p53 Mutation Directs AURKA Overexpression via miR-25 and FBXW7 in Prostatic Small Cell Neuroendocrine Carcinoma

Zhen Li1, Yin Sun1, Xufeng Chen1, Jill Squires1, Behdokht Nowroozizadeh1, Chaozhao Liang2, and Jiaoti Huang1

Abstract

Prostatic small cell neuroendocrine carcinoma (SCNC) is a rare but aggressive form of prostate cancer that is negative for androgen receptor (AR) and not responsive to hormonal therapy. The molecular etiology of this prostate cancer variant is not well understood; however, mutation of the p53 (TP53) tumor suppressor in prostate neuroendocrine cells inactivates the IL8–CXCR2–p53 pathway that normally inhibits cellular proliferation, leading to the development of SCNC. SCNC also overexpresses Aurora kinase A (AURKA) which is considered to be a viable therapeutic target. Therefore, the relationship of these two molecular events was studied, and we show that p53 mutation leads to increased expression of miR-25 and down-regulation of the E3 ubiquitin ligase FBXW7, resulting in elevated levels of Aurora kinase A. This study demonstrates an intracellular pathway by which p53 mutation leads to Aurora kinase A expression, which is critically important for the rapid proliferation and aggressive behavior of prostatic SCNC.


Introduction

Prostate cancer is the leading cause of cancer-related death for men in western countries. Understanding the molecular mechanisms of prostate carcinogenesis and progression is the foundation and a challenge for the development of effective therapy. Patients with low grade and early stage of prostate cancers can be cured by surgery or radiotherapy. For those with advanced and metastatic prostate cancers that are not amenable for local therapies, hormonal therapy targeting androgen receptor (AR) pathway has been the treatment of choice for many decades. Unfortunately, this therapy is not curative, and the cancer invariably progresses to castration-resistant state with few therapeutic options.

The majority of human prostate cancers are classified as adenocarcinoma with the bulk tumor cells showing luminal differentiation including the expression of AR and PSA. Interestingly, all adenocarcinomas of the prostate contain some neuroendocrine (NE) cells (1, 2). Unlike the bulk tumor cells, the scattered NE tumor cells are usually quiescent. In contrast, an important histologic variant prostate cancer called small cell neuroendocrine carcinoma (SCNC) is composed of NE tumor cells that are highly proliferative and aggressive. Although SCNC is occasionally diagnosed in patients without any previous history of prostate cancer, it more commonly occurs as a recurrent tumor in patients with a history of adenocarcinoma who have received hormonal therapy. It has been suggested that the novel drugs abiraterone and enzalutamide (formerly known as MDV3100) that further inhibit AR signaling will induce even more cases of SCNC.

We recently demonstrated that the IL8/CXCR2/p53 signaling pathway keeps the NE cells in adenocarcinoma in a quiescent state, and mutant p53 inactivates this pathway, leading to hyperproliferation of NE cells and the development of SCNC (3). Meanwhile, previous study also found that Aurora kinase A was overexpressed in the majority of cases of SCNC, indicating a potential role of Aurora Kinase A in the development of SCNC (4). In this study, we provide evidence showing that p53 mutation leads to elevated expression of Aurora kinase A through regulation of miR-25 and FBXW7 (F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase) thus revealing a potential molecular mechanism of p53 mutation in promoting the rapid proliferation and aggressive behavior of NE tumor cells in prostatic SCNC.

Materials and Methods

Cell lines

Human prostate LNCaP Clone FGC, PC-3, and NCI-H660 cells were from American Type Culture Collection (ATCC) and were authenticated utilizing short tandem repeat profiling. LNCaP Clone FGC cells were cultured in ATCC-formulated RPMI-1640
medium supplemented with 10% FBS, 2 mmol/L l-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin in a humidified atmosphere of 5% CO₂ maintained at 37°C. PC-3 cells were cultured in ATCC-formulated F-12K medium with 10% FBS.

NCI-H660 cells were cultured in RPMI-1640 medium with 0.005 mg/ml insulin, 0.01 mg/ml transferrin, 30 mmol/L sodium selenite, 10 mmol/L hydrocortisone, 10 nmol/L beta-estradiol, 4 mmol/L l-glutamine, and 5% FBS (HITES medium). NE1.8 cells were provided by Dr. Ming-Fong Lin (5), and were cultured in phenol red–free RPMI 1640 supplemented with 10% charcoal-stripped FBS.

Nucleic acids

Small interference RNA for TP53 was purchased from IDT as predesigned siRNA: sense strand 5’rCrArCrArCrUrGrUrGrUrArGrUrGrUrGrUrGrGrArUrGrGrUrGrGrU-3’, antisense strand 5’rCrA-crCrArGrUrGrUrGrUrArGrUrGrUrGrUrGrU-rAr3’. Small interference RNA for FBXW7: sense strand 5’rGrCrUrGrGrUrGrGrUrGrGrArUrGrUrGrUrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrUrCrCrArArCrArCrArArCrUrCrCrArG-3’, antisense strand 5’rGrArGrUrGrGrUrGrGrUrGrGrArUrGrUrGrUrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGrUrGrGr UrGrArGrUrGrUrGrArArG-3’. cDNA of firefly luciferase was cloned into pCI-Neo vector followed by 3’ untranslated region (UTR) of FBXW7, which was joined by two separate PCR fragments (left fragment: 5’CTACTGCTAGAAGAGCAGAAAAGATGAATTT3’ and right fragment: 5’TGTGCCCAACCTCTGACITC3’). miR-25 antisense strand 5’GGAUCC3’. Plasmid DNA encoding wild-type p53 (pCDNA3.1-p53wt) was described previously (6). Plasmid DNA encoding R175H mutation of p53 (DNp53) was generated by mutagenesis PCR. These constructs were verified through restriction digestion and sequencing analysis.

Lentivirus

p53 (R175H) was subcloned into the EcoRI site of FUCRW lentiviral vectors (7). This construct was verified through restriction digestion and sequencing analysis. The lentivirus was prepared and titered as described (8). LNCAp cells were spin infected at 1,800 rpm for 45 minutes at room temperature. All procedures were performed under University of California, Los Angeles, safety regulations for lentivirus usage.

Antibodies

Anti-Aurora A kinase antibody was from Cell Signaling Technology, anti-FBXW7 antibody was from Bethyl Laboratories, anti-p53 antibody and anti-c-Myc were from Santa Cruz Biotechnology, anti-MYC antibody was from Abgent, anti-GAPDH antibody was from GeneTex, Inc.

Immunoblot assay

 celestrols were transfected with p53 in 5% nonfat dry milk in PBS for 30 minutes followed by incubation with primary antibody in 5% BSA overnight. Appropriate horseradish peroxidase–conjugated secondary antibodies and Supersignal West Femto chemiluminescent substrate (Thermo Fisher Scientific) were used to visualize antigen–antibody complexes.

siRNA transfection

Transfections were performed with negative control, TP53, or Fbxw7 siRNA (IDT) using the Xfect siRNA Transfection Reagent (Clontech), according to the manufacturer’s protocol.

Quantitative RT-PCR

Total RNA or miRNA was extracted from cells using the RNeasy Mini Kit (Qiagen) per the manufacturer’s instructions. Conversion to cDNA was achieved through the PrimeScript RT Master Mix (Takara). Quantitative RT-PCR was carried out using SYBR Premix Ex Taq II (Takara), 0.4 μmol/L oligonucleotide primers, and 0.1 μg cDNA. All primer sets for quantitative RT-PCR were illustrated in Supplementary Table S1. miRNA quantification was performed using the miRCURY LNA Universal RT microRNA PCR Starter Kit (Exiqon). Relative fold change in mRNA levels was calculated after normalization to β-actin using the comparative Cₘ method (9).

IHC

For immunohistochemical analysis of p53 and Aurora A kinase, tissue sections were deparaffinized with xylene and rehydrated through graded ethanol. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol for 10 minutes. Heat-induced antigen retrieval (HIER) was carried out for all sections in 0.01 mol/L citrate buffer, pH 6.0, using a vegetable steamer at 95°C for 25 minutes. Mouse monoclonal anti-p53 antibody, clone 1801 (EMD, OP09-100UG) was diluted with BSA to a concentration of 1:50 and applied to the sections. Incubation was for 45 minutes at room temperature followed by anti-mouse secondary antibody (MACH 2 Mouse HRP-Polymer; Biocare Medical; MHRP520L) incubation for 30 minutes at room temperature. Rabbit monoclonal Aurora kinase A antibody (Abcam; 1800-1) was diluted with BSA to a concentration of 1:50 and applied to the sections. Incubation was for 1 hour at room temperature followed by anti-rabbit secondary antibody (Dakocytomation Envision System Labelled Polymer HRP anti rabbit, Cat.# 4003) incubation for 30 minutes at room temperature. Diaminobenzidine was then applied for 10 minutes at room temperature to visualize p53 and Aurora Kinase A. Sections were counterstained with hematoxylin, dehydrated through graded alcohols, and coverslipped. Immunohistochemical semiquantitation was performed using the Quick score (Q) method (10). Results are scored by multiplying the percentage of positive cells (P) by the intensity (I) (0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining). Formula is defined as Q = P × I; maximum = 300.

Immunofluorescence double staining

Slides were deparaffinized with xylene and rehydrated through graded ethanol. HIER was carried out in 0.01 mol/L citrate buffer, pH 6.0, using a vegetable steamer at 95°C for 25 minutes. Sections were permeabilized for 10 minutes with 0.25% Triton X-100 and rinsed with PBS. Blocking was done with 2% BSA for
30 minutes at room temperature. Primary antibody mixtures (Aurora Kinase A 1:100 BSA + p53 1:25 BSA) were applied for 1 hour at room temperature. Slides were rinsed with PBS, and the secondary antibody mixture (goat anti–Mouse-Alexa Fluor 488 + goat anti–rabbit-Alexa Fluor 568, both 1:500 BSA) was applied for 1 hour at room temperature. Slides were rinsed with PBS and coverslipped using VECTASHIELD HardSet Mounting Medium with DAPI (Vector, H-1500).

**Statistical analysis**

Statistical analyses were performed using the Student t test with the Excel 2013 software. Error bars indicate SD calculated from three independent experiments.

**Results**

**P53 mutation leads to increased expression of miR-25 in prostate cancer cells.**

We previously demonstrated that the quiescent NE cells in prostatic adenocarcinoma contain wild-type p53, whereas the rapidly proliferating NE tumor cells of SCNC often contain mutated p53 (3). We proposed that p53 mutation may play a critical role in the development of aggressive behavior of prostatic SCNC, but the detailed mechanisms were unclear. P53 can regulate miRNA expression in cancer cells (11). In glioblastoma cells, for example, p53 has been reported to repress the expression of miR-25 and -32 (12). Thus, it is quite interesting whether there is also a relationship between p53 expression/function and the expression of miRNAs, such as miR-25 and/or -32, and the interaction then contributes to the biologic behavior of prostatic SCNC. We therefore tested this hypothesis in prostate cancer PC-3 and LNCaP cells. Our previous study has shown that LNCaP cells are typical prostate adenocarcinoma cells, and PC-3 cells are characteristic of SCNC (13). In addition, LNCaP cells express wild-type p53 protein, and PC-3 cells contain truncated p53 mutation, which leads to the absence of p53 protein expression.

We expressed either wild-type p53 protein in PC-3 cells, or mutant p53 that is defective in DNA binding (R175H) in LNCaP cells. We found that expression of wild-type p53 protein repressed miR-25 expression in PC-3 cells, and expression of R175H mutant p53 protein increased miR-25 level in LNCaP cells, both with statistical significances (Fig. 1A). However, we noticed that expression of wild-type p53 protein in PC-3 cells did not cause obvious changes in the expression of miR-32 (data not shown). In prostate NE cancer cell line NCI-H660 that contains wild-type p53, we also observed that knockdown of p53 by siRNA or expression of the dominant-negative p53 mutant both resulted in enhanced miR-25 expression (Fig. 1B).

We further examined whether the changes of miR-25 level in these cells were associated with potential regulation of cell cycles induced by changes of p53 status. We found that expression of dominant-negative p53 (DNp53) did not cause obvious changes of cell cycle distribution in LNCaP cells, although miR-25 level changes observed. In PC-3 cells, however, expression of wild-type p53 (WTp53) did induce a change in G2–M transition 24 hours later after transfection of mammalian expressive WTP53 construct. Interestingly, we observed statistically significant reduction of miR-25 levels in cells at this time point (Supplementary Fig. S1).

Taken together, these results suggest that p53 can regulate miR-25 expression in prostate cancer cells, whereas mutant p53
or loss of p53 functions can cause elevated expression of miR-25 expression.

P53 mutation leads to decreased expression of FBXW7 and overexpression of Aurora kinase A

miR-25 has many potential targets including FBXW7 and Wwp2 (WW domain containing E3 ubiquitin protein ligase 2) (14). Indeed, we observed that overexpression of miR-25 could lead to reduced levels of both FBXW7 and WWP2 in PC-3 cells, as well as in NE1.8 cells, a variant of LNCaP cells that resemble NE cells (Supplementary Fig. S2; ref. 5). FBXW7 encodes an E3 ubiquitin ligase whose substrates include several positive cell cycle regulators, such as MYCN (15), MYC (16, 17), Cyclin E (18, 19), and Aurora kinase A (20, 21). Of them, Aurora Kinase A is overexpressed in prostatic SCNC and may play important roles in the development of aggressive prostate tumor (4). We thus further tested whether p53 mutation or loss of function could cause changes of Aurora Kinase A expression via regulation of miR-25 and FBXW7. Indeed, as shown in Fig. 1C, we found that knocking down p53 with siRNA in NCI-H660 cells resulted in increased level of Aurora kinase A expression. And expression of DNP53 in NCI-H660 led to a change of Aurora kinase A expression similar to p53 knockdown. In addition, we observed reduced expression of FBXW7 in NCI-H660 cells with these manipulations of p53 expression.

Next, we determined if change of FBXW7 expression would affect the protein level of Aurora kinase A. In NCI-H660 and PC-3 cells, we found transfections of Fbxw7 siRNA decreased the expression of FBXW7 protein, and increased levels of Aurora kinase A. Similar results were also observed in NE1.8 cells (Fig. 2). In these cells, silencing of Fbxw7 also resulted in elevated protein levels of its targets C-MYC and MYCN. Thus, these results suggested that FBXW7 may also function as the ubiquitin E3 ligase targeting Aurora kinase A.

miR-25 mediates mutant p53–induced expression of Aurora A kinase

We next determined the potential role of miR-25 in the regulations of Aurora kinase A upon loss of p53 function in these prostate cancer cells. For this, we cotransfected p53 siRNA with miR-25 inhibitor into LNCaP cells. Figure 3A and B showed that miR-25 inhibitor prevented p53 knockdown–induced downregulation of FBXW7 and upregulation of Aurora kinase A in these LNCaP cells, indicating that loss of function of p53 may regulate Aurora kinase A expression through a linear pathway involving miR-25 and FBXW7. To further clarify the roles of miR-25 in this process, we transfected miR-25 into NE1.8 cells. As expected, our results showed that overexpression of miR-25 reduced FBXW7 level and increased Aurora kinase A protein expression (Fig. 3C).

To determine whether miR-25 can regulate FBXW7 expression through its likely target in its 3′UTR region, we generated a reporter construct where coding sequence for firefly luciferase was followed by a 3′UTR sequence of FBXW7, or by a mutant 3′UTR sequence of FBXW7. As shown in Fig. 3D, exogenous expression of miR-25 caused approximately 50% reduction of the luciferase activity with the wild-type 3′UTR of FBXW7, whereas no obvious changes of luciferase activity was observed with the mutant 3′UTR in response to the miRNA expression. Thus, our results indicated that miR-25 could directly regulate FBXW7 expression through the miRNA binding site in its 3′UTR.

We also tested the potential roles of miR-25 in the biologic behaviors of SCNC PC-3 cells. Our results showed that inhibition of miR-25 in PC-3 cells attenuates cell proliferation and reduced invasion capability (Supplementary Fig. S3).

Taken together, our results suggested a likely signaling pathway through which p53 mutation induces upregulation of miR-25 and downregulation of FBXW7, eventually leading to the overexpression of Aurora kinase A, which may promote rapid proliferation of the NE tumor cells of SCNC.

Coexpression of nuclear p53 and Aurora kinase A in human SCNC tissue

We further verified the coexpression of p53 and Aurora Kinase A in 12 cases of human prostatic SCNC and an equal number of cases of prostate adenocarcinoma. Our IHC study showed that, eight of the 12 prostatic SCNC cases had positive nuclear p53 staining, which usually results from mutation of p53 with increased p53 protein stability. Nine of the 12 cases also showed overexpression of Aurora kinase A. Of them, 6 cases were positive for both nuclear p53 and Aurora kinase A overexpression (Fig. 4A). We also noticed that all 12 cases of adenocarcinoma were negative for both p53 nuclear staining and Aurora kinase A overexpression. Furthermore, we found the coexpression of nuclear p53 and Aurora kinase A in these SCNC tissues (Fig. 4B). These results supported our hypothesis that p53 mutation might lead to the overexpression of Aurora Kinase A in prostatic SCNC.

We have shown previously that p53 mutation is common in prostatic SCNC and rare in untreated adenocarcinoma (3). Similarly, Rubin’s group (22) showed that Aurora kinase A is
overexpressed in prostatic SCNC but not in adenocarcinoma. Therefore, we performed analysis for miR-25 expression between the two types of tumors. In this study, total RNA was isolated from the parafﬁn section of the cancerous area from 12 cases of SCNC and an equal number of adenocarcinoma cases. The levels of miR-25 were measured and normalized to miR-191 as the internal control, and the ratios of these two miRNAs were then plotted. The box-and-whisker plots showed that almost half of the cases of prostatic SCNC have higher levels of miR-25 expression when compared with prostate adenocarcinoma (Fig. 4C). Protein overexpression of Aurora kinase A in human prostatic SCNC was conﬁrmed by IHC (Fig. 4D and E). Thus data from the human prostate cancer tissues also support the notion that p53 mutation in SCNC may lead to a higher miR-25 expression that contributes to the higher expression of Aurora kinase A.

**Discussion**

Prostatic small cell carcinoma is an underdiagnosed entity because patients with widely metastatic disease after hormonal therapy usually do not undergo biopsy or resection for histologic diagnosis. Its incidence is expected to rise after the recent approval of super-blockers of AR signaling pathway such as abiraterone and enzalutamide. In addition to a lack of effective therapy, the molecular mechanisms driving the development of SCNC remain unclear.

We recently showed that p53 mutation may be a critical molecular responsible for the aggressive behavior of SCNC (23), and the study from Rubin’s group reported gene ampliﬁcation and overexpression of MYCN and Aurora kinase A in these tumors (4). Aurora kinase A is an evolutionarily conserved serine/threonine kinase critical for mitotic regulation (23). It can phosphorylate multiple mitosis-associated proteins (e.g., Tacc and Nde1), thus modulating their activities (24, 25) and orchestrating centrosome maturation, spindle assembly, and mitotic entry. Aurora kinase A can also regulate protein translation through CPEB phosphorylation (26, 27). Thus, Aurora kinase A plays important roles in cell proliferation and has been considered a potential therapeutic target for prostatic SCNC. In addition, it has been also reported that wild-type p53 suppresses the expression of miR-25 (12), and mutant p53 or loss of p53 function resulted in increased miR-25 expression. The relationship between mutant
p53 and overexpression of Aurora kinase A in SCNC is thus quite interesting. In present study, we show that expression of mutant p53 protein leads to enhanced expression of Aurora kinase A in prostate cancer cells, and this was most likely mediated by increased miR-25 expression and decreased expression of FBXW7 subsequent to p53 mutation.

miR-25 is a well-studied oncogenic miRNA. It is 22 nucleotides long, localized in the minichromosome maintenance protein-7 (MCM7) gene, and transcribed as part of the miR-106b/C24 miRNA poly-cistron. It is overexpressed in several human cancers, including pediatric brain tumors (28), gastric adenocarcinoma (29), EGFR-positive lung adenocarcinoma (30), and prostate carcinoma (31), and has been reported to target different regulators of the apoptotic pathway, such as BIM (32), PTEN (31), and TRAIL (33). miR-25 also affects Ca^{2+} homeostasis by regulating mitochondria calcium efflux through targeting the mitochondria calcium uniporter (34), causing a strong decrease in mitochondrial Ca^{2+} uptake and, likely, conferring resistance to Ca^{2+}-dependent apoptotic stimuli. We found that p53 mutation–induced miR-25 overexpression downregulates the expression of ubiquitin E3 ligase FBXW7. FBXW7 is a potent ubiquitin E3 ligase that can degrade Aurora kinase A (35), lower level of FBXW7 thus leads to increased protein level of Aurora kinase A. In PC-3 and NE1.8 cells, we noticed that transfection with miR-25 reduced mRNA expressions of Aurora kinase A, but significantly increased protein levels of Aurora kinase A which can be affected by exposure to cycloheximide, a protein synthesis inhibitor (Supplementary Fig. S4), suggesting that the elevated protein level of Aurora kinase A in these cells was caused by the FBXW7-induced blockage of Aurora kinase A degradation. Inactivation of FBXW7 has also been noticed to be critical for the proliferation of leukemic stem cells, and contributes to the development of leukemia (36, 37). Thus, our results suggest a potential signaling pathway that how mutant p53 regulates level of Aurora kinase A in prostate cancer cells that

Figure 5.
A diagram depicting multiple pathways that lead to overexpression of Aurora kinase A in human prostatic small cell carcinoma.
may be correlated to rapid proliferation and aggressive behavior of prostatic SCNC.

Although our data suggest the presence of a linear pathway of p53 → miR-25 → FBXW7 → Aurora kinase A in SCNC, there are likely other important players in the pathogenesis of prostatic SCNC. In a significant number of SCNC cases, Aurora kinase A overexpression is associated with gene amplification, which involves different genetic events. Of note, Rubin’s group has shown that MYCN is also amplified and overexpressed in prostatic SCNC (4). Because expression of FBXW7 can also cause degradation of MYC, it would be interesting to study if p53 mutation also leads to MYC overexpression. In addition, Collins’ group reported that downregulation of the REST transcription complex may lead to the development of SCNC (38). These diverse findings suggest that the pathogenesis of SCNC is a complex process that may involve different players and multiple signaling pathways (Fig. 5).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: Y. Sun, X. Chen, C. Liang, J. Huang
Development of methodology: Z. Li, Y. Sun, C. Liang, J. Huang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Z. Li, Y. Sun, X. Chen, J. Squires
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z. Li, Y. Sun, B. Nowrooziadadeh, J. Huang

Writing, review, and/or revision of the manuscript: Z. Li, Y. Sun, X. Chen, J. Squires, J. Huang

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Li

Study supervision: J. Huang

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