ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 456–463

UROLOGIC ONCOLOGY

Review article

Glycogen synthase kinase-3: A potential preventive target for prostate cancer management

Benyi Li, M.D., Ph.D.[a,*], James Brantley Thrasher, M.D.[a], Paul Terranova, Ph.D.[b,c]

[a] *Department of Urology, University of Kansas Medical Center, Kansas City, KS*
[b] *Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS*
[c] *Department of Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, KS*

Received 6 March 2015; received in revised form 30 April 2015; accepted 5 May 2015

Abstract

Objectives: 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, whereas high-risk cases are actively treated. Unfortunately, there is no cure for patients with late-stage disease. Glycogen synthase kinase-3 (GSK-3, α and β) is a protein serine/threonine kinase and has diverse cellular functions and numerous substrates. We sought to summarize all the studies done with GSK-3 in prostate cancers and to provide a prospective direction for future work.

Methods and materials: A comprehensive search of the literature on the electronic databases PubMed was conducted for the subject terms of GSK-3 and prostate cancer. Gene mutation and expression information was extracted from Oncomine and COSMIC databases. Case reports were not included.

Results: Accumulating evidence indicates that GSK-3α is mainly expressed in low-risk prostate cancers and is related to hormone-dependent androgen receptor (AR)–mediated gene expression, whereas GSK-3β 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-3inhibitors 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.

Conclusions: 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 and treatment

1. 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 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 approximately 30 thousand lives annually in United States [1]. In Europe, it is reported that prostate cancers were the third leading cause of cancer-specific death following lung and colorectal cancers [2].

When compared with most other types of solid malignancies, prostate cancer is highly heterogeneous in 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

The research activities in Dr Benyi Li's laboratory were supported by the SWOG HOPE Foundation, USA, DoD PCRP Grants (DAMD17-03-1-0121, W81XWH-04-0214, W81XWH-07-1-0021, W81XWH-09-1-0455), NIH, USA NCI (1R21CA175279-01A1), NIH-COBRE Grant (1P20RR015563), the KU William L. Valk Foundation, the KUMC Mason Foundation, and Lied Foundation, as well as a Chinese Natural Science Foundation, China Grant (CNSF81172427).

* Corresponding author. Tel.: +1-913-588-4773.
E-mail address: bli@kumc.edu (B. Li).

http://dx.doi.org/10.1016/j.urolonc.2015.05.006
1078-1439/

therapy in the 1940s [6] and recent advances of novel therapeutics including antiandrogens and immunotherapy [7–9], aggressive castration-resistant prostate cancers are not curable. Since Food and Drug Administration approval of prostate-specific antigen 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 2 types of prostate cancers, indolent and aggressive, of which the latter comprises 20% of all cases leading to cancer-specific mortality [1,12,13]. As indolent tumors are slow growing with a 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 owing to the heterogeneous properties of prostate cancers between individual patients and 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 owing to the anxiety associated with a cancer diagnosis [19]. In this scenario, preventive treatments with existing drugs such as 5α-reductase inhibitors [20] (as used in the Prostate Cancer Prevention 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 are also worthy of further exploration.

2. Basic aspects in glycogen synthase kinase-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 2 isoforms encoded by 2 distinct genes in humans, namely GSK3A (GSK-3α, 51 kDa) and GSK3B (GSK-3β, 47 kDa). They have 97% sequence homology within their kinase domains; however, GSK-3α has an extended N-terminal glycine-rich tail [33]. In addition, alternative splicing of GSK-3β 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], and 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 prephosphorylation (priming) and availability [29]; and (vi) association in distinct protein complexes and subcellular localization [29].

Kinase activities of GSK-3α and GSK-3β 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 pseudosubstrate because it occupies the primed substrate docking site [47]; therefore, GSK-3 N-terminal phosphorylation might not be inhibitory for nonprimed substrates [48]. In addition, it has been shown that GSK-3 (α or β) is associated with different cellular compartments or protein complexes, so as 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-3β complex [49] and adenosine monophosphate-activated protein kinase (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, more than 500 proteins have been proposed to be GSK-3 substrates [52], but only 77 proteins were reported in cell-based assays [51]. There are 2 types of GSK-3 substrates: priming-dependent and nonpriming substrates [29,51]. Priming is deferred as a prior phosphorylation of the substrate by another kinase to form the motif -S/T-x-x-x-S/T(P). Most of the substrates belong to the first category and only a few proteins such as Axin, C/EBPβ, Histone H1.5, MARK2, tau, and AMPK were considered as nonpriming substrates [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-3β deletion caused embryonic lethality but GSK-3α deletion resulted in enhanced glucose and insulin sensitivity accompanied by reduced fat mass in mice [48,54–56]. Most interestingly, there are also some