Prostate Cancer Indolence

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There has been recent work demonstrating a use of gene products as a marker for indolent versus aggressive Prostate Cancer. This report discusses some of the results and examines some implications. We also attempt to look at the markers in a holistic manner and also as a causative approach.

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Contents

1 INTRODUCTION

One of the most critical tools for assessing prostate cancer in its earlier stages is the potential for the tumor to be or become an aggressive tumor. Most PCa tumors are indolent, growing at a slow rate and often not being the ultimate cause of death. However there are a few PCa which are quite aggressive going from a low level to death in a short period, just two to four years. Being able to identify these tumors is becoming a significant area of study. Morbidity and costs can be significantly reduced if one can identify what cell hold the potential for such aggressive growth.

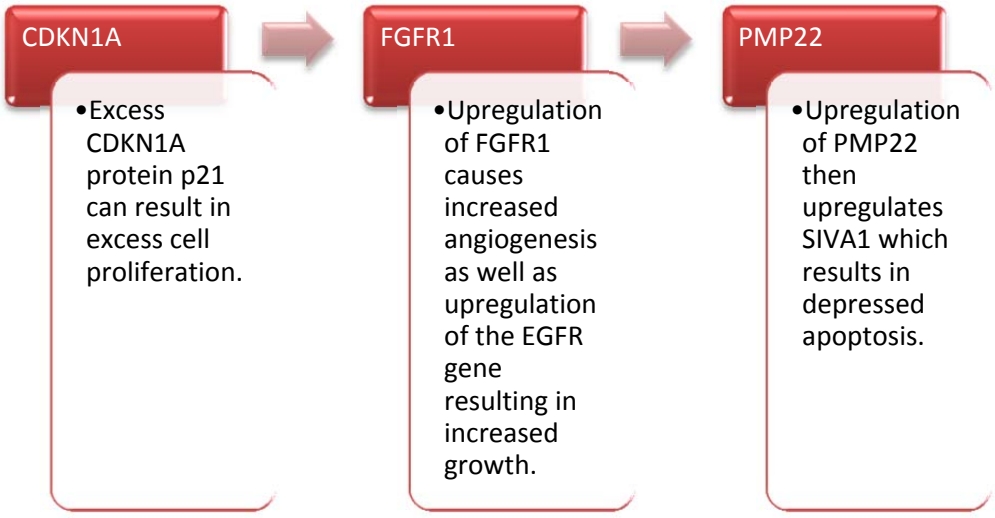
In a recent paper by Irshad et al presents three markers that they contend are significant for ascertaining aggressiveness. The genes and markers are:

1. CDKN1A, a gene which encodes a protein p21. This is a cyclin dependent kinase ("CDK") inhibitor. The CDKs function as cell cycle controls and by inhibiting them the cell cycle, namely proliferation, can be inhibited. p21 expression is controlled by p53 and by the PI3K/AKT pathway which itself is controlled by PTEN. Thus failure of either PTEN or p53 can lead to down regulation of p21 and thus up regulation of cell cycle proliferation. This is a logical gene product to measure.

2. FGFR1: This is a fibroblast growth factor gene. It has a powerful impact on angiogenesis and thus can be a significant factor in the development of blood flow to tumors. Excess expression of the gene may be a significant factor in malignant angiogenesis. It also is a driver for the EGFR gene which in turn is a growth factor modulator as well.

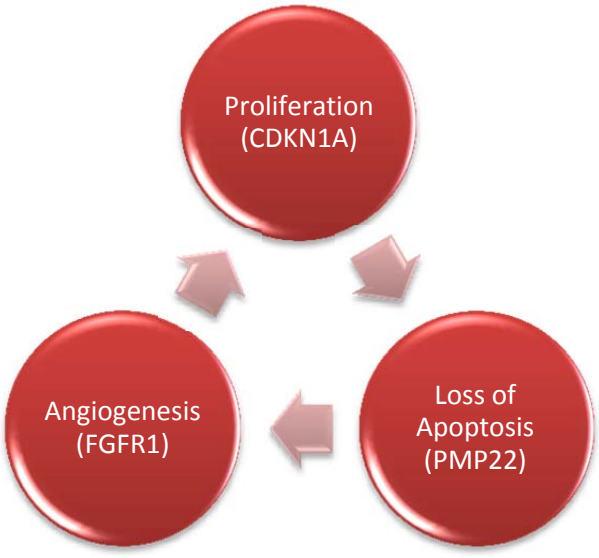
3. PMP22: This gene encodes a protein which relates to peripheral myelin control. Mutations in this gene result in Charcot–Marie–Tooth disease (CMT), a hereditary neuropathy of the distal joints and muscles. However PMP22 controls SIVA1 which is a critical gene controlling apoptosis. Thus any down regulation of this gene would logically down regulate apoptosis and allow the cell to survive. Combined with the CDKN1A dysregulation we then have a potentially lethal spiral.

Thus we have three separate and distinct factors which we summarize below in the graphic.



Thus there may be some significant impact on the aggressiveness of tumors with aberrant expression of these genes.

We therefore have a putatively deadly spiral which results in the aggressive form of PCa as we graphically demonstrate below:



The authors summarize their work as follows:

Many newly diagnosed prostate cancers present as low Gleason score tumors that require no treatment intervention. Distinguishing the many indolent tumors from the minority of lethal ones remains a major clinical challenge.

We now show that low Gleason score prostate tumors can be distinguished as indolent and aggressive subgroups on the basis of their expression of genes associated with aging and

senescence. Using gene set enrichment analysis; we identified a 19-gene signature enriched in indolent prostate tumors.

We then further classified this signature with a decision tree learning model to identify three genes—FGFR1, PMP22, and CDKN1A—that together accurately predicted outcome of low Gleason score tumors. Validation of this three-gene panel on independent cohorts confirmed its independent prognostic value as well as its ability to improve prognosis with currently used clinical nomograms.

Furthermore, protein expression of this three-gene panel in biopsy samples distinguished Gleason 6 patients who failed surveillance over a 10-year period. We propose that this signature may be incorporated into prognostic assays for monitoring patients on active surveillance to facilitate appropriate courses of treatment.

One must ask if these genes are the cause of the effect; if the cause then why and if the effect then what is driving them? We examine some details herein and discuss the results.

2 ELEMENTS

We first summarize the details on each of the genes. This is done in the following Table. We also present some ancillary data worth examining.

Gene	***Location***	***Function***
FGFR1[1]	*8p12*	*The protein encoded by this gene is a member of the fibroblast growth factor receptor (FGFR) family, where amino acid sequence is highly conserved between members and throughout evolution. FGFR family members differ from one another in their ligand affinities and tissue distribution.* *A full-length representative protein consists of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain.* *The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation. This particular family member binds both acidic and basic fibroblast growth factors and is involved in limb induction.* *Mutations in this gene have been associated with Pfeiffer syndrome, Jackson-Weiss syndrome, Antley-Bixler syndrome, osteoglophonic dysplasia, and autosomal dominant Kallmann syndrome 2. Chromosomal aberrations involving this gene are associated with stem cell myeloproliferative disorder and stem cell leukemia lymphoma syndrome. Alternatively spliced variants which encode different protein isoforms have been described; however, not all variants have been fully characterized.* *The heparin-binding growth factors are angiogenic agents in vivo and are potent mitogens for a variety of cell types in vitro. There are differences in the tissue distribution and concentration of these 2 growth factors.*[2]
PMP22[3]	*17p12*	*This gene encodes an integral membrane protein that is a major component of myelin in the peripheral nervous system. Studies suggest two alternately used promoters drive tissue-specific expression.* *Various mutations of this gene are causes of Charcot-Marie-Tooth disease Type IA, Dejerine-Sottas syndrome, and hereditary neuropathy with liability to pressure palsies. Alternative splicing results in multiple transcript variants.*
CDKN1A[4]	*16p21*	*This gene encodes a potent cyclin-dependent kinase inhibitor. The encoded protein*

[1] http://www.ncbi.nlm.nih.gov/gene/2260

[2] http://string-db.org/newstring_cgi/show_network_section.pl?identifier=993654&additional_network_nodes=10&chemicalmode=-1&input_query_species=9606&interactive=no&internal_call=1&limit=10&minprotchem=0&network_flavor=actions&previous_network_size=11&required_score=400&sessionId=VKykuVYmhEFX&targetmode=proteins&userId=CY1OMLuTnCFR

[3] http://www.ncbi.nlm.nih.gov/gene/5376

Gene	*Location*	*Function*
		binds to and inhibits the activity of cyclin-CDK2 or -CDK4 complexes, and thus functions as a regulator of cell cycle progression at G1. *The expression of this gene is tightly controlled by the tumor suppressor protein p53, through which this protein mediates the p53-dependent cell cycle G1 phase arrest in response to a variety of stress stimuli.* *This protein can interact with proliferating cell nuclear antigen (PCNA), a DNA polymerase accessory factor, and plays a regulatory role in S phase DNA replication and DNA damage repair.* *This protein was reported to be specifically cleaved by CASP3-like caspases, which thus leads to a dramatic activation of CDK2, and may be instrumental in the execution of apoptosis following caspase activation. Multiple alternatively spliced variants have been found for this gene.*
SIVA1[5]	*14q32*	*This gene encodes a protein with an important role in the apoptotic (programmed cell death) pathway induced by the CD27 antigen, a member of the tumor necrosis factor receptor (TFNR) superfamily. The CD27 antigen cytoplasmic tail binds to the N-terminus of this protein. Two alternatively spliced transcript variants encoding distinct proteins have been described.*

In the next section we discuss these genes in detail and discuss their pathways and related genes.

[4] http://www.ncbi.nlm.nih.gov/gene/1026

[5] http://www.ncbi.nlm.nih.gov/gene/10572

3 PATHWAYS

We briefly examine the three genes and their pathways. These three genes are quite disparate and do not appear to have any common functionality or proximate causality in cell degeneration.

1. PMP22 is a myelin controlling gene which is connected to Charcot Marie Tooth disease a disorder of the distal muscles where in there is a degenerative process resulting in such characteristics as club foot.

2. FGFR is a fibrogen growth receptor which when activated can create fibrogen.

3. CDKN1A is a cyclin kinase and a significant factor in cell cycle activation.

3.1 PMP22

Peripheral Myelin Protein 22 (PMP22) is a product of a gene related to myelin production. In addition a disruption in its function is often seen in Charcot Marie Tooth disease, a myelo-disruptive disease of the distal muscles.

As D'Urso et al had stated:

Recent molecular and genetic studies have provided some insights into the structure and function of one of the integral membrane proteins of peripheral myelin, the peripheral myelin protein 22 (PMP22). The pattern of expression of PMP22 is synchronous with myelin formation, and it localizes almost exclusively in the compact sheath

They conclude by stating:

In summary, our data provide the first direct evidence for the formation of P0–PMP22 complexes at the plasma membrane. These protein interactions probably participate in holding adjacent Schwann cell membranes together and in stabilizing myelin compaction. Our results could explain why genetic alterations in one of the two partner molecules lead to very similar disease phenotypes.

Normally, a critical number of functional P0 and PMP22 molecules are necessary to maintain membrane adhesion and myelin compaction. Mutations could affect the amount of functional PMP22 or P0 in the myelin membrane through either impaired membrane targeting of the mutated protein or the disability of the altered protein to establish correct interactions with the partner molecule because of changes in their conformation. We believe that the outcome of the present study provides new insight into the molecular basis of myelin assembly and peripheral dysmyelinating diseases.

As Sereda and Nave state:

The most frequent genetic subtype of Charcot-Marie-Tooth disease is CMT1A, linked to chromosome 17p11.2. In the majority of cases, CMT1A is a gene dosage disease associated with a 1.5 Mb large genomic duplication.

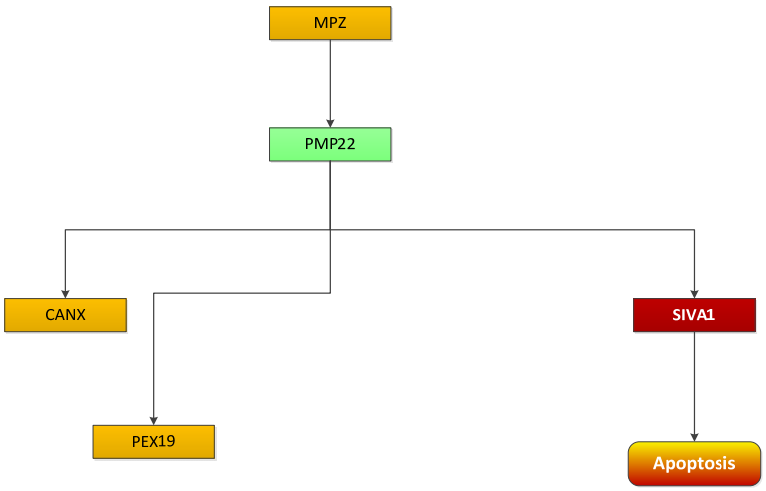
Transgenic models with extra copies of the Pmp22 gene have provided formal proof that overexpression of only this candidate gene is sufficient to cause peripheral demyelination, onion bulb formation, secondary axonal loss, and progressive muscle atrophy, the pathological hallmarks of CMT1A. The transgenic CMT rat with about 1.6-fold PMP22 overexpression exhibits clinical abnormalities, such as reduced nerve conduction velocity and lower grip strength that mimic findings in CMT1A patients

From Bolus we have:

A vast majority (over 70%) of CMT cases are due to a DNA duplication event that consequently leads to abnormal levels of protein synthesis, which disrupts the normal myelin sheath of peripheral nerves. The duplicated section of DNA is approximately 1.5 Mb in length and located on chromosome 17 region p11.2-p12. Within this region is the gene that codes for Peripheral Myelin Protein 22 (PMP22). As the name suggests, this protein plays a significant role in the myelin formation among peripheral nerves. The phenotype of classic CMT is a caused by a "gene dosage effect". A healthy individual will have two normal copies of PMP22, one from the mother and one from the father.

Disease is present when this dosage is altered. When there is a single copy of PMP22 (deletion of one copy), a mild phenotype is present; Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). When three copies of PMP22 are present (duplication of one copy), a more severe phenotype is present; recognized as Charcot Marie Tooth Type 1A (CMT1A). Four copies of PMP22 (duplication of both copies), though rare, result in the most severe phenotype Dejerine-Sottas Syndrome (DDS)

The putative simplified pathway elements of PMP22 are shown below:



http://string-db.org/newstring_cgi/show_network_section.pl?identifier=979938%20989600%20988870%20977586%20983338%20985581%20994422&additional_network_nodes=10&caller_identity=gene_cards&chemicalmode=-1&input_query_species=9606&interactive=no&internal_call=1&limit=10&minprotchem=0&network_flavor=actions&previous_network_size=17&required_score=400&sessionId=pwLyW63vL4Lp&targetmode=proteins&userId=i3j2aCYMAb4y

It demonstrates the effect on SIVA1 gene product and the inhibition of apoptosis. As we have stated from NCBI:

This gene encodes a protein with an important role in the apoptotic (programmed cell death) pathway induced by the CD27 antigen, a member of the tumor necrosis factor receptor (TFNR) superfamily. The CD27 antigen cytoplasmic tail binds to the N-terminus of this protein. Two alternatively spliced transcript variants encoding distinct proteins have been described.

3.2 FGFR

The FGFR appears to have a significant effect on angiogenesis and growth. This is essential for an aggressive tumor.

As Yang et al state regarding the function of FGFR:

The fibroblast growth factor receptor FGFR1 is ectopically expressed in prostate carcinoma cells, but its functional contributions are undefined. … Mice lackingFGFR1 in prostate cells developed smaller tumors that also included distinct cancer foci still expressing fgfr1 indicating focal escape from gene excision.

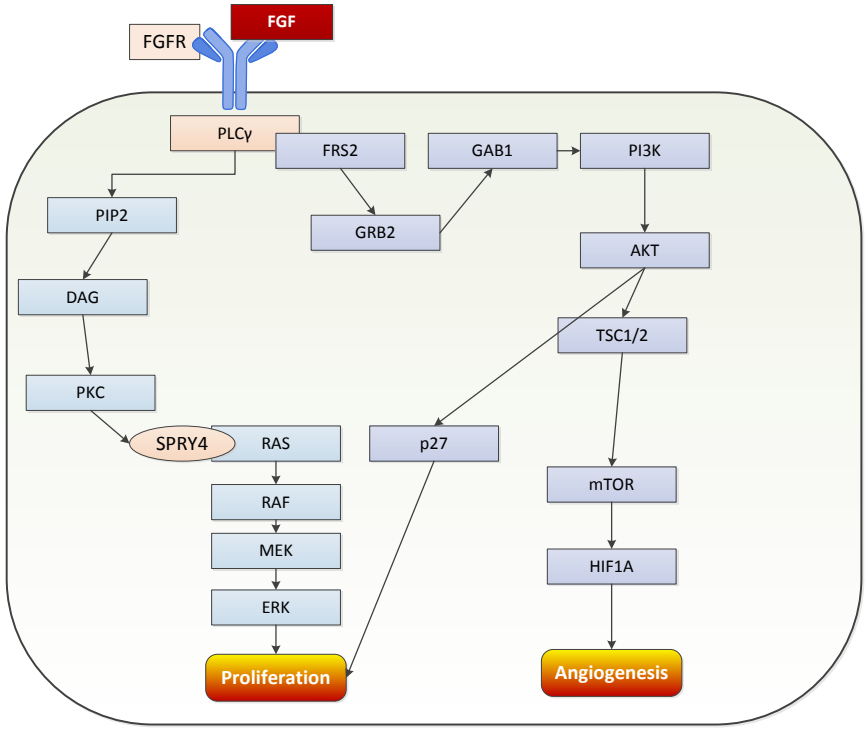
Tumors with confirmed FGFR1 deletion exhibited increased foci of early, well-differentiated cancer and phyllodes-type tumors, and tumors that escaped fgfr1 deletion primarily exhibited a poorly differentiated phenotype. Consistent with these phenotypes, mice carrying the fgfr1 null allele survived significantly longer than those without FGFR1 deletion.

Most interestingly, all metastases were primarily negative for the FGFR1 null allele, exhibited high FGFR1 expression and a neuroendocrine phenotype regardless of FGFR1 status in the

primary tumors. Together, these results suggest a critical and permissive role of ectopic FGFR1 signaling in prostate tumorigenesis and particularly in mechanisms of metastasis.

Clearly in murine models it is a gene which if uncontrolled has highly aggressive characteristics.

From Acevedo we have the following pathway characterization (as modified and simplified:



Note that it reflects on both angiogenesis and proliferation. The above has been somewhat simplified to highlight the key elements. The FGFR is activated by the FGF, one of many growth factors.

3.3 CDKN1A

As Bunz relates there is a direct connection between p53 and the regulation of cell cycle dynamics. CDKN1A is a direct target of p53 transcriptional transactivation. CDKN1A encodes the gene p21 which is a universal CDK, cyclin dependent kinase, which regulates multiple cell cycle transitions. Thus having an activated and over-expressed p21 with excess CDKN1A we have a significant driver to cell cycle activation and resulting cell proliferation.

p53 associates with a binding motif in the CDKN1A promoter and significantly increases CDKN1A transcription. Cancer cells which have impaired p53 also have impaired CDKN1A transcription and thus the cell is restricted in managing cell cycle response to damaged and incompletely chromosomes[6].

[6] See Bunz, p 222.

As Bau et al state:

The protein p21 (Cdkn1a/Waf1/Cip1), encoded by the CDKN1A locus, is a universal inhibitor of cyclin-dependent kinases (Cdks), which suggests its widespread role in regulating the cell cycle. The human CDKN1A gene consists of three exons of 68, 450 and 1600 bp. In normal cells, p21 exists predominantly in quaternary complexes with cyclins, Cdks, and PCNA to inhibit the activity of Cdks and control the G1- to S-phase transition (3).

The CDKN1A gene has a p53 transcriptional regulatory motif and cells lacking functional p53 tumor suppressor protein express very low levels of p21, suggesting that p53 regulates CDKN1A expression directly. The expression of p21 induces differentiation of normal and transformed cells, and the involvement of p21 in terminal differentiation has been observed in several cell systems.

Differential regulation of p21 by p53 and retinoblastoma has been reported in cellular response to oxidative stress. In addition, several recent studies suggest a role for p21 in apoptosis. Quercetin-induced apoptosis in hepatocytes was also associated with the regulation of p21 protein expression in a p53-independent pathway.

[CDKN1A] This gene encodes a potent cyclin-dependent kinase inhibitor. The encoded protein binds to and inhibits the activity of cyclin-CDK2 or -CDK4 complexes, and thus functions as a regulator of cell cycle progression at G1. The expression of this gene is tightly controlled by the tumor suppressor protein p53, through which this protein mediates the p53-dependent cell cycle G1 phase arrest in response to a variety of stress stimuli.

This protein can interact with proliferating cell nuclear antigen (PCNA), a DNA polymerase accessory factor, and plays a regulatory role in S phase DNA replication and DNA damage repair. This protein was reported to be specifically cleaved by CASP3-like caspases, which thus leads to a dramatic activation of CDK2, and may be instrumental in the execution of apoptosis following caspase activation. Two alternatively spliced variants, which encode an identical protein, have been reported.

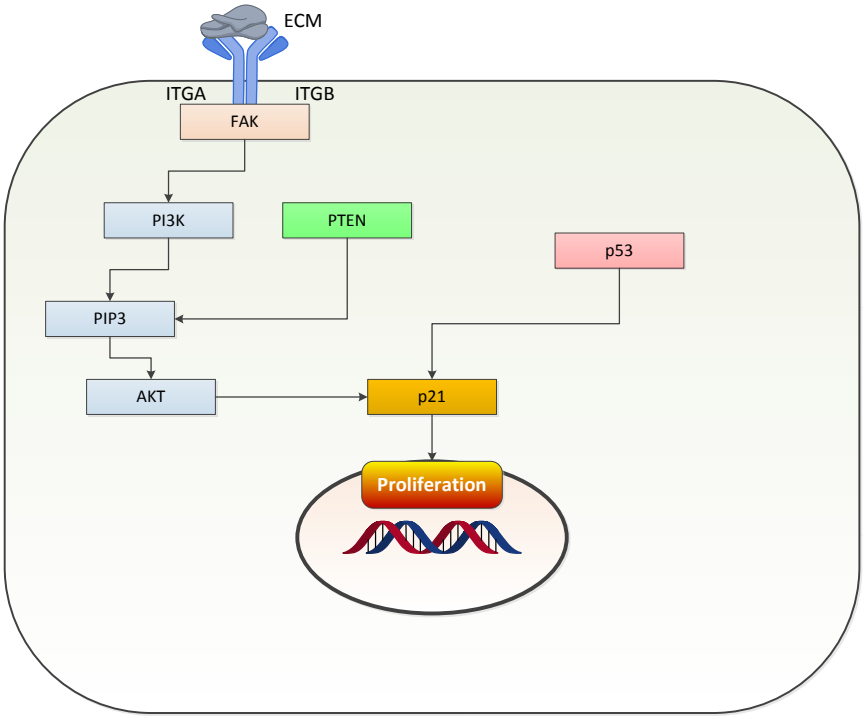
Cyclin D is one of the key regulators of the cell cycle. As Bunz states (Bunz, pp 218-221) the cell cycle goes through several well-known phases. There are phase specific kinases which are cyclins which are called that because they were found to increase or decrease in a cyclical manner as the cell cycle phase progressed. [7]

From Porath and Weinberg we have:

The molecular circuitry of senescence. p53 and Rb are the main activators of senescence. p53 can activate senescence by activating Rb through p21 and other unknown proteins, and also, in human cells, can activate senescence independently of Rb. Rb activates senescence by shutting down the transcription of E2f target genes. Rb is activated either by p21, or by the p16INK4a

[7] http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=human&c=Gene&l=CDKN1A

product. p53 activation is achieved by phosphorylation, performed by the ATM/ATR and Chk1/Chk2 proteins, and by the p19ARF product of the INK4a locus, which sequesters Mdm2 in the nucleolus. The transcriptional control of the INK4a products is not fully elucidated, indicated are some of these regulators.



In the cycles the cyclin binds with a cyclin-dependent kinas or CDK. The activated cyclin-CDK complex phosphoralates phase specific substrates. Cyclin D along with CDK4 and CDK6 facilitate the transition through G1 to the start of S for example. Cyclin E with CDK2 facilitates the transition from G1 to S. Cyclin A with CDK2 moves through S. Cyclin A/B with CDK1 moves through G2. Thus activation of Cyclin D is a sign that cell replication has commenced.

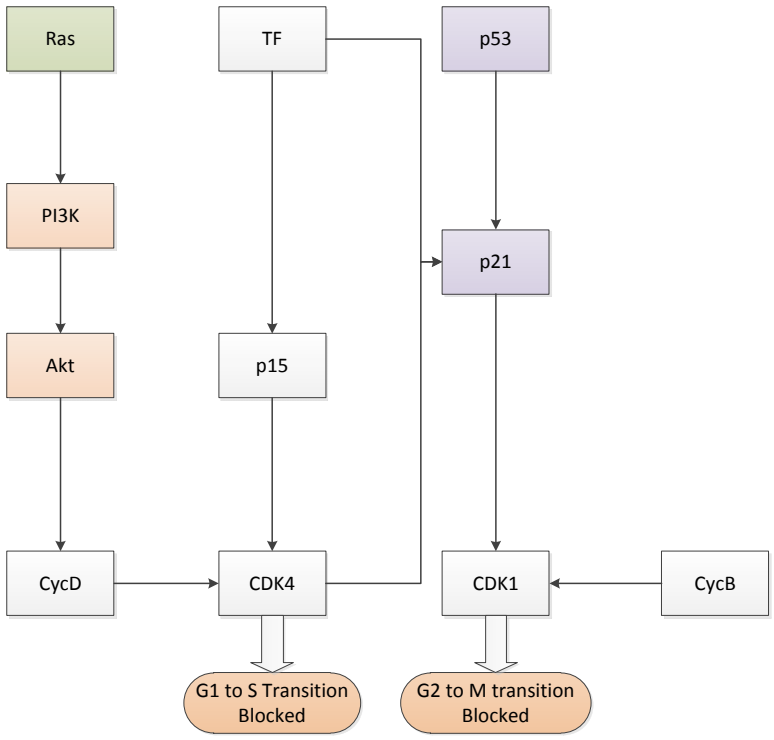
As stated in NCBI[8]:

The protein encoded by this gene belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance throughout the cell cycle. Cyclins function as regulators of CDK kinases. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event. This cyclin forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is, required for cell cycle G1/S transition. This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb.

[8] http://www.ncbi.nlm.nih.gov/gene/595

Mutations, amplification and overexpression of this gene, which alters cell cycle progression, is observed frequently in a variety of tumors and may contribute to tumorigenesis

Now we can look more closely at Cyclin D, CycD, as we show below. This we show as follows:

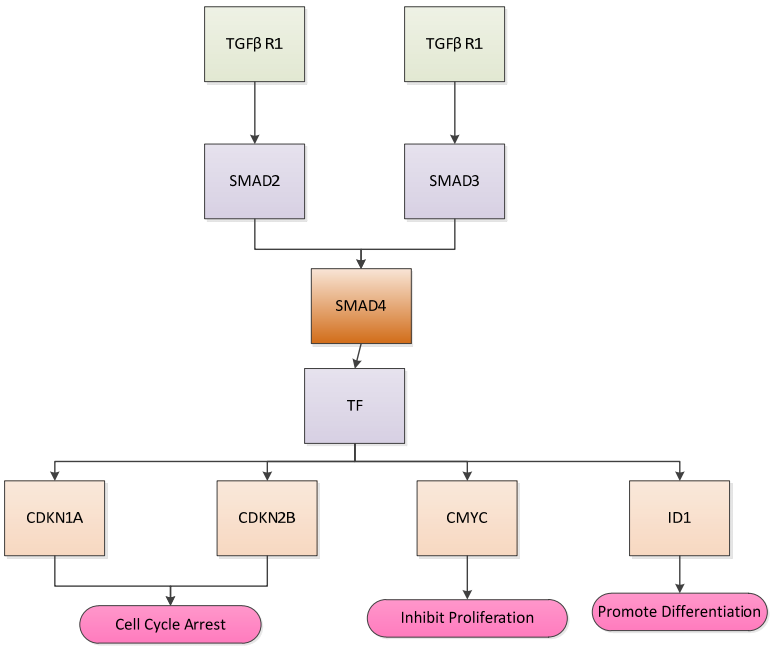


Note that Cyc D if not regulated will in turn fail to regulate the blocking of the G1 to S transition.

SMAD4 is an element in the TGF-β signalling chain. TGF is a cytokine, specifically a transforming growth factor cytokine. Like the Wnt-Apc pathway, the TGF pathway links defective development to cancer. The pathway is shown in part below (from Bunz p 199). Normal TGF signalling down-regulates the growth of most normal cells. Several of the genes in the TGF/SMAD pathway activation suppress growth. Specifically the genes CDKN1A and CDKN2B encode the cyclin dependent kinase inhibitors which suppress growth. Activated SMAD pathways also appear to suppress the transcription of other genes including c-Myc.

Gene	***Function***	***Disease***	***Pathway***
EWSR1	Translocation	Ewing's sarcomas, lymphomas, leukemias	SMAD
RUNX1	Translocation	Leukemias	SMAD
SMAD2	Inactivating codon change	Colon, breast	SMAD
TGFBR1, TGFBR2	Inactivating codon change	Colon, stomach, ovarian	SMAD

We show some of the TGF SMAD signalling below. We will elaborate this later.



SMAD4 controls the G1 to S transition. As stated in NCBI[9]:

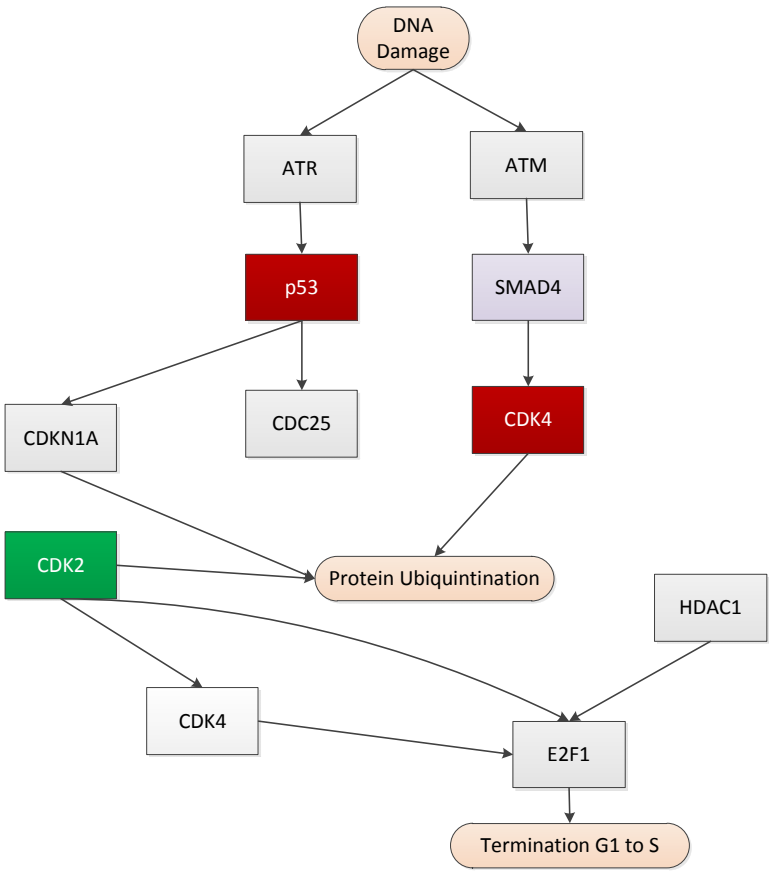
This gene encodes a member of the Smad family of signal transduction proteins. Smad proteins are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to TGF-beta signaling. The product of this gene forms homomeric complexes and heteromeric complexes with other activated Smad proteins, which then accumulate in the nucleus and regulate the transcription of target genes.

This protein binds to DNA and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad-binding element (SBE). The Smad proteins are subject to complex regulation by post-translational modifications. Mutations or deletions in this gene have been shown to result in pancreatic cancer, juvenile polyposis syndrome, and hereditary hemorrhagic telangiectasia syndrome.

We use the NCI data set for its pathway[10]:

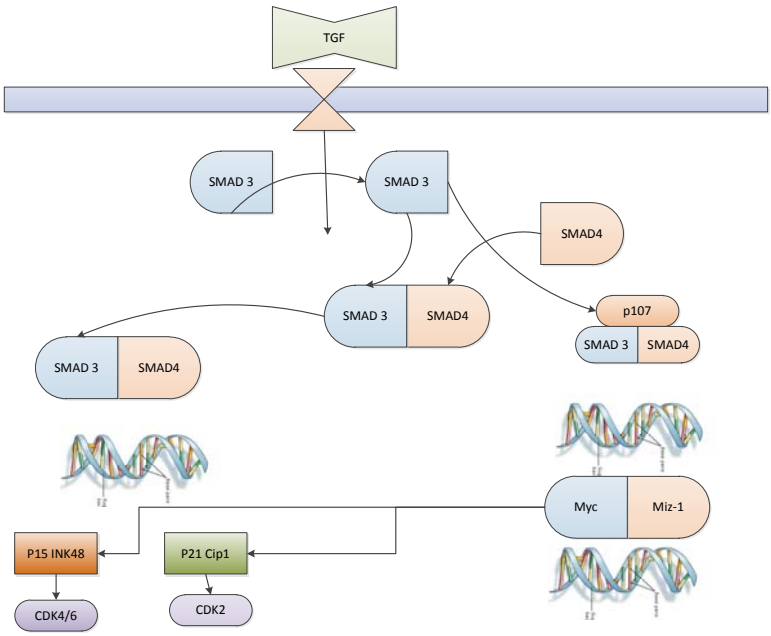
[9] http://www.ncbi.nlm.nih.gov/gene/4089

[10] http://pid.nci.nih.gov/search/pathway_landing.shtml?pathway_id=100160&source=BioCarta&genes_a=4089&genes_b=&what=graphic&jpg=on&ppage=1



The SMAD pathway is also detailed by NCI and one is referred to that source for further detail.

From Weinberg (p 291) we also have the SMAD4 pathway showing its immediate control of the DNA transcription.



As Weinberg states (p 292):

"… Half of all pancreatic carcinomas and more than a quarter of all colon carcinomas carry mutant inactivated Smad4 proteins. Without the presence of Smad4 neither Smad2-Smad4 nor Smad3-Smad4 complexes can form. These two complexes are the chief agents dispatched by the TGF-β receptor to the nucleus with the important assignment to shut down proliferation."

This control mechanism is shown above.

4 OBSERVATIONS

There has been a proliferation of putative gene expression findings related to a multitude of cancers. We have argued that behind any putative marker that there should be some causal model reflective of reality. Our prior focus has been primarily on pathway modifications and specifically the gene which has been changed in terms of expression that is reflected in that pathway change.

Let me provide a few observations:

1. The need to determine markers for assessing aggressive PCa is a critical factor in managing the disease. It is well known that a small fraction is aggressive but the aggressive forms have devastating morbidity and mortality effects. The arguments over PSA testing are oftentimes done by those who have been least affected and even more so least knowledgeable. Having some definitive test is of help.

2. These three genes arguably cover three of the most significant factors in PCa. However one must look at them in the context of the overall networks controlling cells. Namely pathways and causative gene must be studied. What of methylation and PCa? How is that factors assessed?

3. Sampling genes for the protein levels may be much more complex than realized. What cells do we sample? What is a metastatic stem cell has already moved out into distant sites, how is that ascertained? The failure rates of this approach must be seriously studied.

4. This study appears to be better than many others that just do some genome wide study and finding a dozen or so genes with some “correlation”. Here we have some genes with putative causative factors for the specific disease characteristics.

5. What of the methylation issue and what of the stem cell issues? How do these fit into this profile?

This work is an excellent step in getting a better hold on PCa. It will be interesting to see how it progresses.

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