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Glycogen Synthase Kinase-3: A Potential Preventive Target for Prostate Cancer Management

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Abstract

Prostate cancers are the frequently diagnosed cancers in men and patients with metastatic disease only have 28% chance for 5-year survival. Patients with low risk tumors are subjected to active surveillance while high risk cases are actively treated. Unfortunately, there is no cure for late-stage patients. Glycogen synthase kinase-3 (GSK-3, α and β) is a protein serine/threonine kinase and has diverse cellular functions and numerous substrates. Accumulating evidence indicates that GSK-3 α is mainly expressed in low-risk prostate cancers and is related to hormone-dependent androgen receptor (AR)-mediated gene expression, while GSK-3 β is mainly expressed in high-risk prostate cancers and is related to hormone-independent AR-mediated gene expression. GSK-3 has been demonstrated as a positive regulator in AR transactivation and prostate cancer growth independent of the Wnt/ β -catenin pathway. Different types of GSK-3 inhibitors including lithium show promising results in suppressing tumor growth in different animal models of prostate cancer. Importantly, clinical use of lithium is associated with reduced cancer incidence in psychiatric patients. Taken together, GSK-3 inhibition might be implicated in prostate cancer management as a preventive treatment.

Keywords

GSK-3; small chemicals; prostate cancer; lithium Chloride; cancer prevention; treatment

A. Prostate cancer management

The prostate produces the major fluid components of the semen to protect and to nourish sperm in the female reproduction system after ejaculation. The gland is located immediately

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below the urinary bladder surrounding the proximal urethra but in front of the rectum. Its growth and functionalities are predominantly maintained by androgens. Adenocarcinoma derived from epithelial cells of the prostate gland is a major type of prostate cancer that claims about 30K lives annually in US [1]. In Europe, it is reported that prostate cancers were the third leading cause of cancer-specific death behind lung and colorectal cancers [2].

Compared to most other types of solid malignancies, prostate cancer is highly heterogeneous in terms of genomic alterations and gene expression, tissue structure and morphology, as well as responses to treatment and patient outcome [3–5]. In spite of the seminal work of castration-based therapy in the 1940s [6] and recent advances of novel therapeutics including anti-androgens and immunotherapy [7–9], aggressive castration-resistant prostate cancers are not curable. Since FDA approval of prostate-specific antigen (PSA) screening in 1994, most prostate cancers were diagnosed at their early stage and often followed by active treatment such as radical prostatectomy and radiotherapy. Unfortunately, the death rate has not significantly improved [10, 11], indicating the need for improved treatment of aggressive cases.

In the clinic, there are two types of prostate cancers, indolent and aggressive, of which the latter comprises 20% of all cases leading to cancer-specific mortality [1, 12, 13]. Since indolent tumors are slow growing with low risk of progression, active surveillance is imposed for this population of patients [14]. Meanwhile, distinguishing the indolent cases from aggressive malignancies is challenging [3]. Despite extensive efforts in developing novel biomarkers in this regard, no single biomarker can accurately predict the aggressiveness of this cancer thus far [15]; largely due to the heterogeneous properties of prostate cancers between individual patients and/or even among different loci within a given tumor mass [3]. By recognizing the distinct genetic differences between patients [16], personalized medicine is emerging as a new strategy for prostate cancer management. Still, adequate biomarkers are needed to determine tumor aggressiveness.

Active surveillance with minimum intervention for low risk indolent patients is beneficial in practice because it reduces unnecessary invasive treatment [14, 17, 18]. Patient's psychological stress during active surveillance has become a new challenge due to the anxiety associated with a cancer diagnosis [19]. In this scenario, preventive treatments with existing drugs such as 5 α -reductase inhibitors [20] (as used in PCPT trial [21]) might be a valuable option [22, 23]. In addition, Aspirin [24], calcium channel blockers [25, 26], adrenergic receptor- β blockers [27] and Lithium [28] for improving the quality of life of these patients is also worthy of further exploration.

B. Basic aspects in GSK-3 regulation

Glycogen synthase kinase-3 (GSK-3) is an old gene with a homolog identified in every eukaryotic species examined and belongs to a family of conserved serine/threonine kinases present in all eukaryotic groups [29–31]. It was initially named because of its phosphorylation of glycogen synthase [32]. GSK-3 consists of two isoforms encoded by two distinct genes in humans, namely GSK3A (GSK-3 α , 51 kDa) and GSK3B (GSK-3 β , 47 kDa). They have 97% sequence homology within their kinase domains, whereas GSK-3 α

has an extended N-terminal glycine-rich tail [33]. In addition, alternative splicing of GSK-3 β with a 13-amino acid insert within the catalytic domain was identified in brain tissue [34]. Although these isoforms share substrates, their expression patterns, substrate preferences and cellular functions are not identical [29]. Regulation of GSK-3 activity involves multiple mechanisms, including **i**) inactivating phosphorylation on N-terminal serine α -21/ β -9 by protein kinase A (PKA) [35], protein kinase B (PKB/AKT) [36], ribosomal S6 kinases (p90RSK [37] and p70S6K [38]); **ii**) inactivating phosphorylation on threonine β -390 by p38 mitogen-activated protein kinase (p38MAPK) [39]; **iii**) priming phosphorylation on threonine β -43 by extracellular-signal-regulated kinases (ERK) followed by p90RSK-mediated serine β -9 phosphorylation [40]; **iv**) activating phosphorylation on tyrosine α -279/ β -216 within the catalytic domain by itself [41], by the Src kinase family member Fyn [42], by proline-rich tyrosine kinase-2 (PYK2) [43] or by ZAK1 in *Dictyostelium* [44]; **v**) substrate pre-phosphorylation (priming) & availability [29]; **vi**) association in distinct protein complexes and subcellular localization [29].

Kinase activities of GSK-3 α and GSK-3 β are regulated similarly in some cases [45] but differently in others [46]. The GSK-3 α -21/ β -9 phosphorylated N-terminal tail is considered a pseudo-substrate because it occupies the primed substrate docking site [47]; therefore, GSK-3 N-terminal phosphorylation might not be inhibitory for non-primed substrates [48]. In addition, it has been shown that GSK-3 (α or β) is associated with different cellular compartments or protein complexes, so to exert diverse functionalities by integrating various upstream stimuli with site- or pathway-specific substrates [29, 31]. For example, once GSK-3 is associated with certain protein complexes such as APC-Axin-GSK-3 β complex [49] and AMPK-AKT-GSK-3 complex [50], N-terminal phosphorylation had no effect on its kinase activity.

It has been revealed that GSK-3 regulates a wide range of cellular functions such as energy homeostasis, cell growth and survival, neural degeneration, organism development and immune responses [51]. It is also involved in a variety of disease processes including tumorigenesis [31]. As a protein kinase, over 500 proteins have been proposed to be GSK-3 substrates [52], but only 77 proteins were reported in cell-based assays [51]. There are two types of GSK-3 substrates; priming-dependent and non-priming substrates [29, 51]. Priming is deferred as a prior phosphorylation of the substrate by another kinase to form the motif-S/T-xx-x-S/T(P). The majority of substrates belong to the first category and only a few proteins, such as Axin, C/EBP β , Histone H1.5, MARK2, tau and AMP-activated protein kinase (AMPK), were considered as non-priming substrate [50, 51].

Growing evidence revealed isoform-specific preferences between GSK-3 α and β [29, 30, 53]. Genetic ablation of GSK-3 α or β in mice yielded totally different physiological consequences, of which GSK-3 β deletion caused embryonic lethality but GSK-3 α deletion resulted in enhanced glucose and insulin sensitivity accompanied by reduced fat mass in mice [48, 54–56]. Most interestingly, there are also some disparities of upstream stimuli that regulate these isoforms. For instance, protein kinase C (PKC) phosphorylated GSK-3 β but not GSK-3 α [57] while κ -B related kinase-i (IKKi) affects only GSK-3 α [58]. AKT family members have been extensively studied for regulation of GSK-3 β and all three isoforms phosphorylate serine 9 of GSK-3 β but only AKT2 phosphorylates serine 21 of GSK-3 α [59].

Nonetheless, these isoforms and substrate-specific regulation requires further examination in *in vivo* settings to uncover their physiological relevance.

C. GSK-3 expression in prostate cancer

Expression of GSK3A and GSK3B genes is ubiquitous but the regulation at the transcription level is largely unknown. During development, a drastic increase of GSK-3 gene expression was found in the juvenile and adolescent mouse brain [60]. In blood, Th17 T cells express a 10-fold higher level of GSK-3 β compared to other T cells [61]. In adult, early studies with northern blot techniques revealed higher levels of GSK3A and GSK3B mRNA in testis, thymus, prostate and ovary. However, GSK-3 α protein was highest in lung, then ovary, kidney and testis whereas GSK-3 β protein was highest in brain, then kidney and lung [62]. The discordance between the mRNA and protein levels reflects additional regulation of GSK-3 gene expression likely at the post-transcriptional level.

In human cancers, mixed findings were reported for the expression of GSK-3 α or β proteins in surgical specimens detected with immunohistochemical (IHC) technique. Early reports showed a positive correlation of GSK-3 α overexpression with tumor progression in multiple human malignancies including colon [63], urinary bladder [64], liver [65], cervix [66] and thyroid cancers [67]. Recent studies showed that elevated levels of GSK-3 protein or activation (tyrosine α -279/ β -216 phosphorylation) were associated with adverse prognosis in patients with lung cancer (positive in 41% cases) [68], gastric cancer (44%) [69] and glioblastoma (55%) [70]. GSK-3 β protein nuclear accumulation was found in the majority of solid malignancies such colon cancers (39%) [71], pancreatic cancers (51%) [72], urinary bladder cancer (62% non-invasive or 91% invasive TCC) [73], renal cancers (91.89%) [74]. In contrast, GSK-3 β serine-9 inactive phosphorylation was found in 47.2% breast cancers and was significantly correlated with a worse clinical outcome [75]. It is worth noting that antibodies for tyrosine α -279/ β -216 phosphorylated GSK-3 used in IHC often recognize non-specific nuclear antigens [76]; therefore, the results should be interpreted with caution.

In prostate cancers, an IHC study of surgical specimens from 499 patients revealed that increased cytoplasmic (but not nuclear) accumulation of GSK-3 β protein correlated with aggressive clinicopathological parameters including late clinical stage, lymph node metastasis, extracapsular extension, high Gleason score and 2-fold shorter recurrence-free survival with up to 12-year followup [77]. A recent report carefully examined the expression patterns of GSK-3 α and β proteins in prostate cancers [78] and found that in benign prostatic tissues GSK-3 α expression was relatively low and was mainly detected in the cytoplasm of both epithelial and stromal cells; whereas stromal cells expressed higher levels of GSK-3 α protein than epithelial cells. In prostate cancers, elevated GSK-3 α expression was found mainly in the cytoplasmic compartment in 31.6% cases mostly with low (< 7) Gleason sum score. In benign prostatic tissues, GSK-3 β protein was rarely detectable in epithelial cells but positive in stromal cells. Conversely, in the cancerous region, cytoplasmic GSK-3 β expression was detected in about 30% of prostate cases mainly with high (> 7) Gleason score while no GSK-3 β was detected in stromal cells. These data strongly suggest that higher levels of cytoplasmic GSK-3 β expression are associated with aggressive prostate cancers whereas GSK-3 α protein expression is associated with low risk

cases, and thus both might serve as novel biomarkers to distinguish indolent cases from aggressive diseases.

GSK-3 gene expression data at the mRNA levels is available from the online Oncomine™ and TCGA databases. Alterations of GSK-3 α or β gene expression at the mRNA levels are less than 2-fold in all cancer types including prostate cancers. These results suggest that the alterations observed in prostate cancers with immunochemistry technique [77, 78] are mainly due to changes in protein stability and distribution regulated through post-transcriptional mechanisms.

In addition, genetic alterations including GSK-3 genes in human cancer cell lines are available at the COSMIC online database (<http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>). In prostate cancer cell lines only one somatic GSK3A gene mutation, an in-frame deletion of c.553–555 (pK186), was identified in 22RV1 cells. In addition, GSK3A DNA copy loss was found in Ewings sarcoma-peripheral primitive neuroectodermal tumor line EW-11, while GSK3A DNA copy gain (5–10 copies) was found in four other cell lines (lung cancer NCI-H1299/NCI-H250 and gastric cancer SCH/GCIY). For the GSK3B gene, DNA copy loss was found in skin malignant melanoma MMAC-SF cells but no DNA copy gain was identified so far. Additionally, 5 different nonsense deletions and 13 missense mutations in the GSK3B gene were found in other cancer cell lines; however, none was found in prostate cancer cells. These data indicate that somatic alterations in GSK3 genes are not common in prostate cancers.

D. GSK-3 involvement in prostate cancer

The androgen receptor (AR)-related signaling pathway is considered the most critical player and a prime therapeutic target in prostate cancer [79–81]. Early studies showed that β -catenin interacts with the AR [82, 83] and that phosphatidylinositide 3-kinase (PI3K) activity is elevated in prostate cancers due to PTEN loss [84]. Because GSK-3 is the major regulator of β -catenin stability in the Wnt signaling pathway [85] and is a substrate of PI3K/AKT in the insulin signaling pathway [36], its involvement in AR transactivation was evaluated by three groups with *in vitro* models [86–88]. When exogenous β -catenin, GSK-3 β and AR proteins were overexpressed, GSK-3 β was found to negatively regulate AR transactivation either by promoting β -catenin degradation [86], by phosphorylating the AR ligand-binding domain [88] or by phosphorylating AR N-terminal ligand-independent activation function (AF)-1 domain [87]; all were regulated by PI3K/AKT activity. However, GSK-3-dependent AR phosphorylation was not identified in prostate cancer cells after androgen stimulation using a proteomic approach [89].

In contrast, we and other groups using more physiologically relevant model systems convincingly demonstrated that GSK-3 is a positive regulator in AR transactivation and prostate cancer tumor growth. These groups showed that: **i)** from multiple reporter gene assays driven by different AR responsive promoters, the classical GSK-3 inhibitor lithium and other small chemical GSK-3 specific inhibitors abrogated androgen-stimulated gene expression in prostate cancer cells [78, 90, 91]; **ii)** GSK-3 gene-specific silencing reduced AR transactivation in reporter gene assay or by assessing endogenous AR-regulated genes

[27, 91, 92]; iii) sequestering GSK-3 with its binding proteins Axin or FRAT suppressed AR transactivation [90]; iv) depleting endogenous β -catenin did not suppress but increased AR-mediated gene expression [90, 92]; v) GSK-3 specific inhibitors suppressed cell proliferation of prostate cancer cells *in vitro* [77, 90, 92–95] and xenograft tumor growth *in vivo* [96]; vi) most importantly, androgen stimulation of prostate cancer cells largely increased GSK-3 activating Y279/216 phosphorylation [92] and ablation of GSK-3 β Y216 phosphorylation with the Src inhibitor Dasatinib suppressed tumor growth of prostate cancer *in vitro* and *in vivo* [94]. Taken together, these data suggest that GSK-3 activity is involved in AR transactivation in prostate cancer development and progression and that GSK-3 inhibitor might serve as a potential preventive agent for prostate cancer management.

The mechanisms for GSK-3 inhibition-mediated tumor suppression are not fully clear and might be very complicated since GSK-3 has multiple functions involved in numerous cellular processes. Studies from our group revealed multiple clues, including reduced AR transactivation [92], disruption of E2F-DNA interaction and subsequent S-phase arrest [93], as well as accumulation of C/EBP α that interferes with E2F1 transactivation [96]. Other mechanisms include AR nuclear export and AR protein degradation after GSK-3 inhibition in prostate cancer cells [90, 91, 97]. In addition, GSK-3 inhibitors were shown to disrupt the DDX3/GSK-3 complex and thus sensitize prostate cancer cells to death receptor ligand TRAIL or chemodrug CCDO-induced apoptosis [98, 99], because GSK-3 interacts with anti-apoptotic proteins DDX3 and cellular inhibitor of apoptosis protein-1 (cIAP-1) to suppress apoptosis [100]. A very recent report [101] uncovered distinct phenotypes after silencing GSK3A or GSK3B individually using isoform-specific small hairpin RNA (shRNA) in prostate cancer cells. GSK3A shRNAs reduced cell survival while GSK3B shRNAs reduced cell-cell interaction and epithelial-mesenchymal transition. These data clearly indicate functional diversity between GSK-3 α and β proteins.

E. GSK-3 inhibitors for prostate cancer intervention

There is a long list of GSK-3 inhibitors reported, ranging from natural compounds, small peptides, and small synthetic chemicals [31, 102, 103]. The inhibitors are either reversible ATP competitive or non-ATP competitive. Usually, ATP competitive kinase inhibitors are not very specific because most of the ATP-binding domains are conserved in different kinases.

Therefore, a non ATP-competitive compound will present more specificity. Although most ATP-competitive inhibitors have not entered in clinical trials, one such inhibitor LY2090314 from Eli Lilly has completed two clinical trials and its third phase II trial with the chemodrug Gemcitabine is open now for metastatic pancreatic cancer (NCT01632306). TDZD-8 was the first non-ATP competitive GSK-3 inhibitor [104], its second generation Tideglusib has an irreversible property [105] and was tested in clinical trials for neuronal diseases [106–109]. Our studies showed that TDZD-8 treatment reduced prostate weight in mice and suppressed prostate cancer growth in the TRAMP mice, a murine transgenic prostate cancer model, and in a subcutaneous xenograft model of prostate cancer derived from AR-positive C4-2 or AR-negative PC-3 cells in nude mice [96].

Other types of GSK-3 inhibitors are Lithium salt and substrate-competitive peptides like L803-mts. Lithium competes with magnesium for a binding site on GSK-3 catalytic domain [110–112]. The clinical relevance of lithium use as potential cancer preventive agent was from an early report [28], which showed that in a cohort of 609 psychiatric patients treated with lithium, cancer incidence was significantly lower than that in 2396 controls and an inverted trend of cancer incidence was associated with lithium doses. Our group and others demonstrated that lithium treatment significantly suppressed xenograft tumor growth derived from human cancer cells including prostate cancer [96, 113, 114]. Although there is no report yet for its clinical efficiency on human cancers, an open-label phase-1 clinical trial is now recruiting patients for lithium safety and effect on clinically localized prostate cancers (NCT02198859) by our group.

The peptide L803-mts is a GSK-3 specific inhibitor acting as a primed pseudo-substrate [115]. It was derived from a GSK-3 substrate heat shock factor 1 (HSF-1). In animal experiments, L803-mts exerts a safe profile and specific inhibitory effect on GSK-3 to lower serum glucose levels as insulin mimetic [115]. Our studies showed that L803-mts had a similar effect as TDZD-8 in suppressing prostate cancer growth in the TRAMP mouse model [96]. Taken together, GSK-3 inhibitors might be considered as alternative agents for prostate cancer intervention, either for indolent tumors as a preventive treatment during active surveillance or as an adjunctive treatment with existing chemo-drugs or anti-androgens.

F. Conclusion and Future direction

GSK-3 α or β proteins have quite distinct roles in cell fate determination such as cellular survival and glucose metabolism [48, 56]. These proteins are differently expressed in prostate cancers [78] and are involved in positive regulation of AR transactivation and tumor growth of prostate cancer. GSK-3 α is associated with indolent low risk tumor and hormone-stimulated AR-mediated gene expression, while GSK-3 β is associated with aggressive high risk tumor and hormone-independent AR activity. Meanwhile, GSK-3 β suppression triggered alteration in other cellular signal pathways such as NF- κ B in prostate cancer cells and simultaneous inhibition of GSK-3 β and NF- κ B pathways enhanced the blockage of cancer cell proliferation [116]. Although structurally distinct GSK-3 inhibitors including lithium, TDZD-8 and L803-mts have showed promising results in mouse models of prostate cancer [96], their clinical effect is still await for the initial report.

Also, it is necessary to identify GSK-3 isoform-specific substrates that are critical in prostate cancer development and progression at different disease stages. Given the huge diversity of GSK-3 functionalities and substrates, isoform-specific and substrate-selective GSK-3 inhibitors will be ideal for clinical applications to avoid un-wanted adverse effects. Development of GSK-3 isoform-specific substrate-selective inhibitors with advanced technologies [117] should provide a superb safety profile and will be easily adapted in personalized medicine for prostate cancer management.

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Highlights

- We summarized the genetic information, gene expression at the mRNA and protein levels of GSK-3 in human prostate cancer cell lines and specimens.
- We provided a literature summary about the functional role of GSK-3 in prostate cancer cell proliferation, the AR-mediated gene expression, xenograft tumor growth and some molecular mechanisms.
- We discussed the potential use of GSK-3 inhibitors as a biomarker and a preventive agent in prostate cancer management.
- We listed the information of current clinical trials using GSK-3 specific inhibitors for various human disease including prostate cancers.