and lead to the promigratory cell behavior.[25]

Wnt

The Wnt signaling pathway is another major of oncogenic signaling pathway involved in the carcinogenesis of prostate cancer. It is apparent that the Wnt pathway is important in the preliminary development of the prostate.[26] The Wnt/B catenin pathway is an important player in prostate oncogenesis, particularly in giving tumor cells their invasiveness. The suppression of Wnt signaling by an inhibitor of the pathway, WIF1, has been shown to significantly reduce the size of tumors in addition to reducing MMP2 and 9 in PC3 cells[27] in addition to increasing the expression of the epithelial metalloprotease, MMP7[28] Foxa2, which may be important in the local invasiveness of prostate cancer is increased by the Wnt signaling pathway. To further highlight the relevance of the Wnt pathway on invasiveness of prostate adenocarcinoma, a study revealed that CamKII, which is a transducer in the Wnt pathway, increases cytoskeletal remodeling and cell motility[29] that may possibly facilitate future tumor invasiveness. A Wnt family protein, Wnt11, confers increased invasiveness for both LNCaP and PC3 cell lines.[30]

Her-2/neu (ERBB2)

The Her2/neu protein is a notorious proto-oncogene that has been implicated in a number of different cancers, particularly in breast cancer and the target of a number of current and experimental therapies.[31] Her2/Neu is a transmembrane tyrosine kinase that is important in assisting differentiation and cell growth. Despite its major role in the diagnosis and treatment of breast cancer, Her2/Neu plays an important role in the understanding of prostate adenocarcinoma oncogenesis. Although Her2/Neu is not necessarily correlated with a Gleason's score,[32] patients suffering from metastatic prostate cancer were more likely to have higher levels of serum Her2/neu versus those with nonmetatstatic or localized disease[33] suggesting that Her2/Neu may be an important marker for advanced disease[34] or clinically worse outcomes;[35] however, Her2/Neu expression does not seem to be related to the Gleason score of the biopsy.[36]

Similar to the other major oncogenes discussed so far, Her2/Neu is capable of activating the androgen receptor in the androgen independent stage. Her2/Neu can promote survival of LNCaP cells through the Akt pathway, even in the absence of androgens. Interestingly, this effect can be halted by the addition of Dn-Akt, an inhibitor of Akt.[37] Additionally, Her2/neu can provide androgen independent activation of the AR via a pathway modulated by both MAPK and c-Jun,[38] which is also important in stabilizing the androgen receptor. This interaction between Her2/neu and the androgen receptor is regulated by an miRNA, miR-331-3p, the addition of which can inhibit both the downstream activation of PI3K/Akt signaling, in addition to reducing the AR-regulated PSA expression.[39] Additionally, Her2/Neu can, via PYK2, help facilitate the cell adhesion that allows for the tumor's metastatic potential.[40] Her2/Neu's relationship with the AR, however, is not universally accepted as LNCaP cells have decreased AR mRNA in addition to decreased AR and AR regulated PSA.[41]

Her2/Neu may also play an important role in the metastasis of prostate cancer into the bone. In patients with bone

metastases, Her2/Neu over expression is associated with a poorer prognosis.[42] As we have described previously, the receptor is also important in facilitating metastasis. The orthotropic transfection of Her2/Neu facilitates changes downstream that allow for the tumor's cell's increased metastatic capacity. A PC-3 cell line that was transfected with orthotropic Her2/Neu produced numerous metastases all over the abdomen, including the retroperitoneum and the kidney.[43] Molecularly, the Her2/Neu receptor is part of a signaling cascade that involves the downstream enhancement of Akt and MMP-9, whereby the cancer cell is allowed to penetrate the matrix and facilitate angiogenesis.[44]

Epidermal growth factor receptor

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is related to the ErbB2, and participates in several signaling cascade including Akt, MAPK, and STAT, whereby it plays an important role in tumor cell growth. Overexpression of EGFR is correlated with time to biochemical relapse[45] and the interference of EGFR with miRNA 28, does allow for increased apoptosis of prostate tumor.[46] Additionally, immunohistochemically speaking, higher association of EGFR was statistically correlated with a higher serum PSA. Additionally, the relevance of EGFR to prostate cancer oncogenesis can be further revealed by the fact that specimens with a diagnosis of Gleason's scores above 7 were significantly more likely to have co-expression of EGFR with an association Her2, c-erb-2[47]

There has been a plethora of studies regarding the targeting of EGFR in chemotherapeutics, in particular, the synthetic antibody Geftinib, which is currently marketed as an EGFR inhibitor for use in non small cell lung cancer. The knockout of EGFR via siRNA resulted in autophagosomes and in increased levels of calpain, a proapoptotic protein both of which are characteristic of apoptosis. Additionally, knocking down EGFR but not altering its tyrosine kinase activity made tumor cells more susceptible to adriamycin, which allowed for increased levels of caspase 3 and 7.[48]

EGFR seems to display a rather complicated interaction with androgens and the androgen receptor. Normally androgens are responsible for the down regulation of EGFR. In the cancer cell, however, the introduction of androgens may increase the levels of EGFR mRNA, and antibody mediated inhibition of EGFR prevented androgen mediated proliferation, although this remains debatable as another study revealed that EGFR was shown to have increased ubiquitination and degradation following activation of the androgen receptor.[49]

Phosphoinositide-3 Kinase/AKT

Phosphoinositide-3 Kinase (PI3K) is a critical mediator of multiple oncogeneic signaling pathways. PI3K is activated by the receptor tyrosine kinases generating PI3, 4P2, and PI3,4,5P3 (PIP3), which acts as secondary messengers triggering downstream signaling events. Most important PI3K downstream targets include Akt family of serine-threonine kinases, which are then recruited by PIP3 to the plasma membrane and phosphorylated by PDK1 kinase. Once phosphorylated, Akt is activated which then promotes cellular proliferation and survival by regulating several downstream targets. The most critical negative regulator of PI3K-Akt pathway includes PTEN, a phosphatase that has high specificity for lipid substrates.[50] In prostate cancer, PTEN is frequently lost resulting in hyperactive PI3K/Akt pathway promoting prostate cancer progression.

Somatic alterations in the *PTEN* gene have been identified in prostate cancer patients for both localized and metastatic disease. These include deletions, and inactivating missense and nonsense mutations in ~15% of primary tumors.[51] PTEN alterations are more common in metastatic cancers and studies have identified biallelic loss of PTEN in ~50% of metastatic hormone-refractory prostate cancer.[52] Genomic amplifications in AKT1 and AKT2 in prostate cancer are rarely found, however, loss of PTEN results in constitutively activated Akt which promotes tumor growth. Crucial downstream signaling cascade of PI3K/Akt include mTOR pathway that is deregulated by loss of function mutations in PTEN. Activated mTOR phosphorylates substrates critical for protein synthesis, including ribosomal subunit S6 kinase (S6K) and initiation factor 4E-binding protein 1(4E-BP-1) thereby activating protein translation and tumor growth.[53] Akt/mTOR-dependent stabilization of Hif1α transcription factor and increased expression of Hif1α target genes have been detected in PIN mouse models[54] that includes enzymes of the glycolytic pathway.

We have identified a novel gene *MIEN1* (previously referred to as C17orf37) highly overexpressed in prostate cancer, which modulates the Akt activity as a membrane bound adapter protein.[55] MIEN1 is post-translationaly modified by addition of prenyl groups that translocates the protein to the inner face of the plasma membrane.[56] Ectopic expression of MIEN1 activates Akt and cascades downstream signaling through NF-κB pathway upregulating expression of several migratory and invasive genes. MIEN1 may act as a scaffolding protein blocking PTEN binding to Akt; however, the exact mechanism is not known.

Targeting PI3K-Akt pathway to treat prostate cancer patients is an active area of research. Several small molecule inhibitors

have been developed that are currently undergoing clinical trials for prostate cancer therapy. mTOR inhibitor RAD001 (everolimus) is currently under clinical trials for castration resistant prostate cancer (CRPC) patients either alone or in combination with gefitinib. A new mTOR inhibitor AP23573 is currently in phase II clinical trials as a single agent treatment for CRPC patients. PI3K and Akt are also attractive drug targets for prostate cancer therapy, but despite serious efforts inhibitors targeting the kinase activity lack specificity.[57]

Proteases

The MMPs and promigration

Like the Wnt pathway, the MMPs are essential in facilitating the invasiveness of prostate cancer. These proteins are important in the degradation of the extracellular matrix, whereby the invasive prostate cancer cells can metastasize to distant site throughout the body [Figure 1]. Additionally, this protease activity, not only allows for cell migration, but also plays a role in facilitating angiogenesis, whereby the tumor in provided with nutrition allowing its continued proliferation. In bone metastases, the prostate metastatic tissue might allow for angiogenesis via the MMP9 derived from osteoclasts.[59] As such, the metalloproteases are particularly important players later on in prostate cancer, when the cancer is most invasive. Some of the MMPs have a higher expression with higher Gleason's scores.

The targeting of the zinc proteases has become a major spotlight in possible future chemotherapeutic interventions.[60] Of the many different members of the homologous MMP family, MMP 2, 7, and 9 in addition to

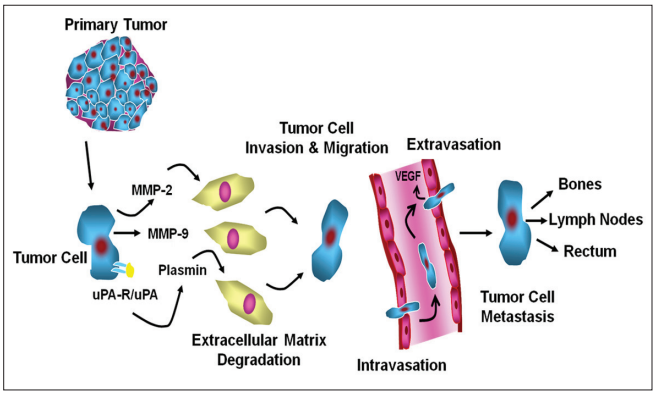

Figure 1: Multistep metastatic process of prostate cancer cells. The molecular basis of tumor progression depends on local invasion, intravasation, survival in the circulation, extravasation and colonization. Tumor cells secrete several factors including proteases like MMPs and plasmin which degrade extracellular matrix facilitating their migration and invasion. Tumors cells then intravasate through the endothelial lining of blood vessels into the circulation, and extravasate to distant organs like lymph nodes, bones and rectum. Prostate cancer cells then colonize and proliferate in foreign tissue thereby spreading the disease. (Taken from Dasgupta S, Ph.D thesis,[58])

MT1MMP are the most relevant in terms of relevance in prostate adenocarcinoma metastasis. There is a particularly higher level of MMP9 expression in prostate cancer compared with other cancers. While the lack of MMP 2, 7, or 9 in CR2-Tag mice all can lead to reduced tumor vascularity, the dearth of MMP2 also conferred decreased lung metastasis and increased survival, while interestingly, the lack of MMP 9 lead to increased perivascular invasion, in addition to reduced vessel size,[61] highlighting the unique functions that the different members of the MMP family have. Several of the major metalloproteases related to prostate adenocarcinoma, namely MMP 2, 9, and MT1MMP are inhibited by the DNA enzyme Dz13, which reduced tumor growth of PC3 cells.[60]

MMP 9

MMP 9 is a major player in prostate adenocarcinoma invasiveness. Pathologically speaking, higher levels of matrix metalloproteinase 9 as revealed by DAB staining, is correlated with higher Gleason's score, with 94.1% of cancer cell expressing MMP9 in the cytosol. It is apparent, therefore, that MMP9 expression intracellularly is directly correlated with a tissue Gleason's score.[62] With MMP-9 there is a correlation between an increase in MMP9 expression and the loss of PDEF, a possible inhibitor of MMP9, the loss of which results in a more aggressive phenotypic prostate cancer,[63] and to further confirm the relationship of aggressiveness with MMP9, downstream silencing of MMP-9 *in vivo* reduces the amount of metastasis of prostate cancer.[64] Normally, proMMP9 is in complex with tissue inhibitor of metalloproteinase (TIMP), preventing its immediate action. In the case of the neutrophils, however, lies an exception to this rule, releasing proMMP9 without its inhibitor, TIMP.[65]

MMP 7

The elevated expression of MMP7 in both the serum and resected prostate tissue is associated with a poorer prognosis[66] most likely due to the more invasive phenotype that increased levels of MMP7 confers. Although there has not been a published correlation between the expression of MMP7 and Gleason's score, a study investigating the serum levels of various MMPs in relation to the invasiveness of the prostate cancer, found that individuals with distant metastases, circulating serum MMP7 was significantly elevated, suggesting that MMP7 is a protein particularly more relevant in facilitating prostate cancer's distant metastases.[66] The applicability of such techniques has been shown through a number of different studies. One possible protein that MMP7 may interact with is a metalloproteinase regulator, E1AF, which is correlated with a more metastatic phenotype in prostate adenocarcinomas.[67] An additional role for MMP7 in prostatic adenocarcinoma can be seen in bone metastases. The secretion of MMP7 by both osteoclasts and the tumor

cells allows for the solubilization of osteoblast RANKL, which activates osteoclasts and tumor mediated osteolysis.[68]

MMP 2

MMP2 is another major metalloproteinase, whose activity is important in the invasiveness and metastasis of prostate cancer. Its expression and upregulation is associated with Rho mediated activation of Pyk2, FAK, MAPK, and Akt.[69] Similar to the other MMPs discussed polymorphisms in *MMP2* gene is correlated with a higher Gleason's score.[70] In a study investigating the immunohistochemistry with the Gleason's score of various MMPs, it was found that the tissues that observed the highest level of MMP2 expression, also had the highest grade prostate cancer, as determined by their Gleason's score, scores between 8 to 10, suggesting MMP2's possible oncogenic role in prostate cancer.[71] Several studies have found many different influences on the expression of MMP2. In WPMY-1 cell stroma, ER stimulation either by estradiol, or by an agonist of the receptor increased the expression of MMP2 in the stroma indirectly via increased production of TGF-β, the inhibition of which yielded MMP2 levels comparable to that of the control.[72] Cyclin A1 may also play a role in influencing MMP2 production, in that areas of prostate tumor tissues with high expression of cyclin A1 are correlated with high expression of MMP2 and cells over expressing cyclinA1 also had statistically higher levels of MMP2.[73]

Transcription factors and coactivators

TMPRSS2-ERG

Recurrent genomic rearrangement in prostate cancer results in the fusion of androgen regulated gene *TMPRSS2* to *ERG*, which encodes an oncogenic transcription factor ETS. ETS family of transcription factors can bind specifically to DNA sequence 5′-GGA(A/T)-3′ in the promoter of genes and thus can regulate expression of genes involved in different pathways including proliferation, migration, and oncogenesis. Expression of TMPRSS2-ERG fusion transcript has been found in the early stages of prostate carcinogenesis prevalent in the low-grade prostate intraepithelial neoplasia (PIN).[74] FISH analysis has also confirmed 16–20% of ERG rearrangements in high grade PIN,[75] suggesting TMPRSS2-ERG an early event in prostate carcinogenesis. However, certain studies have identified increased ERG and ETV1 expression in metastatic prostate cancer both in androgen-dependent and castration-resistant disease,[76-78] suggesting *ETS* gene fusions can be maintained in advanced disease.

ETS gene perturbations in prostate cancer primarily involve fusions with androgen-activated genes and majority of studies have focused on mechanistic role of the fusion genes in carcinogenesis. In cultured prostate cancer cells androgen treatment induces ERG expression in cell lines harboring TMPRSS2-ERG fusion,[76] but not in androgen insensitive cells carrying the fusion gene.[79] Additional fusion partners have been identified for ETV1, ETV4, and ETV5 that includes TMPRSS2(21q22), SLC45A3(1q32), HERV-K(22q11.23), HERV-K17(17p13.1), FOXP1(3p13), C15orf21(15q21.1), HNRPA2B1(7p15), KLK2(19q13.33), CANT1(17q25.3), DDX5(17q24.1). Most of these translocation partners contribute to androgen inducible sequences, except C15orf21 which is repressed by androgen treatment and HNRPA2B1 insensitive to androgens.[76,80] Thus, differential androgen responsiveness driving *ERG* gene fusion could affect androgen ablation therapy in prostate cancer patients, and may provide resistance to androgen withdrawal therapy.

Aberrant expression of ETV1 in prostate cancer cells results in increased invasiveness, a phenotype associated with malignant progression of the disease.[81] Transgenic mice overexpressing prostate specific ETV1 develops mouse PIN[82] consistent with the clinical observations in human patients, although it failed to develop tumor thus suggesting gene fusions are early events in prostate tumorigenesis. However, other investigators demonstrated knockdown of TMPRSS2-ERG expression resulted in reduced cellular proliferation and tumor growth in nude mice, suggesting ERG and ETV1 as potential therapeutic target.[83,84]

Several strategies have been used to block the *ETS* gene function including dominant negative mutants, antisense, and RNAi knockdown that were effective *in vitro* but less so *in vivo*.[85] Other approaches include inhibiting modulators of ETS transcription factors such as upstream signaling kinases and also downstream targets of ERG protein to block its activity.[86] Discovery of estrogen, progesterone, retinoic acid pathway alterations in nonandrogen responsive prostate cancers containing *ETS* gene rearrangements, suggests additional drug targets.[87]

Understanding the mechanisms of *ETS* gene translocations in prostate cancer has certainly provided important breakthrough about the disease. Clinically however the prognostic importance of *ETS* gene rearrangement is still controversial and additional studies are needed to identify and verify different variants of translocations. Furthermore, differential regulatory networks that drives ETS oncogenic rearrangements in prostate cancer with respect to androgen signaling need to be elucidated. This will provide additional benefits in treating the disease for both androgen responsive and castration resistant metastatic prostate cancer patients. Discovery of alternative estrogen signaling pathway signature genes also provide potential clues to elucidate mechanism of *ETS* gene activation in androgen insensitive cases.

MYC

One of the most commonly studied oncogene in prostate cancer pathogenesis is MYC, a regulator gene that codes for transcription factor. MYC is thought to regulate 15% of all genes in humans and is located in the human genome on chromosome 8q24 amplicon that is frequently amplified in prostate cancer patients. FISH analysis identified MYC overexpression in ~9% of primary prostate tumors but ~75% in advanced prostate cancer patients.[88] In a separate study, using comparative genomic hybridization investigators detected gain of the 8q region in 72.5% of cases whereas only 29% of them had genomic amplification as identified by FISH.[89] MYC overexpression has also been correlated with FOXP3 downregulation, and deletion of FOXP3 in human primary prostate cells resulted in concomitant increased MYC mRNA and protein level. At molecular level, FOXP3 binds to the promoter region of MYC and repress its transcription, and hence loss of FOXP3 increased MYC expression in prostate cancer patients.[90]

In vitro overexpression of MYC by viral transduction transformed prostate epithelial cells and immortalizes the cells in single step that were sufficient to generate tumors with increased proliferative capacity. Genetically engineered mouse models overexpressing MYC have been developed which uses either modified rat probasin promoter to drive MYC expression known as LOW-MYC or ARR_2/probasin promoter known as Hi-MYC.[82] These mouse models develop PIN and progress to invasive adenocarcinomas; however, the kinetics of tumor progression is different.

Several important MYC target genes, commonly known as MYC signature, have been identified which regulates numerous pathways involved in prostate cancer progression and metastasis. MYC regulates the transcription of these signature genes directly or indirectly in prostate cancer cells. One of the most well studied MYC downstream target gene includes PIM1, a serine/threonine kinase which has been identified to be frequently upregulated in subset of prostate cancers with poor clinical outcome.[91,92] *In vitro* and *in vivo* studies indicated that PIM1 alone is insufficient or weak to transform prostate cells, but in combination with MYC overexpression has increased proliferative rate. PIM1 also enhances the MYC transcriptional activity by directly phosphorylating histone H3 at MYC binding sites thereby enhancing transcription of MYC signature genes.[93] Another corollary experiment by inhibition of MYC resulted in reduced tumorigenicity of PIM1 overexpressing prostate cancer cells, validating the functional cooperation of the two proteins. NKX3.1 is a pleiotropic transcription factor that is involved in prostate gland development and morphogenesis, but lost during cancer pathogenesis and progression.[94] However, some studies have detected NKX3.1 expression in high grade invasive and metastatic prostate cancer patients.[95] In MYC transgenic prostate cancer mouse models, loss of NKX3.1 have been observed with the development of adenocarcinoma, suggesting MYC can repress NKX3.1 expression. This suggests oncogenic activation of MYC can block tumor suppressor protein resulting in the pathogenesis of prostate cancer.

Several therapeutic strategies have been used to target MYC and its signature genes in prostate cancer. Antisense oligonucleotides specifically designed to target MYC mRNA have been shown to reduce MYC protein resulting in reduced nuclear entry and decreased stability of the protein. *In vivo* studies utilizing mouse xenografts, MYC antisense oligonucleotides reduced tumor growth by suppressing tumor cell proliferation and increased animal survival.[96] One particular antisense with modified oligomer diamidate moroholino directed against MYC showed promising efficacy in phase I clinical trials with limited side effects and toxicity. These studies suggest antisense therapeutic approach targeting MYC may be beneficial for cancer treatment.

Another therapeutic approach utilizing cardiac glycosides to target MYC has shown promising effects in prostate cancer development. Both *in vivo* and *in vitro* studies demonstrated the antitumor potential of cardiac glycosides, particularly synthetic cardnolide UNBS1450 that blocks several MYC signature genes and inducing apoptosis.[97] This compound also showed reduced toxicity in normal cells; however, exact mechanism of its action is poorly understood.

Oncogenic transcriptional coactivators

Transcription factors and nuclear receptors bind to coregulatory molecules (coactivators or corepressors) that directly or indirectly regulate the transcription by recruiting several proteins to build the transcription complex at the target gene promoter. The most important nuclear receptor in context of prostate cancer is AR, which belongs to the large nuclear receptor superfamily of ligand activated transcription factor. In the absence of hormone, AR is located in the cytoplasm bound to heat shock proteins (hsp) but upon hormone induction dissociates from the hsp protein complex, dimerizes and translocates to the nucleus. AR dimer binds to specific DNA sequences known as androgen response elements (ARE) and recruits series of coactivator molecules necessary for chromatin remodeling and transcriptional complex. Large number of AR coactivators have been identified that are known to the potentiate AR activity,[98] of which steroid receptor coactivators (SRCs) have been studied extensively.

SRCs also known as Nuclear Receptor Coactivators (NCOA) consists of three homologous proteins SRC-1, SRC-2 and SRC-3 comprising the p160 SRC family. SRCs have three distinct structural domains that include most conserved region bHLH-PAS for protein–protein interaction, central nuclear receptor interacting domain containing three LXLL motifs, and C-terminal two transcriptional activation domains (AD1 and AD2). In addition to interacting with nuclear receptors, SRCs coactivates other transcription factors including NF-κB, STATs, HIF1, and Smads. Along with these transcription factors, SRCs have been found to be highly overexpressed or amplified in prostate cancer. Studies have shown SRC-1 messenger and protein expression positively correlates with prostate tumor grades; however, frequency of SRC-1 gene amplification in prostate cancer patients is less. SRC-1 can enhance AR-dependent growth of prostate cancer cells in culture, and knockdown of SRC-1 can significantly reduce growth of LNCaP cells. However, in AR-negative PC-3 and DU-145 cells SRC-1 has minimal effect, suggesting SRC-1 promotes prostate cancer growth by enhancing AR function. Expression of SRC-2, another member of SRC family has been found to be increased in prostate cancer and correlates positively with grade and stage of cancer. Recently, integrative genomic profiling has identified SRC-2 to be highly overexpressed in prostate cancer patients and has been classified as an oncogene in prostate cancer pathogenesis. Out of 218 prostatic tumors, 8% of primary tumors and 37% of metastatic tumors showed gain in SRC-2 expression.[99] Microarray analysis also confirmed increased expression of SRC-2 correlated with tumor proliferation and inhibition of apoptosis. Prostate cancer patients who underwent ADT, showed increased expression of SRC-2, and *in vitro* studies confirmed that high levels of androgen can repress SRC-2 expression, suggesting androgen ablation therapy can lead to increased SRC-2 in prostate cancer patients. Functionally, SRC-2 acts as potent transcriptional coactivator of AR, thereby modulating expression of AR target genes in both androgen dependent and castration resistant prostate cancer (CR-CaP) cells.[100,101] SRC-3 expression has been found to be increased in 38% of prostate cancer patients and its expression positively correlates with disease recurrence.[102] Mechanistically, SRC-3 regulates Akt-mTOR growth promoting pathways in prostate cancer cells and silencing of SRC-3 reduces tumor proliferation both *in vitro* and *in vivo*.[103,104] Functional role of SRC-3 was also evaluated in spontaneous TRAMP mouse models of prostate cancer, in which SRC-3 expression was higher in the advanced stages of the disease. SRC-3 gene deletion significantly increased TRAMP mice life expectancy suggesting SRC-3 inhibition may be an attractive therapeutic strategy for prostate cancer patients.[105]

Although several strategies have been used to silence SRCs to study their role in prostate cancer, effective inhibitors targeting the coactivators are still lacking. Disrupting the androgen receptor-SRC interaction using small molecule inhibitors or peptides may be a possible strategy along with conventional direct targeting of the coactivators using small molecules for prostate cancer therapy.

CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Over the last two decades increased research efforts to understand the basic nature of prostate cancer biology has advanced our understanding about the disease. However, a number of fundamental questions concerning the heterogeneity of the disease, resistance to prevailing therapies, and therapeutic opportunities for advanced metastatic prostate cancer will be the prime focus for prostate cancer researchers. Technological advances to define the intricate details and molecular circuits within tumor cell and tumor microenvironment will identify prospective targets for prostate cancer.

Recent research has succeeded in implicating several oncogenic activations, either through genomic or nongenomic pathways, to neoplastic progression of prostate cancer cells

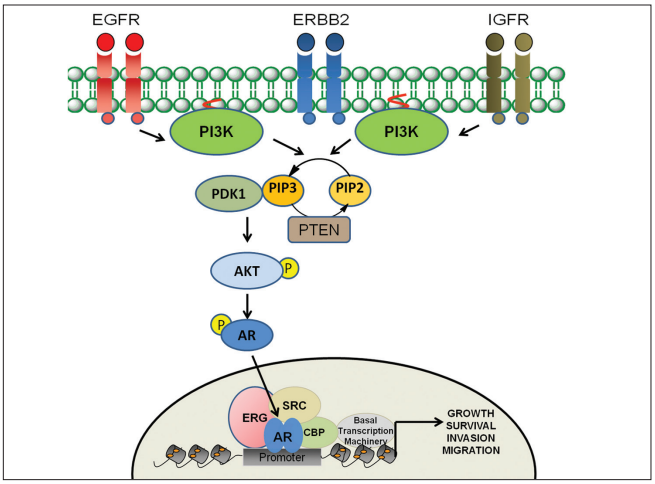

Figure 2: Cellular localization of various oncogenes and their signaling network promoting growth and survival of prostate cancer cells. Overexpressed growth factor receptors on ligand binding activate PI3K which converts PIP2 to PIP3. Phosphoinositide dependent kinase (PDK1) then binds to PIP3 and phosphorylate Akt. In prostate cancer, loss of PTEN, a lipid phosphatase responsible for converting PIP2 back to PIP3 favors in constitutively activated Akt which then phosphorylates and activates broad range of transcription factors including AR. Activated AR translocates to the nucleus and recruits general transcription factors, coativators (SRC), and other transcription machinery at the target gene promoter enhancing growth, survival and invasiveness. Fused oncogenes like ERG, an AR target gene can also upregulate expression of several genes promoting prostate cancer progression.

[Figure 2]. These hyperactive oncogenes confer metabolic and growth promoting advantages to tumor cells, which differ enormously within patient population. Understanding the genetic nature of prostatic tumor will be important for effective personalized treatment opportunity for prostate cancer patients. Growing concern lies in understanding the metastatic potential of primary prostatic tumor and ways to distinguish the lethal from dormant tumor subtype. Metastasis research over the years has identified several important molecules in the regulation of biological activities of tumor cell invasion and migration. Detailed understanding has identified potential oncogenes and their functional activities that provide prostate tumor cells invasive and migratory power to cross the primary tumor site and colonize at a distant organ. We hope that with this rapid pace of discovery continued with simultaneous translation of basic findings to clinical arena will offer us effective ways to treat and finally eliminate prostate cancer.

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