Prostate Cancer and Vitamin D

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There has been a great deal of focus on the use of various vitamins and supplements in managing Prostate Cancer. We examine this here with some of the most recent data. The answer still seems ambiguous and as such there is no clear path. On the one hand some Australian data suggest that lower Vitamin D means lower risk for PCa. On the other hand higher Vitamin D in PCa patients results in better outcomes. No clear answer seems available.

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Contents

1 INTRODUCTION

There has been a significant amount of confusion as to the role of Vitamin D in either preventing or in controlling prostate cancer, PCa. The results are often conflicting and have lacked details on why this may be the case. In some cases it is seen as beneficial and in others it is actually seen as having a deleterious effect. Just what the answer is may very well still be uncertain.

In a recent paper by Boland et al state the authors summarize their clinical trial which demonstrates a negative correlation between Vitamin D levels and the incidence of PCa. Specifically they state[1]:

Vitamin D insufficiency is associated with many disorders, leading to calls for widespread supplementation. Some investigators suggest that more clinical trials to test the effect of vitamin D on disorders are needed. We did a trial sequential meta-analysis of existing randomized controlled trials of vitamin D supplements, with or without calcium, to investigate the possible effect of future trials on current knowledge.

We estimated the effects of vitamin D supplementation on myocardial infarction or ischemic heart disease, stroke or cerebrovascular disease, ***cancer****, total fracture, hip fracture, and mortality in trial sequential analyses using a risk reduction threshold of 5% for mortality and 15% for other endpoints. The effect estimate for vitamin D supplementation with or without calcium for myocardial infarction or ischemic heart disease (nine trials, 48 647 patients), stroke or cerebrovascular disease (eight trials 46 431 patients),* ***cancer (seven trials, 48 167 patients)****, and total fracture (22 trials, 76 497 patients) lay within the futility boundary, indicating* ***that vitamin D supplementation does not alter the relative risk of any of these endpoints by 15% or more****.*

Vitamin D supplementation alone did not reduce hip fracture by 15% or more (12 trials, 27 834 patients). Vitamin D co-administered with calcium reduced hip fracture in institutionalized individuals (two trials, 3853 patients) but did not alter the relative risk of hip fracture by 15% or more in community-dwelling individuals (seven trials, 46 237 patients). There is uncertainty as to whether vitamin D with or without calcium reduces the risk of death (38 trials, 81 173). Our findings suggest that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%. Future trials with similar designs are unlikely to alter these conclusions.

Thus the above makes a clear assertion that the use of excess Vitamin D does not alter end points in cancer cases.

Even more so, the work by Wong et al states:

Lower levels of vitamin D may reduce prostate cancer risk in older men. By contrast, levels of vitamin D did not predict incidence of colorectal or lung cancers. Further studies are needed to

[1] http://www.thelancet.com/journals/landia/article/PIIS2213-8587%2813%2970212-2/fulltext

determine whether a causal relationship exists between vitamin D and prostate cancer in ageing men…. As illustrated …, every 10 nmol/l decrease in 25(OH)D concentration was associated with a 4% reduction in prostate cancer incidence, after adjustment for age, education, living circumstance, smoking status, physical activity, CCI, BMI, creatinine, seasonality and previous diagnosis of cancer (other than prostate) (SHR 0.96, 95% CI 0.92–1.00). Similarly, every halving of 25(OH)D concentration was associated with a 21% reduction in incident prostate cancer after adjustment for other risk factors.

In this study in Australia they clearly note that there is a strong indication that lower Vitamin D blood levels yield lower PCa incidence. However the authors (Wong et al) also note the conflicting results on those with existing PCa. They write:

Whilst there is lack of conclusive evidence on the benefit of vitamin D supplementation in the development of prostate cancer, previous studies on the effect of pre-existing prostate cancer have so far produced ambiguous results. A research team in the United States explored the influence of vitamin D3 supplementation at 4000 IU daily for one year on the outcome of early stage, low-risk prostate cancer ... More than half of the study subjects remained stable or improved with supplementation, compared to a fifth of the control group who did not receive supplementation (p= 0.025). Conversely, vitamin D3 supplementation did not benefit 40% of the subjects in this open-label clinical trial. Another study involves the randomization of 37 patients with histologically proven adenocarcinoma of the prostate who had selected prostatectomy as primary therapy. Calcitriol was administered to the treatment group at 0.5 mg/kg per week for a 4-week period prior to surgery. When prostatectomy specimens were processed and analyzed, VDR expression was significantly reduced in samples from calcitriol treated patients (p = 0.004) but there was no statistically significant difference in the fraction of cells expressing the specific molecules involved with cell-cycle regulation and proliferation

Thus with evidence of reduction with lower Vitamin D and conflicting results with existing PCa patients it is useful to have some baseline model of what Vitamin D does and why it may be effective.

In a NEJM paper by Hollick, the author states regarding cancers:

In a study of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors. … Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.1-3 Furthermore, in a vitamin D– insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated. The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1α- hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check. It has been suggested that if a cell becomes

malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.

Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the CYP24 gene to produce the inactive calcitroic acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism. This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.

The issue with the above set of observations is that they lack causative linkages which can be carried through in the cellular analysis.

2 GDF-15 AND PCA

It is always useful to have a clear understanding of what effect a molecule like Vitamin D has on specific pathways and particularly regarding cellular control.

As Lambert et al have noted[2]:

Accumulating evidence suggests that chronic prostatic inflammation may lead to prostate cancer development. Growth differentiation factor-15 (GDF-15) is highly expressed in the prostate and has been associated with inflammation and tumorigenesis. To examine the relationship between GDF-15 and prostatic inflammation, GDF-15 expression was measured by immunohistochemical (IHC) staining in human prostatectomy specimens containing inflammation. The relationship between GDF-15 and specific inflammatory cells was determined using non-biased computer image analysis. To provide insight into a potential suppressive role for GDF-15 in inflammation, activation of inflammatory mediator nuclear factor of kappa B (NFκB) was measured in PC3 cells.

GDF-15 expression in luminal epithelial cells was decreased with increasing inflammation severity, suggesting an inverse association between GDF-15 and inflammation. Quantification of IHC staining by image analysis for GDF-15 and inflammatory cell markers revealed an inverse correlation between GDF-15 and CD3+, CD4+, CD8+, CD68+, and inos+ leukocytes. GDF-15 suppressed NFκB activity in luciferase reporter assays. Expression of the NFκB target, interleukin 8 (IL-8), was downregulated by GDF-15. The inverse relationship between GDF-15 and inflammation demonstrates a novel expression pattern for GDF-15 in the human prostate and suppression of NFκB activity may shed light on a potential mechanism for this inverse correlation.

Note from the above:

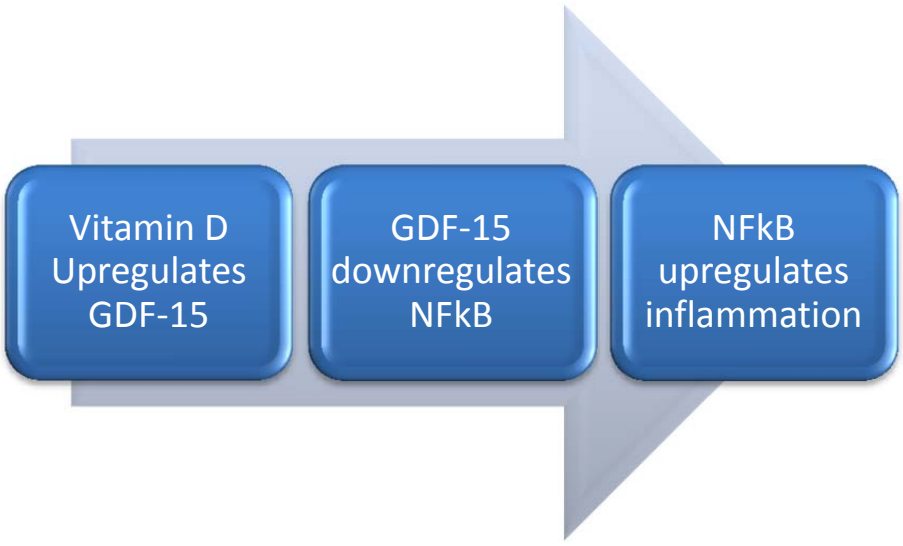
1. GDF-15 suppressed NFκB
2. GDF-15 downregulates IL-8
3. GDF-15 concentration is inversely related to inflammation

and also shown below:

4. Vitamin D upregulates GDF-15

We summarize this below:

[2] http://www.ncbi.nlm.nih.gov/pubmed/25327758



From Newswise we have the following report[3]:

A University of Colorado Cancer Center study recently published in the journal Prostate offers compelling evidence that inflammation may be the link between Vitamin D and prostate cancer. Specifically, the study shows that the gene GDF-15, known to be upregulated by Vitamin D, is notably absent in samples of human prostate cancer driven by inflammation.

"When you take Vitamin D and put it on prostate cancer cells, it inhibits their growth. But it hasn't been proven as an anti-cancer agent. We wanted to understand what genes Vitamin D is turning on or off in prostate cancer to offer new targets," says James R. Lambert, PhD, investigator at the CU Cancer Center and associate research professor in the CU School of Medicine Department of Pathology.

Since demonstrating that Vitamin D upregulates the expression of GDF-15, Lambert and colleagues, including Scott Lucia, MD, wondered if this gene might be a mechanism through which Vitamin D works in prostate cancer. Initially it seemed as if the answer was no.

"We thought there might be high levels of GDF-15 in normal tissue and low levels in prostate cancer, but we found that in a large cohort of human prostate tissue samples, expression of GDF-15 did not track with either normal or cancerous prostate tissue," Lambert says.

But then the team noticed an interesting pattern: GDF-15 was uniformly low in samples of prostate tissue that contained inflammation.

This observation is an interesting nexus. It is well known that inflammation is a driver of PCa. It is seen increased in patients with Type 2 Diabetes and obesity, two conditions with co-incident inflammatory responses. The authors continue:

[3] http://www.newswise.com/articles/finally-a-missing-link-between-vitamin-d-and-prostate-cancer

"Inflammation is thought to drive many cancers including prostate, gastric and colon. Therefore, GDF-15 may be a good thing in keeping prostate tissue healthy – it suppresses inflammation, which is a bad actor potentially driving prostate cancer," Lambert says.

The study used a sophisticated computer algorithm to analyze immunohistochemical (IHC) data, a task that in previous studies had been done somewhat subjectively by pathologists. With this new technique, Lambert, Lucia and colleagues were able to quantify the expression of the GDF-15 protein and inflammatory cells by IHC staining on slides taken from these human prostate samples.

Additionally encouraging is that the gene GDF-15 was shown to suppress inflammation by inhibiting another target, NFkB. This target, NFkB, has been the focus of many previous studies in which it has been shown to promote inflammation and contribute to tumor formation and growth; however, researchers have previously been unable to drug NFkB to decrease its tumor-promoting behavior.

As we shall further show, this may be a bit contradictory to other evidence. As we had speculated before, increases in GDF-15 reduced NF-κB, and thus reduced inflammatory factors. They then argue that it is the inflammation and not the excess NF-κB that is the problem. However one must ask what the cause of the inflammation is. They conclude:

"There's been a lot of work on inhibiting NFkB," says Lambert. "Now from this starting point of Vitamin D in prostate cancer, we've come a long way toward understanding how we might use GDF-15 to target NFkB, which may have implications in cancer types far beyond prostate."

Now from a second report, Prostate Cancer News, they state[4]:

"GDF-15 may be a good thing in keeping prostate tissue healthy – it suppresses inflammation, which is a bad actor potentially driving prostate cancer," explained Dr. Lambert.

We must note this statement since we will show some contrary versions later. They continue:

The road to understanding was not as clear in the beginning. At first, Dr. Lambert's group tested the theory that vitamin D itself could be protective against prostate cancer in general. "When you take Vitamin D and put it on prostate cancer cells, it inhibits their growth. But it hasn't been proven as an anti-cancer agent. We wanted to understand what genes Vitamin D is turning on or off in prostate cancer to offer new targets."

After the group identified GDF-15 upregulation as a downstream result of vitamin D stimulation, they looked for GDF-15 in human prostate cancer tissue samples. "We thought there might be high levels of GDF-15 in normal tissue and low levels in prostate cancer, but we found that in a

[4] http://prostatecancernewstoday.com/2014/10/24/cu-cancer-center-study-strengthens-prostate-cancer-vitamin-d-link/

large cohort of human prostate tissue samples, expression of GDF-15 did not track with either normal or cancerous prostate tissue."

Then they turned to immunohistochemistry and noticed a pattern: GDF-15 protein expression was greater in samples with inflammatory cells. It seemed GDF-15 was acting to suppress inflammation by inhibiting the transcription factor NFkB. "There's been a lot of work on inhibiting NFkB," said Dr. Lambert.

Since NFkB is well-studied, there may be a few new potential treatments to explore for prostate cancer. "Now from this starting point of vitamin D in prostate cancer, we've come a long way toward understanding how we might use GDF-15 to target NFkB, which may have implications in cancer types far beyond prostate."

Now as NCBI states:

(GDF-15 is one of the) bone morphogenetic proteins are members of the transforming growth factor-beta superfamily and regulate tissue differentiation and maintenance. They are synthesized as precursor molecules that are processed at a dibasic cleavage site to release C-terminal domains containing a characteristic motif of 7 conserved cysteines in the mature protein

In a similar fashion:

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens

From Zimmers et al we have a description of GDF-15:

The immunoregulatory cytokine macrophage inhibitory cytokine-1 (MIC-1), a divergent TGF-beta family member, and its murine ortholog, growth/differentiation factor-15 (GDF-15) are induced in hepatocytes by surgical and chemical injury and heat shock. To better understand the in vivo role this factor plays in organ injury, we examined the regulation of GDF-15 in murine models of kidney and lung injury.

We demonstrate herein induction of GDF-15/MIC-1 after surgical, toxic/genotoxic, ischemic, and hyperoxic kidney or lung injury. Gdf15 induction was independent of protein synthesis, a hallmark of immediate-early gene regulation. Although TNF induced GDF-15 expression, injury-elicited Gdf15 expression was not reduced in mice deficient for both TNF receptor subtype. Furthermore, although the stress sensor p53 is known to induce GDF-15/MIC-1 expression, injury-elicited Gdf15 expression was unchanged in p53-null mice. Our results demonstrate that GDF-15 induction after organ injury is a hallmark of many tissues. These data demonstrate that GDF-15/MIC-1 is an early mediator of the injury response in kidney and lung that might regulate inflammation, cell survival, proliferation, and apoptosis in a variety of injured tissues and disease processes.

The GDF factor regulates the inflammatory and apoptotic pathways in cells. Zimmers et al demonstrates several specific issues regarding it regulatory effects.

As Vanhara et al state:

Deregulation of expression and function of cytokines belonging to the transforming growth factor-β (TGF-β) family is often associated with various pathologies. For example, this cytokine family has been considered a promising target for cancer therapy. However, the detailed functions of several cytokines from the TGF-β family that could have a role in cancer progression and therapy remain unclear.

One of these molecules is growth/differentiation factor-15 (GDF-15), a divergent member of the TGF-β family.

This stress-induced cytokine has been proposed to possess immune-modulatory functions and its high expression is often associated with cancer progression, including prostate cancer (PCa).

Now the above is possibly in contradiction to the observation made in the most current paper. However, this work was done earlier and the statement made is perhaps speculative at best.

However, studies clearly demonstrating the mechanisms for signal transduction and functions in cell interaction, cancer progression and therapy are still lacking. New GDF-15 roles have recently been identified for modulating osteoclast differentiation and for therapy for PCa bone metastases.

Moreover, GDF-15 is as an abundant cytokine in seminal plasma with immunosuppressive properties. We discuss studies that focus on the regulation of GDF-15 expression and its role in tissue homeostasis, repair and the immune response with an emphasis on the role in PCa development.

As Bruzzese et al note about the upregulation of GDF-15[5].

The tumor stroma is vital to tumor development, progression, and metastasis. Cancer-associated fibroblasts (CAF) are among the abundant cell types in the tumor stroma, but the range of their contributions to cancer pathogenicity has yet to be fully understood.

Here, we report a critical role for upregulation of the TGFβ/BMP family member GDF15 (MIC-1) in tumor stroma. GDF15 was found upregulated in situ and in primary cultures of CAF from prostate cancer. Ectopic expression of GDF15 in fibroblasts produced prominent paracrine effects on prostate cancer cell migration, invasion, and tumor growth.

[5] http://cancerres.aacrjournals.org/content/74/13/3408.long

Notably, GDF15-expressing fibroblasts exerted systemic in vivo effects on the outgrowth of distant and otherwise indolent prostate cancer cells. Our findings identify tumor stromal cells as a novel source of GDF15 in human prostate cancer and illustrate a systemic mechanism of cancer progression driven by the tumor microenvironment. Further, they provide a functional basis to understand GDF15 as a biomarker of poor prognosis and a candidate therapeutic target in prostate cancer.

Perhaps one may interpret the above in either way. Namely GDF-15 upregulated may have been an attempt by the cell to reduce the imputed inflammation of PCa. Now McCarty notes in the review of multiple targets for PCa. First he discusses NF-κB:

Constitutive activation of the transcription factor NF- κB has been observed in a high proportion of androgen-independent prostate cancers. Presumably, the ability of NF-κB to promote transcription of the prominent antiapoptotic protein Bcl-2aids the survival of cells that otherwise would be at risk owing to loss of androgen activity. This constitutive activation reflects increased activity of the IκB kinase (IKK) complex, but why IKK is activated remains unclear. A report that dominant negative NF-κB-inducing kinase (NIK) and tyrosine kinase inhibitors suppress the constitutively elevated NF-κB activity in various prostate cancer cell lines suggests that NIK, possibly downstream from a tyrosine kinase, may mediate the constitutive activation of IKK.

Other factors suggested to play a role in the constitutive activation of NF-κB in prostate cancer include 12-(S)-HETE, Id-1, bombesin, and RhoA. In addition to suppressing apoptosis, NF-κB promotes malignant behavior in other ways: stimulating transcription of cell cycle progression factors (c-myc, cyclin D1), proteolytic enzymes (MMP-9, uPA), and angiogenic factors (VEGF, IL-8). Thus, it is not surprising that nuclear localization of NF-κB in prostate cancer biopsies has been shown to correlate with poor clinical prognosis….

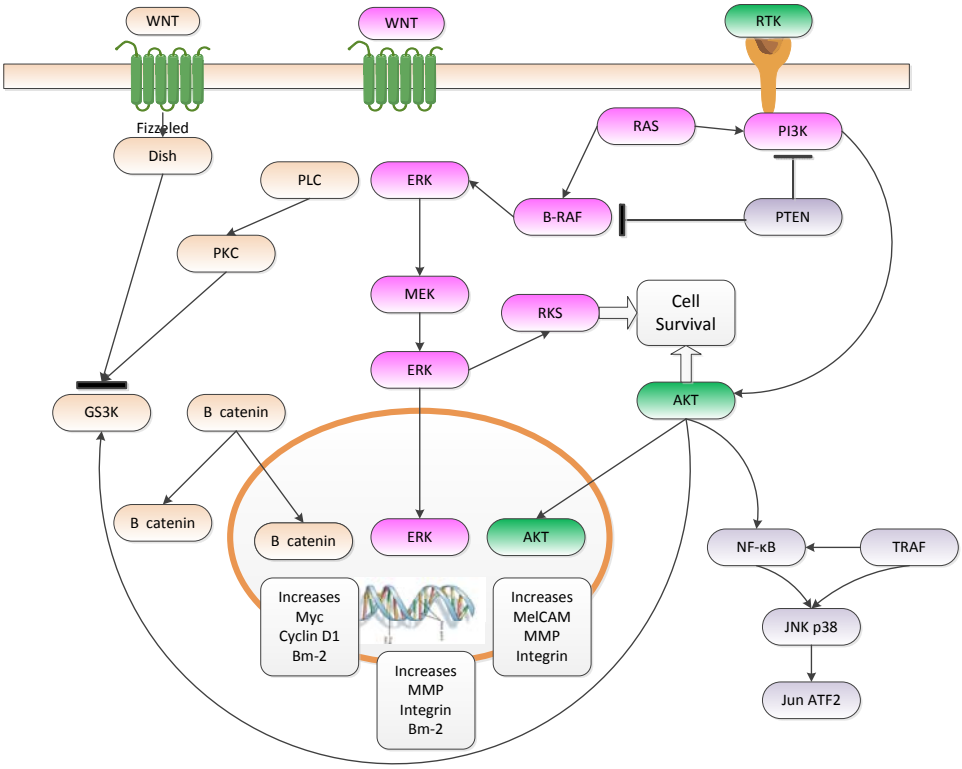
This is consistent with what we have shown before.
Normal prostate epithelium expresses vitamin D receptors, and calcitriol, the natural agonist for these receptors, exerts a growth-inhibitory effect.390-392 These cells also express 1-α-hydroxylase activity and thus can generate their own calcitriol from circulating 25-hydroxycholecalciferol.391,393,394 Since the serum level of 25-hydroxycholecalciferol is determined largely by exposure of skin to ultraviolet light, these findings have encouraged the speculation that good vitamin D status might reduce prostate cancer risk. Although epidemiological studies correlating assessed sunlight exposure with subsequent prostate cancer risk are reasonably supportive of this thesis,395-401 prospective studies examining serum levels of calcitriol or 25- hydroxyvitamin D have been much less so.402-407 Thus, the role of vitamin D status in prostate cancer induction remains unclear. Since supra-physiological concentrations of calcitriol have been employed in most in vitro studies, it is conceivable that the growth inhibitory impact of this hormone on prostate epithelium is pharmacological rather than physiological.

In the above by McCarty there is no clear nexus drawn between NFκB and Vitamin D. The work in question regarding the nexus through GDF-15 may have some promising results therefore.

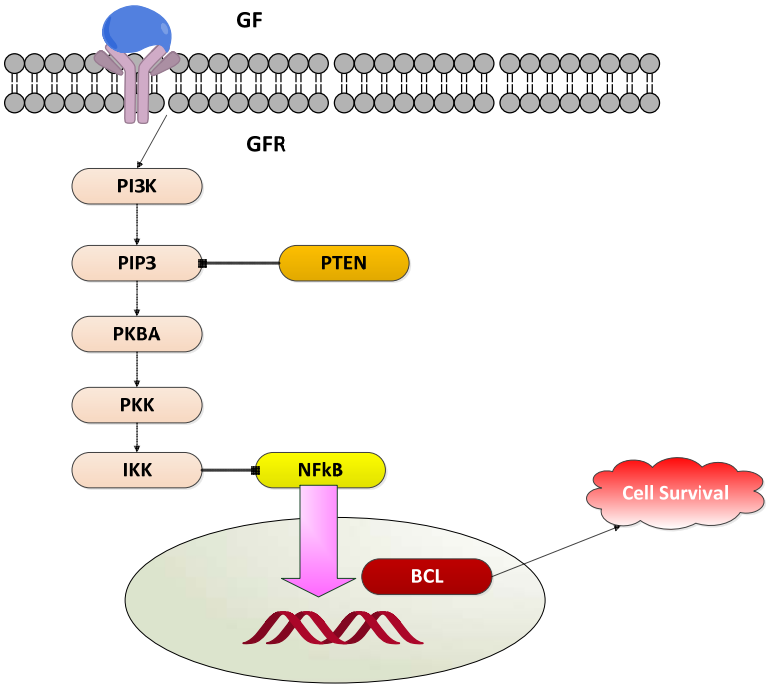
Finally in a paper by Jeet the authors discuss Vitamin D in murine models. They state:

The potential efficacy of vitamin D as a chemopreventive agent for PC has been observed in large cohort studies of human patients with PC [153, 154]. Based on these studies, precancerous and cancerous cohorts of Nkx3.1; Pten compound mutant mice have been treated with 1α, 25 dihydroxyvitamin D3 (biologically active form of vitamin D3) for 4 months continuously [155]. This results in a significant reduction in the occurrence of HGPIN only in the precancerous cohort, whereas mice with already established PIN lesions do not respond to this treatment. However, cancerous cohorts display a less aggressive phenotype with small and focal lesions compared to the wild type controls. Another study has used androgen-independent Gγ/T-15 transgenic mice to test the efficacy of EB1089 (a vitamin D3 analog) in preventing prostate carcinogenesis [156]. Treatment of these mice with EB1089 at three different time points does not cause any significant reductions in tumor onset or delay; however, tumor growth is adversely affected by 60% at a higher dose of the compound albeit with attendant hypercalcemia and weight loss.

We now show some of the pathways:



Now the specific pathway for what we have been discussing:



Now the presence of GDF-15 is as a specific activating growth factor, GF, as shown in the above. Namely the activation moves down through to NF-κB to activate cell survival and allow for proliferation.

3 WARBURG EFFECT

The Warburg effect was proposed by Warburg in 1922 when studying cancer. As Vender Heiden et al state in a recent review paper:

In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed "the Warburg effect." Aerobic glycolysis is an inefficient way to generate adenosine 5'-triphosphate (ATP), however, and the advantage it confers to cancer cells has been unclear.

Namely the alternate pathway is powerful yet confusing. As Wang et al state in examining this effect in PCa:

The Warburg effect, the inefficient metabolic pathway that converts glucose to lactate for rapid energy generation, is a phenomenon common to many different types of cancer. This process supports cell proliferation and promotes cancer progression via alteration of glucose, glutamine and lipid metabolism. Prostate cancer is a notable exception to this general process since the metabolic switch that occurs early during malignancy is the reverse of the Warburg effect. This "anti-Warburg effect" is due to the unique biology of normal prostate cells that harbor a truncated TCA cycle that is required to produce and secret citrate.

In prostate cancer cells, the TCA cycle activity is restored and citrate oxidation is used to produce energy for cancer cell proliferation. 1,25(OH) 2 D 3 and androgen together modulates the TCA cycle via transcriptional regulation of zinc transporters, suggesting that 1,25(OH) 2 D 3 and androgen maintain normal prostate metabolism by blocking citrate oxidation. These data demonstrate the importance of androgens in the anti-proliferative effect of vitamin D in prostate cancer and highlight the importance of understanding the crosstalk between these two signaling pathways

Thus much of the analysis we have been discussing is good science with some excellent observation based conjecture. However there is also the dynamics of the Warburg effect that can be drawn into the analysis.

4 OBSERVATIONS

We can now make several observations about this continuing investigation into Vitamin D and PCa. Lambert et al present an interesting paradigm to consider in our understanding of PCa.

We leave with a few observation:

1. No clear benefit of Vitamin D enhancements seems to be present. The data is still a bit confusing. On the one hand we have a trial that says the lower the better the chance of not getting PCa and on the other hand we have the statement that Vitamin D helps people with lesions as least in murine models and petri dishes.

2. A logical pathway is presented. The GDF-15 path seems to have a good logical basis and one approachable by targeted therapeutics. That is always a benefit and can be helpful for many who have the problem.

3. Inflammation is a strong and viable source of a precipitating event. This is a well-known observation and the relationship between inflammation and PCa has always been strong. The use of NASIDS has been observed as a putative preventive. The actual biochemical processes leading to this need to be better understood.

4. HGPIN is reversible and this model should include such an observation. Why does it reverse is an open question but its existence is without question.

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