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Chapter 5

Aberrant SGK1 Transcription in LNCaP: A Novel Feedback Mechanism of TGF-beta1 Regulation in Prostate Carcinogenesis

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Abstract

SGK1, a serum- and glucocorticoid-inducible kinase implicated in cancer, is regulated by TGF-beta1 and PI3-kinase. In a comparative study of different benign and cancerous breast and prostate cells, we demonstrate in this study that exon 11 deletion in SGK1 occurs only in LNCaP prostate cancer cells in association with the deficient TGF-beta1 mRNA message and FOXO3A-driven promoter activity. Using protein modeling approaches, we discovered that exon11 deletion in SGK1 could redistribute electrostatic surface potential around the major kinase domain and affect phosphorylation of SGK1 target proteins including FOXO3A. Concordantly, we found that LNCaP cells displayed FOXO3A hyperphosphorylation at the Ser218/321 (a site next to Ser315 with the marked SGK1 preference) along with changes in gene expression profile of TGF-beta relevant regulators (such as SMAD2/4, MAD4 and SKIP). Oncomine-interactome analysis further validated a possibility of reciprocal TGF-beta1 regulation by its transcriptional target SGK1 through alterations in FOXO/SMAD and steroid hormone nuclear receptor interactions.

Keywords: SGK1, TGF-beta1, FOXO-SMAD, LNCaP, prostate cancer

1. Introduction

SGK1 plays a major role in carcinogenesis in association with FOXO3A (or FKHRL1), p53 and GR [1–3]. Since TGF-beta1 is turned on by cancer cells from a tumor suppressor into a mediator of metastasis [4], its transcriptional target SGK1 can contribute to pleiotropic TGF-beta actions in homeostasis and carcinogenesis [5]. Glucocorticoid (GC) control of

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SGK1 can provide more clues to dual TGF-beta1 effects on the coregulation by endogenous steroids on cell growth. Furthermore, serum and glucocorticoid (GC)-inducible SGK1 regulates ion channel conductance, cell cycling, and apoptosis. Additionally, SGK1 enzymatic activity is also regulated by PI3-kinase [6], and the PI3K/Akt/mTOR cascade is known to be involved in TGF-beta1 resistance in cancer [7]. SGK1 downregulation was identified in prostate carcinogenesis with its mRNA levels specifically reduced in hormone-refractory carcinomas [8, 9]. In the current study, we first examined TGF-beta1 and SGK1 mRNA message and gene expression in benign and cancerous breast and prostate cells differing in their hormone sensitivity. Aberrant SGK1 transcription (Δexon11) in LNCaP prostate cancer cells coincided with alterations in TGF-beta1 mRNA message and FOXO3A-driven promoter activity indicating a possible feedback regulation of TGF-beta1 by SGK1. Our protein simulation studies (DeepView/Swiss-PdbViewer) suggested that the defective translation in the Δexon11-SGK1 could affect its kinase domain and thereby phosphorylation of target proteins including a major TGF-beta1 transcriptional regulator FOXO3A. Consequently, we demonstrated FOXO3A hyperphosphorylation in LNCaP, which suggested FOXO3A deficient transcriptional activity that was concordant to altered gene expression in the FOXO-SMAD and other components of TGF-beta signaling. Analysis of TGF-beta1-SGK1 reciprocal regulatory circuits (Oncomine) suggested possible coregulation of TGF-beta1 by its downstream SGK1 linking FOXO-SMAD to nuclear steroid receptors (AR and GR).

2. Materials and methods

2.1. Cell cultures

Benign as well as cancerous breast and prostate cells (ATCC, Manassas, VA) were routinely grown in media (184B5—MEGM, PrEC—PrEGM; LNCaP—RPMI1640; PC3—F12 K; DU145, MCF7 and MDA-MB-231—MEM; MDA-MB-435—50%DMEM+50%F12) containing FBS and antibiotics (Invitrogen, Carlsbad, CA; Cambrex, East Rutherford, NJ). RNA was extracted (RNAqueous-4 PCR Kit, Ambion, Austin, TX) from confluent cells and used (2 μg) for reverse transcription reactions (SuperScript First-Strand Synthesis System for RT-PCR, Invitrogen, Carlsbad, CA).

2.2. Multiplex PCR and sequencing

Multiplex PCR was performed using following primers for TGF-beta1 (forward—5′-GCCCTGGACACCAACTATTGC-3′ and reverse—5′-GCTGCACTTGCAGGAGCGCAC-3′), SGK1 (forward—5′-CTCCTGCAGAAGGACAGGA-3′ and reverse—5′-GGACAGGCTCTTCGGTAAACT-3′) and beta-actin (forward—5′-CTGGCCGGGACCTGACTGACTACCTC-3′ and reverse—5′-AAACAAATAAAGCCATGCCAATCTCA-3′, ratio to other primers 1:10).

Following TGF-beta1 primers were used to amplify almost entire coding region (1250 bp) or its 3′-fragment (499 bp): forward 5′-AGGCCCTCCTACCTTTTGC-3′ or 5′ATTGAGGGCTTTCGCCTTAG-3′ with reverse 5′-ACAGCTGCTCCACCTTGG-3′. Both fragments from DU145 control were successfully amplified using 1ul of 0.1× cDNA, whereas amplification with 1ul cDNA from LNCaP produced only the smaller fragment.

Sequencing was verified for the SGK1 amplicon with expected size (193 bp) and identified a missing exon11 (90 bp) in the extra amplicon from LNCaP. Amplification and sequencing of full-length SGK1 (~1.4 kbp; primers: forward—5′-TTTGAGCGCTAACGTCTTTCTGT-3′ and reverse—5′-TTGCTAAGCTTCCAGAGATGTGC-3′; *data not shown*) from DU145 and LNCaP confirmed a single exon11 deletion in the apparently smaller amplicon in LNCaP that could cause a lack of following protein sequence: MEIKSHVFFSLINWDDLINKKITPPFNPNV.

2.3. TGF-beta1 promoter analysis

TGF-beta1 promoter (~2400 bp) inspection by the Genomatix software (GmbH, Munich, Germany) identified a single FOXO3A-specific regulatory element (V$FKHRL1.01, core and matrix similarity ~1; within the -350–450) as well as numerous elements with possible modifying effects on TGF-beta transcription (upstream ~600 bp). TGF-beta1 promoter activities were assessed in different cells (MDA-MB-435—N/A) using Firefly Luciferase Reporter System (Promega, Madison, WI) and presented as normalized ratios from quadruple measurements. pGL3-Basic Vector lacking eukaryotic promoter and enhancer sequence was used to insert functional promoters containing first 5 ′-UTR nucleotides (ACCTCCCCTCCG) in exon1 in addition to the -323, -453 or -1132 sequences in TGF-beta1 promoter.

2.4. Protein modeling

Using the DeepView/Swiss-PdbViewer, v3.7 software developed at GlaxoSmithKline and available for download through public access at Expasy (http://www.expasy.org/spdbv), we simulated C-terminal SGK1 protein based on a crystallographic model of Rac-beta protein kinase (Kinase Domain 146–460, PDB: 1gzk). According to aminoacid composition, a homologous structure was successfully assigned to SGK1 (UniProtKB/SwissProt Entry: O00141) and C-terminal SGK1 fragment (102–372) was correctly "threaded" on a structural template of the Ser/Thr Rac-beta kinase. In order to complete SGK1 C-terminal (102–376) protein modeling with low threading energy levels, we fixed side chains of some aminoacids with possible clashes and built four 3′end-exon11 SGK1 residues (the NPNV fragment did not have corresponding residues in a structural template). Based on the simulated wt-SGK1, we created a Δexon11-SGK1 (102–346) model that lacked 30 3′end-residues (M347-V376) corresponding to the deleted exon11. In order to predict possible structural effects of the Δexon11 in SGK1 protein, surface (including internal cavities) and electrostatic potential were computed using the DeepView/Swiss-PdbViewer software. In addition, SGK1 nucleotide and protein analysis were performed using databases such as Entrez, Ensembl and Expasy Tools.

2.5. cDNA microarray analysis

cDNA microarray analysis of prostate cancer cells was performed using Atlas Human Cancer 1.2 arrays and the corresponding software AtlasImage 2.01 (Clontech, Palo Arto, CA). Gene expression in two compared arrays was assessed using the ratios of adjusted intensities after subtraction of external background and global normalization based on sum method (signal difference threshold >4000; ratio threshold R > 2: upregulation—R > 2; downregulation—R < 0.5).

2.6. Western blotting

Lysates from LNCaP and DU145 were concentrated by TCA, precipitated and equivalently loaded on polyacrylamide SDS gel (*entire image, left*), then transferred to nitrocellulose membranes for Western Immunoblotting (*enlarged fragment, middle)* with the 1:1000 dilution of Phospho-FOX03A (Ser318/321) antibody (Cell Signaling Technology, Danvers, MA).

3. Results

3.1. In LNCaP prostate cancer cells, aberrant SGK1 transcription was associated with altered TGF-beta1 message and promoter activity

To evaluate the relationship between TGF-beta1 and its transcriptional target SGK1 in prostate and breast cancer cells, we examined their gene expression. Benign prostate (PrEC) and breast (184B5) cells displayed expectedly high TGF-beta1 and low SGK1 gene expression that was maintained in most cancer cells (**Figure 1A**). Among the tested benign and cancerous prostate

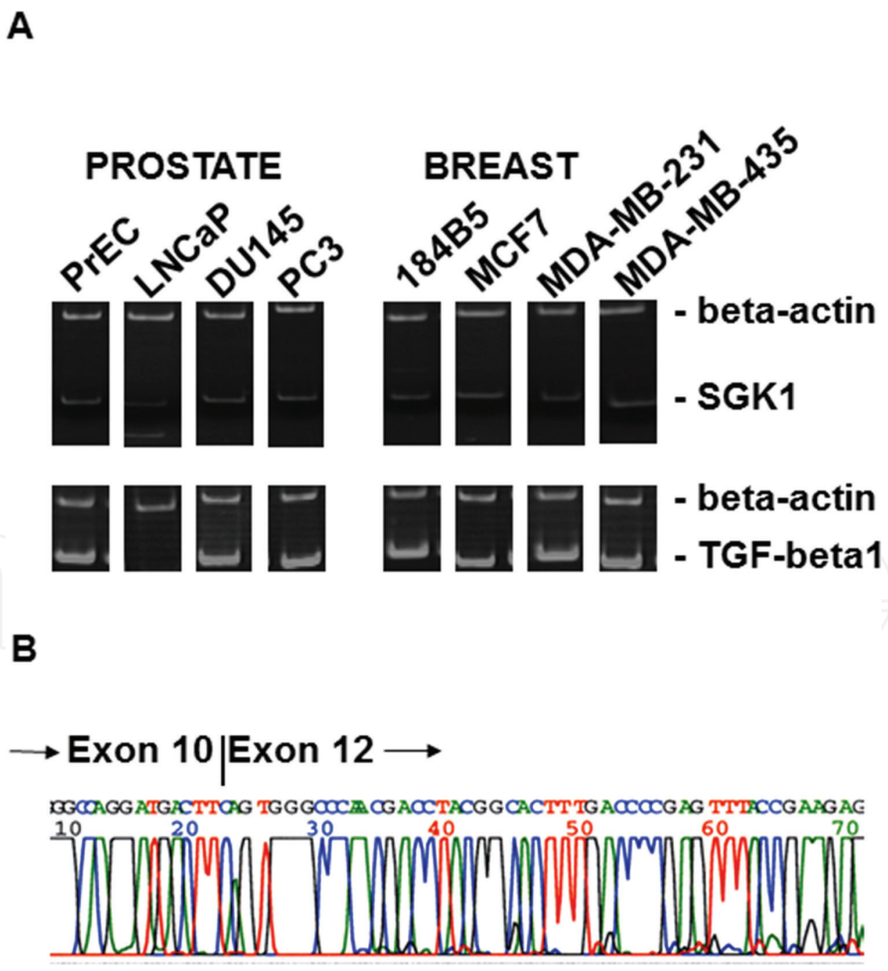


Figure 1. SGK1 transcription in association with TGF-beta1 message. (A) Multiplex PCR was performed using primers for TGF-beta1 and SGK1 as described under "materials and methods." (B) sequencing verified that the SGK1 amplicon with expected size (193 bp) was missing exon11 (90 bp) in the amplicon from LNCaP.

(LNCaP, DU145, and PC3) and breast (MCF7, MDA-MB-231, and -435) cells, LNCaP was the only cell line with the almost undetectable TGF-beta1, which coincided with an additional aberrant Δ-exon11-SGK1 transcript of 90 kb (**Figure 1A**). Unlike similar profiles of transcription in breast and prostate cells, mRNA message of SGK1 in the LNCaP prostate cancer cells displayed a double-band for full-length SGK1 cDNA, thereby validating a slightly smaller size of the extra-*SGK1*-transcript. SGK1 amplicon with the expected size (193 bp) and the identified missing exon11 (90 bp) in the extra amplicon from LNCaP were verified by sequencing (**Figure 1B**). Identification of the two PCR amplicons of SGK1 in the LNCaP cells suggests the presence of a heterozygous mutation in genomic DNA that apparently results in an alternative splicing of the SGK1 mRNA.

We analyzed TGF-beta1 promoter (~2400 bp) by the Genomatix software (GmbH, Munich, Germany) and identified a single FOXO3A-specific regulatory element (V$FKHRL1.01, core and matrix similarity ~1; within the -350–450) as well as numerous elements with possible modifying effects on TGF-beta transcription (upstream ~600 bp). Therefore, TGF-beta1 promoter activities were assessed in different cells using the Firefly Luciferase Reporter System (Promega, Madison, WI) and presented as normalized ratios from quadruple measurements. TGF-beta1 promoter activity analysis (**Figure 2A**) identified hormone-sensitive LNCaP as prostate cells with the lowest average activity (~50% compared to the rest). Similarly, hormone-sensitive MCF7 cells had the lowest TGF-beta1 promoter activity among breast cells. Drastically enhanced promoter activity in the -453-fragments compared to -323 in MDA-MB-231 cells in comparison with MCF7 cells can be attributed to the FOXO3A (Genomatix) elements contributing to their hormone-sensitive functionality. Further extension of the promoter fragment (-1132) suggested cell-specific TGF-beta1 transcriptional modulation by auxiliary regulatory elements including SMAD-interacting (FAST-1/FoxH3) and TGF-beta inducible (TIEG/EGR-alpha) proteins as well as Myc/MAX and GR. Remarkably, the FOXO3A-enhanced -453-promoter activity was annulled in the -1132-fragment in the androgen-sensitive LNCaP cells, while the estrogen-sensitive MCF7 breast cancer cells maintained similar TGF-beta1 promoter activity in both fragments. Previous studies have shown that SGK1 co-mediated FOXO3a inactivation [10] contributes to the TGF-beta1-mediated cell survival.

In our further study on the TGF-beta1 message (**Figure 2B**) in LNCaP versus DU145 (two prostate cell lines with most similar TGF-beta1 promoter activity profiles), LNCaP lacked complete TGF-beta1 mRNA but possessed a message which could translate the active form of TGF-beta1 with the 5′-end of its latency-associated peptide responsible for the cell attachment. These results suggested that along with alternative splicing, mRNA processing and stability can be affected by the 5′-UTR sequences (absent in previous amplification, **Figure 1A**) modifying autocrine TGF-beta1 regulation. However, deficient TGF-beta1 message could affect folding and cleavage of the mature TGF-beta-1 in LNCaP, while the remaining latency-associated peptide portion could render it inactive. Consistent with suggested hormonal regulation of TGF-beta1 transcription, TGF-beta mRNA presence and secretion have been previously shown in both androgen-resistant DU145 and PC3, but not in LNCaP [11] where TGF-beta insensitivity was associated with promoter methylation of its cognate receptors [12]. However, LNCaP could secrete active TGF-beta in response to estrogen or androgen [13].

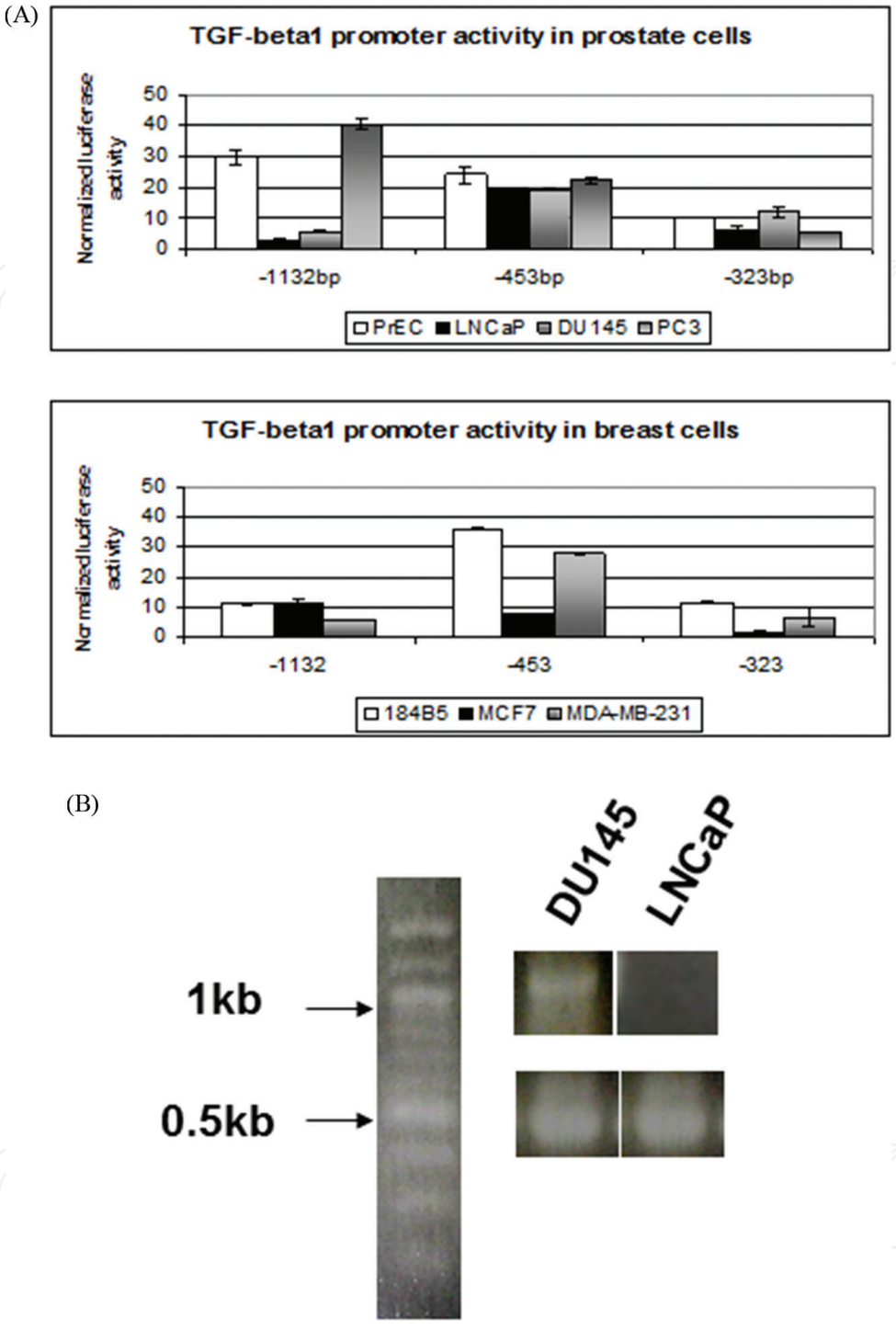


Figure 2. (A) TGF-beta1 promoter activities in prostate and breast cancer cells. TGF-beta1 promoter activities were assessed in different cells using different truncated promoter plasmids as described under "Materials and Methods" and Firefly Luciferase Reporter System (Promega, Madison, WI) and presented as normalized ratios from quadruple measurements. (B) TGF-beta1 cDNA transcripts in DU145 and LNCaP cells. TGF-beta1 primers were used to amplify almost entire coding region (1250 bp) or its 3′-fragment (499 bp) as described under "Materials and Methods." Both fragments from DU145 control (as well as PrEC and PC3, *not shown*) were successfully amplified using 1ul of 0.1× cDNA, whereas amplification with 1ul cDNA from LNCaP produced only the smaller fragment.

3.2. Identified SGK1 exon11 deletion could affect major kinase domain responsible for the phosphorylation of SGK1 target proteins

To our knowledge, this is a first report for alternative transcription of human SGK1 presented by a single transcript (Ensemble: ENSP00000237305) and having effect on TGF-beta. Based on peptide analysis (ExpasyTools), a loss of the 90-bp spanning exon11 is not likely to affect drastically the average MW (reduction only by ~7%) or pI (~8.7 for both). Although none of reported SNPs or mutations implicated the exon11 loss, its missing residues (347–376) in SGK1 protein are included in major Protein Kinase (98–355) or Protein Kinase C (375–427) domains associated with the key phosphorylation function of SGK1 as a Ser/Thr kinase. Defined central SGK1 domain (83–355) included catalytic domain, nuclear localization signal and the PY-domain involved in NEDD4–2 binding [1]. Using DeepView/Swiss-PdbViewer, we simulated both wt- and Δ-SGK1 C-terminals (**Figure 3**). As expected, external area or volume (decrease by 9 and 11%, respectively) as well as disposition and size of internal cavities (images on the left) did not change essentially in the Δ-SGK1 model. However, exon11 deletion reshaped protein surface (*images in the middle*) and redistributed electrostatic potential (images on the right) around the major kinase domain. These changes could influence protein binding and phosphorylation of SGK target proteins (such as FOXO3A and NEDD4–2 involved in the TGF-beta1, GCs or nutrient starvation responses) as well as SGK1 transport between cytoplasm and the nucleus.

3.3. SGK1 aberrant transcription and predicted kinase domain alterations were associated with the increased FOXO3A phosphorylation in LNCaP

As a direct target of SGK1, FOXO3A is phosphorylated in response to PI3K signaling [14]. Unlike two sites (Thr32 and Ser253) in FOXO3A which are catalyzed more effectively by Akt/PKB and are required for FOXO3A binding to 14–3-3 proteins, the Ser315 site next to the nuclear export signal is favored by SGK, which has a primary role in exporting FOXO3A from the nucleus. Consistently, FOXO3A in LNCaP was more phosphorylated at the adjacent Ser318/321 site (**Figure 4**) even when compared to DU145 cells with the most similar reduction profile of TGF-beta1 promoter activity.

3.4. TGF-beta1-specific synexpression profile and interactome associated with aberrant SGK1 and TGF-beta1 mRNA messages in LNCaP

cDNA microarray analysis revealed a distinct TGF-beta1 relevant synexpression pattern in LNCaP as compared to DU145 (**Figure 5**). Most importantly, two major TGF-beta relevant transcriptional regulator SMADs (2 and 4) were greatly reduced in LNCaP consistent with the "logic of TGF-beta signaling" [4] and ability of the SMAD2-lacking cells to escape TGF-beta-mediated growth inhibition [15].

On the other hand, the TGF-beta1 target MAD4 that is upregulated in LNCaP could switch cell growth regulation to Myc pathway [16]. The SMAD3-binding Myc-regulator NOTCH1 [17, 18]

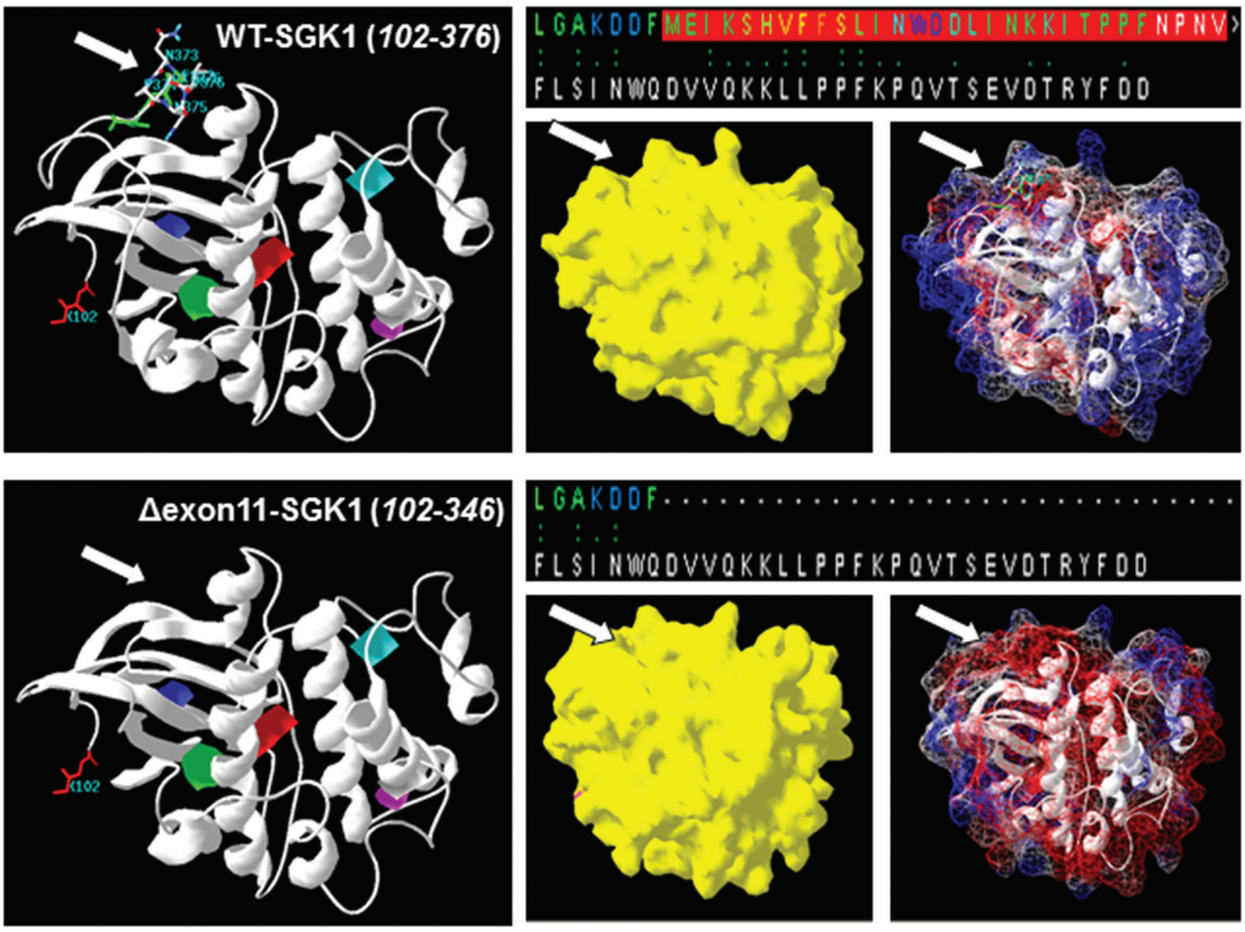


Figure 3. Protein modeling of wt- and Δ-SGK1 C-terminal. In both wt-SGK1 (*top*) and Δ-SGK1 (*bottom*), sequences are colored by threading energy (upper line) except added NPNV residues in the wt-SGK1 (in white). Exon11 residues are highlighted in red in the wt-SGK1 and presented by dots in the Δ-SGK1. Structural template sequences in both models are in white (lower line). In both models, left images represent ribbon structure (in white) with labeled end-residues and internal cavities (in color); middle images—External surface (yellow filled triangles) and right images—The electrostatic potential computed by coulomb method using partial atomic charges (dotted lines, dark red—−1.800 and dark blue—1.800). C-terminals are viewed from the same position with the designated areas corresponding to exon11 (white arrows).

was overexpressed, while two Myc-relevant stress response mediators (GADD-45 and -153) were downregulated in LNCaP cells (data not shown). Intriguingly, spliceosomal component and transcriptional coregulator SNW/SKIP, which activate the SMAD2/3 activity [19], were underexpressed in the LNCaP cells and increased in DU145 pointing to a differential hormonal regulation with aberrantly transcribed SGK1 and TGF-beta1 and reduced SMAD. Gene expression of TGF-beta1 and SGK1 (represented by short downstream 3'UTR fragments) did not change as much accentuating the causative role of alternative RNA processing.

TGF-beta1 and SGK1 interactome (**Figure 6**) substantiated a possible feedback regulation of TGF-beta1 by its transcriptional target SGK1. Alterations in the FOXO3A phosphorylation and following FOXO/SMAD signaling could involve nuclear hormone receptors (GR, AR) and ubiquitination targeting components (UBL1, UBE2L3, UBE2E1) indicating links to steroids and autophagy in the TGF-beta-regulated cell death/proliferation. Consistently, in LNCaP

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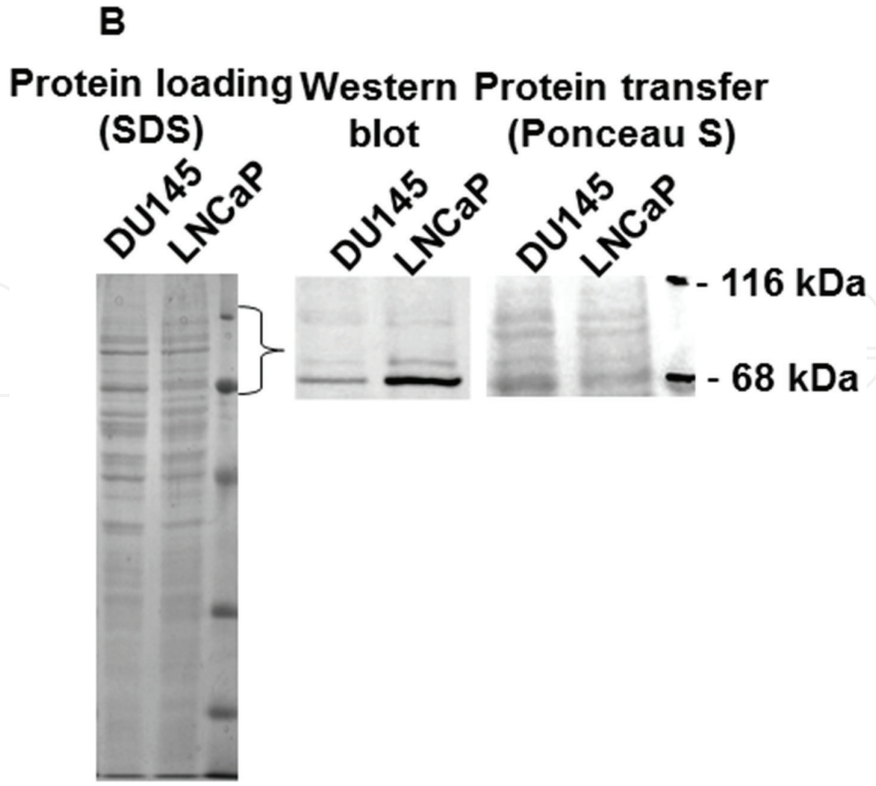


Figure 4. FOXO3A phosphorylation in LNCaP versus DU145. Lysates from LNCaP and DU145 were loaded onto polyacrylamide SDS gel and subjected to immunoblotting (*enlarged fragment, middle)* with the 1:1000 dilution of Phospho-FOX03A (Ser318/321) antibody (Cell Signaling Technology, Danvers, MA). Specific bands with expected size (~97 kDa) were found in the 68–116 kDa gel fragment. Ponceau S staining (*enlarged fragment, right*) marked the standards.

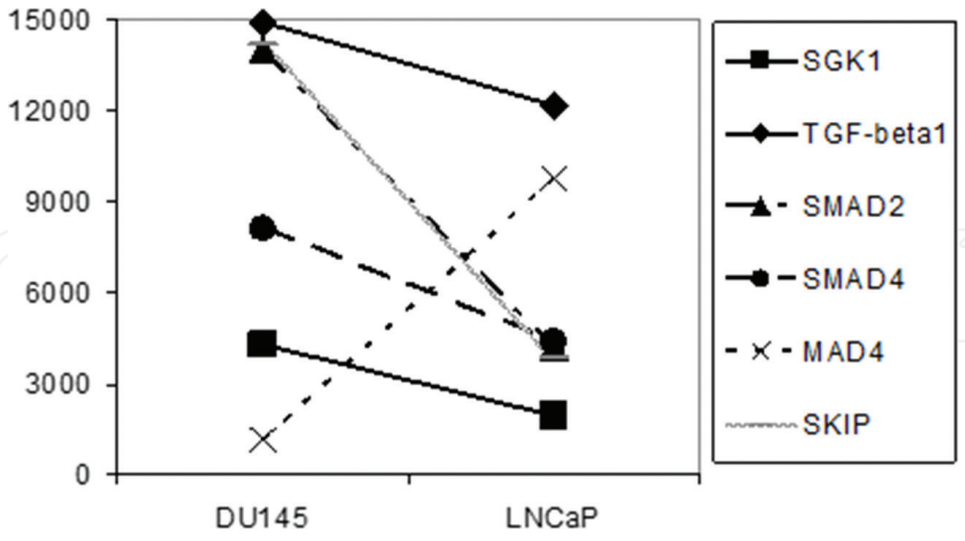


Figure 5. cDNA microarray analysis of prostate cancer cells showing TGF-beta1-relevant synexpression. cDNA microarray analysis of prostate cancer cells was performed using Atlas Human Cancer 1.2 arrays and the corresponding software AtlasImage 2.01 (Clontech, Palo Arto, CA). Gene expression in two compared arrays was assessed using the ratios of adjusted intensities after subtraction of external background and global normalization based on sum method (signal difference threshold >4000; ratio threshold R > 2; upregulation—R > 2; downregulation—R < 0.5). Graphic presentation of adjusted intensities for several listed genes is shown.

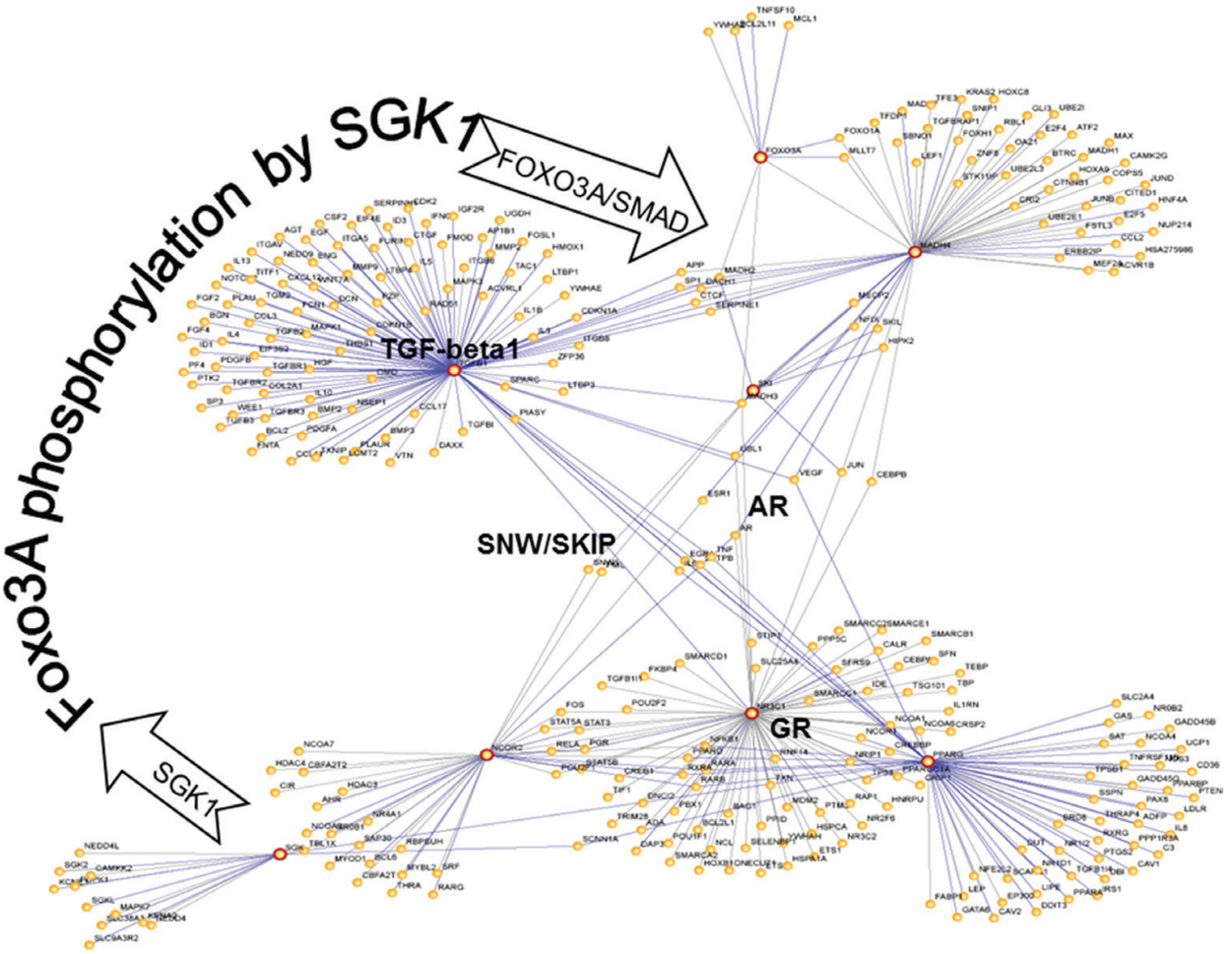


Figure 6. Putative feedback regulation of TGF-beta1 by its transcriptional target SGK1. TGF-beta1 and SGK1 Interactome was created using the Oncomine (http://www.oncomine.org), which represents physically interacting proteins based on the Human Protein Reference Database.

cells with the disturbed PI3K/Akt pathway, the AR-mediated mTOR activation induced cell proliferation, while the serum-induced SGK1 represented modulation of nutrient availability [20]. Our recent studies on cytotoxicity and cell death/proliferation in response to tumor suppressor p53 and ANXA7 suggested deficient PCD-type2 in LNCaP (data not shown).

At last, the spliceosomal regulator SNW/SKIP which mediates TGF-beta, NOTCH, Rb and nuclear hormone receptor signaling [19] may link defective TGF-beta pathway components including FOXO/SMAD to the AR- and GR-dependent alternative splicing in SGK1 and TGF-beta1 RNA in the hormone-sensitive LNCaP.

4. Discussions

Our observations on TGF-beta1 and SGK1 pathways in LNCaP are in line with previously reported evidence that SGK1 altered negative control of FOXO-dependent transcription by Akt/PKB [4]. SGK1 could contribute to the PI3K/Akt and AR controlled cell growth in LNCaP

where constitutive PI3K/Akt activation has been ascribed to phosphatidylinositol-phosphatase PTEN deficiency [21]. Reduced expression and hyperphosphorylation of FOXO3A in progression of LNCaP cells to androgen independence [22] could be also associated with the steroid-regulated SGK1. Correspondent to that, androgen-sensitive and GR-negative LNCaP lacked GC-induced cell growth inhibition unlike the androgen-resistant and GR-expressing prostate cancer cells in which GC could induce TGF-beta1 mRNA [23, 24]. Differential dexamethasone response in LNCaP versus DU145 and PC3 is consistent with the distinct TGF-beta1 and SGK1 mRNA message patterns found in this study. In prostate carcinogenesis, AR and TGF-beta1 interactions were implicated [25], and AR can inhibit TGF-beta-relevant transcription through SMAD3 [26]. Therefore, LNCaP cells could have a shift toward the AR-dominating TGF-beta1 cell survival control where pathological GC-responses could involve SGK1 and GR-mediated FOXO3A inactivation [10].

Another SGK1 target, NEDD4–2 can negatively regulate TGF-beta signaling through the ubiquitin-mediated degradation of SMAD2 and TGF-beta-RI [27], which has intrinsic serine/threonine kinase activity and can stimulate phosphorylation of SMADs [4]. LNCaP cells are defective for conventional TGF-beta-RI (which is not required for TGF-beta1 signaling) but overexpress the TGF-beta-RII in response to dihydrotestosterone [28] that restores cell growth inhibition by TGF-beta1 [29].

Structural changes in SGK1 (which is responsible for phosphorylation in response to various factors including GCs, TGF-beta1 and nutrient starvation) may cause downstream alterations associated with specific target proteins. SGK1 is involved in the cross-talk among FKHRL1 (or FOXO3a), p53 and GR [3, 30] as well as activation of various channels and transporters through the ubiquitin ligase Nedd4–2 [31]. Therefore, suggested electrostatic charge redistribution around a major kinase domain in the Δexon11-SGK1 could affect phosphorylation of the SGK1-related proteins indicating potential targets in a defective response to endogenous steroids with following cell growth imbalance in cancer. Moreover, identified aberrant SGK1 transcription may contribute to prostate carcinogenesis by affecting a reciprocal regulation of TGF-beta by GCs that could uncover a major dysfunction in the homeostatic cell growth control.

5. Conclusions

In summary, LNCaP alternative SGK1 transcription identified in this study may represent a feedback modulation in the TGF-beta1 pathway. Affecting TGF-beta1 signaling by controlling FOXO3A phosphorylation and thereby—nuclear transport and transcriptional activity, SGK1 may uncover cell growth control mechanisms that are lost in cancer. Further studies on the reciprocal TGF-beta-SGK1 associations can elucidate bimodal character of TGF-beta1 responses in the GC and sex hormone coregulated cell death/proliferation in homeostasis and carcinogenesis.

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