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EXPLORING DRUGGABLE TARGETS ASSOCIATED WITH PROSTATE CANCER USING A NETWORK PHARMACOLOGY APPROACH

Omobhude Fidelis Aluefua*[1], Aminu Chika[1], Abdulgafar Olayiwole Jimoh[1], Adamu Ahmed Adamu[1], Ridwanu Zauro Abubakar[1], Ephraim John Atabo[2]

[1]Department of Pharmacology and Therapeutics, Usmanu Danfodiyo University, Sokoto, Nigeria.
[2]University Hospitals, Plymouth NHS Trust, United Kingdom.

***Corresponding Author: Omobhude Fidelis Aluefua**

Department of Pharmacology and Therapeutics, Usmanu Danfodiyo University, Sokoto, Nigeria.

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ABSTRACT

Background: Prostate Cancer (PCa) is the second most prevalent cancer among young Nigerian men under 55 years old, after liver cancer. Although androgen deprivation therapy is commonly utilised, it is associated with significant adverse effects. All PCa will eventually become hormone resistant. Computational methods are useful for determining protein targets for small compounds, identifying novel targets for existing medications, or repurposing them. **Objective:** This study aimed to explore druggable protein targets associated with PCa using a network pharmacology approach. **Method**: Cytoscape (v3.9.1) with the StringApp (v2.2.0) was used to analyse protein targets related to PCa. A network was imported using the STRING: disease query with a confidence score threshold of 0.7, limited to 50 protein targets. The network included proteins associated with PCa, with a likelihood that the proposed association is strong based on the disease score. **Result:** The disease query returned 50 prostate cancer-associated proteins, ranked from highest to lowest in terms of disease scores using Cytoscape software. The proteins with the highest disease scores were AR, FOLH1, TMPRSS2, PIK3CA, PIK3CB, PIK3CG, PIK3CD, EGFR, ERBB2, and MTOR. The disease score reflected how frequently the target proteins were mentioned in the downloaded abstract, with AR earning the highest score. **Conclusion:** This Insilico analysis ranked druggable targets associated with PCa in descending order by disease score. In drug discovery, the emphasis is on nodes with higher disease scores to identify the most promising targets for validation or trial. Therefore, targeting two or more of these proteins together could be a promising treatment approach for PCa.

KEYWORDS: *Cytoscape, Network Pharmacology, Prostate cancer, Proteins, Targets.*

1. INTRODUCTION

Prostate cancer (PCa) is the most frequent malignancy among males over 55 years old. Although it can be seen from the age of 50 and up, the rate of occurrences increases dramatically after the age of 55.[1] Globally, more than 1.44 million cases were detected in 2020, with an age-standardised incidence rate (ASIR) of 30.7 per 100,000 men. Men aged 65 and up account for about 60% of all PCa diagnoses.[1] Age-standardised death rates are highest in the Caribbean (Barbados, Jamaica, and Haiti), South America, and sub-Saharan Africa.[2] PCa is the second most prevalent cancer among young Nigerian men under 55 years old, after liver cancer. The percentage of young men with PCa was 8.86%.[2] The initial therapy and continuous monitoring of patients with PC place a significant strain on the US healthcare system. PC treatment costs approximately $34,000 per patient over their lifetime, accounting for up to one-third of total medical care depletion.[3] Although androgen deprivation therapy (ADT) is commonly utilised, its significance in the treatment of PCa is hotly debated.[4] Adverse effects of LHRH agonists include the flare phenomenon, hot flashes, loss of libido, erectile dysfunction, depression, muscle wasting, anaemia, and

osteoporosis. Furthermore, ADT decreased insulin sensitivity while increasing body weight, serum cholesterol, and triglyceride levels.[4] The first-generation androgen receptor antagonists (ARAs), which include bicalutamide, nilutamide, and flutamide, do not entirely inhibit AR activity. Enzalutamide, apalutamide, and darolutamide are the currently used second-generation ARAs, that share a similar mode of action and side effect profile.[5] All PCa will eventually become hormone resistant. The median survival time after developing hormone-resistant PCa is 6-12 months.[6] Given these challenges, there is an urgent need to investigate alternative therapeutic targets associated with PCa. Current trends in drug discovery prioritise disease processes and their comprehension, followed by target identification and lead compound discovery.[7] Reliable target identification and validation, combined with drug discovery approaches, will pave the way for more efficient computer-aided drug discovery. Target identification can be achieved using direct biochemical approaches, genetic interactions, or computational inference.[7] Computational methods are employed on their own to determine protein targets for small compounds, as well as to provide analytical assistance for proteomic and genomic procedures.[8] These strategies can also be used to identify novel targets for current medications, to repurpose them or to explain their off-target effects. Network-based techniques, sometimes known as 'systems chemical biology', 'network pharmacology', or 'systems pharmacology', broaden systems biology to include drug and ligand target networks. Such techniques are required, as many phenotypes are induced by the impact of chemicals on several targets.[8]

Every living cell's activity is essentially determined by a complex network of interacting proteins that collaborate to contribute to common biological processes via a variety of interaction types, including physical binding, genetic relationships, and regulatory impacts.[9] Unravelling protein networks in their different modalities remains a major research priority. As a result, several databases have been created over the years to address specific research needs. Among these databases, STRING stands out for its extensive evidence base, sophisticated scoring system, user-friendly interface, and full range of enrichment features.[9] However, the increasing volume of data and developments in text-mining tools have subsequently enabled the composite, general-purpose databases to catch up, providing more detailed maps of the interaction space.[9] Hence, this study was designed to explore druggable protein targets associated with PCa using the network pharmacology approach and to rank these proteins according to their disease score.

2. METHODOLOGY

2.1 Retrieval of the STRING network from STRINGApp

Cytoscape software (version 3.9.1) was utilised for this analysis. The StringApp (version 2.2.0) was installed via the Cytoscape App Store. Using the 'File' menu in Cytoscape, we navigated to 'Import' and selected 'Network from Public Database'. To retrieve target-disease association networks, the STRING: disease query was chosen as the data source, with 'prostate cancer' entered as the disease term. The confidence score threshold was set at 0.7, and the number of prostate cancer-related protein targets to be retrieved was limited to 50. StringApp then downloaded the corresponding STRING network, containing proteins associated with PCa. All protein-protein interactions in STRING are assigned precomputed confidence scores ranging from 0 to 1, representing the estimated probability that a proposed association is accurate based on the supporting evidence.[9]

2.2 Data analysis: The data was analysed with Cytoscape software version 3.9.1, with the confidence score of the proteins to be downloaded set at 0.7.

3. RESULTS

3.1 String network for target proteins associated with Prostate cancer

The disease query returned 50 prostate cancer-associated proteins, which were downloaded, including targets that were frequently referenced in published abstracts. Figure I displayed a network of target proteins associated with PCa derived from the STRING database. Nodes in networks represent target proteins, whereas edges indicate protein interactions.

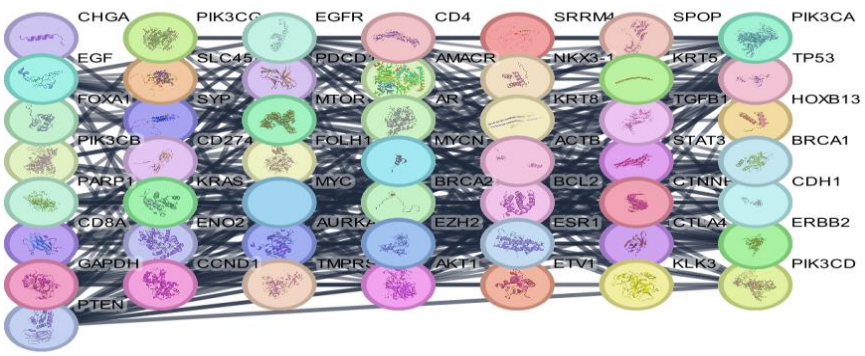

Figure I: Merging string data into a network to uncover relationships between the Prostate cancer-associated target proteins.

3.2 Ranking of Prostate cancer-associated target proteins according to their disease scores

Using Cytoscape software, the target proteins were ranked from top to lowest in terms of disease scores, which reflected how frequently the target proteins were mentioned in the downloaded abstract, with AR earning the highest score (Table I). AR, FOLH1, TMPRSS2, PIK3CA, PIK3CB, PIK3CG, PIK3CD, EGFR, ERBB2, and MTOR were targets with high disease scores.

Tab. I: Disease scores of Prostate cancer-associated target proteins.

S/N*	Display name	Description	Disease Score**	S/N	Display name	Description	Disease Score**
1	KLK3	Prostate-specific antigen	3.341866	26	EZH2	Histone-lysine N-methyltransferase EZH2	2.293458
2	AR	Androgen receptor	3.109409	27	TGFB1	Transforming growth factor beta-1 proprotein	2.282153
3	NKX3-1	Homeobox protein Nkx-3.1	2.927436	28	CTNNB1	Catenin beta-1	2.275767
4	FOLH1	Glutamate carboxypeptidase 2	2.921006	29	ACTB	Actin, cytoplasmic 1, N-terminally processed	2.272801
5	PTEN	Phosphatase and tensin homolog	2.747578	30	MYCN	N-myc proto-oncogene protein	2.26833
6	TP53	Cellular tumor antigen p53	2.73044	31	HOXB13	Homeobox protein Hox-B13	2.25951
7	TMPRSS2	Transmembrane protease serine 2 non-catalytic chain	2.637782	32	MTOR	Serine/threonine-protein kinase mTOR	2.257865
8	AMACR	Alpha-methylacyl-CoA racemase	2.584977	33	CDH1	Cadherin-1	2.247037
9	SPOP	Speckle-type POZ protein	2.537953	34	SLC45A3	Solute carrier family 45 member 3	2.245179
10	AKT1	RAC-alpha serine/threonine-protein kinase	2.512348	35	ETV1	ETS translocation variant 1	2.229777
11	MYC	Myc proto-oncogene protein	2.500352	36	AURKA	Aurora kinase A	2.213586
12	FOXA1	Hepatocyte nuclear factor 3-alpha	2.476783	37	SRRM4	Serine/arginine repetitive matrix protein 4	2.188277
13	PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	2.458293	38	KRT8	Keratin, type II cytoskeletal 8	2.187368
14	CD8A	T-cell surface glycoprotein CD8 alpha chain	2.457663	39	ENO2	Gamma-enolase	2.181434
15	CHGA	p-Glu serpinin precursor	2.437522	40	PARP1	Poly [ADP-ribose] polymerase 1	2.158846
16	CD274	Programmed cell death 1	2.426639	41	BRCA2	Breast cancer type 2 susceptibility protein	2.158827
17	GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	2.38879	42	STAT3	Signal transducer and activator of transcription 3	2.158213
18	PIK3CB	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta isoform	2.380015	43	EGF	Pro-epidermal growth factor	2.152619
19	PIK3CG	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	2.378046	44	BRCA1	Breast cancer type 1 susceptibility protein	2.151161

20	SYP	Synaptophysin	2.373982	45	CCND1	G1/S-specific cyclin-D1	2.138579
21	PIK3CD	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	2.370919	46	BCL2	Apoptosis regulator Bcl-2	2.125777
22	EGFR	Epidermal growth factor receptor	2.340094	47	PDCD1	Programmed cell death protein 1	2.123927
23	CTLA4	Cytotoxic T-lymphocyte protein 4	2.316529	48	ESR1	Estrogen receptor; Nuclear hormone receptor	2.121666
24	ERBB2	Receptor tyrosine-protein kinase erbB-2	2.310928	49	KRAS	GTPase KRas, N-terminally processed	2.115279
25	CD4	T-cell surface glycoprotein CD4	2.297779	50	KRT5	Keratin, type II cytoskeletal 5	2.107336

*According to disease score, from highest to lowest. S/N = Serial Number. **A higher disease score (a lower p-value or higher confidence score) signifies a stronger link between a protein target and PCa.

4. DISCUSSION

Protein networks have grown in popularity as a technique for evaluating and visualising huge lists of proteins or genes generated through proteomics and other high-throughput technologies.[9] One of the most popular sources of such networks is the STRING database (https://www.stringdb.org), which contains protein networks for over 2000 organisms, including both physical interactions from experimental data and functional associations from curated pathways, automatic text mining, and prediction methods.[9]

In this study, we used the Cytoscape software to rank prostate cancer-associated target proteins from highest to lowest in terms of disease scores, with AR, FOLH1, TMPRSS2, PIK3CA, PIK3CB, PIK3CG, PIK3CD, EGFR, ERBB2, and MTOR having high disease scores.

The disease score reflected how frequently prostate cancer-associated target proteins were mentioned in the downloaded abstract, with AR receiving the highest score. In drug discovery or systems biology, the emphasis is on nodes with higher disease scores to identify the most promising targets for validation or trial.[10] In Cytoscape, especially when utilising plugins like STRINGApp or integrating data from DISEASES or DisGeNET, the disease score in the node table reflects the strength of correlation between a target (gene/protein) and a specific disease based on aggregated evidence.[10]In essence, disease scores are critical in cytoscape for prioritising, comprehending, and eventually leading the development of disease therapeutics by emphasising the most promising drug targets and their interactions within complicated biological networks.[10]

The androgen receptor (AR) is a steroid receptor transcriptional factor for testosterone and dihydrotestosterone that consists of four primary domains: the N-terminal domain, the DNA-binding domain, the hinge region, and the ligand-binding domain. AR plays an important role in PCa, particularly castration-resistant PCa (CRPC).[11] Androgen deprivation therapy can decrease hormone-naïve PCa. However, PCa adapts to survive at low androgen levels. These mechanisms include AR point mutations, AR overexpression, changes in androgen biosynthesis, constitutively active AR splice variants without ligand binding, and changes in androgen cofactors. AR was found to be active in CRPC and remains a potential target for treatment.[11]

The majority of pharmaceutical therapies targeting Glutamate carboxypeptidase 2 (FOLH1) are aimed at PCa. FOLH1 expression levels are significantly elevated in androgen-independent and metastatic disease. As a result, the enzyme could also serve as an important therapeutic target.[12]

Transmembrane protease serine 2 non-catalytic chain (TMPRSS2) is a Type II transmembrane serine protease that is overexpressed primarily in pancreatic, thyroid, and cancer tissues.[13] Compared to hepsin, it has an extra low-density lipoprotein receptor class A (LDLA) domain located N-terminal to the SR and SPD domains. The biological mechanism by which TMPRSS2 promotes cancer cell metastasis remains unknown. However, it accelerates cancer progression by stimulating the loss of E-cadherin-mediated cell-cell adhesion and accelerating the epithelial-mesenchymal transition (EMT).[13]

The Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit/Protein Kinase B (PI3K/AKT) signalling system is linked to the development of PCa, with abnormal activation boosting cancer cell growth and proliferation, according to multiple studies.[14] As a result, PI3K and its isoforms PIK3CA, PIK3CB, PIK3CG, and PIK3CD have received significant attention as prospective PCa therapy targets. Furthermore, research has shown that the PI3K/AKT pathway interacts with a variety of other pathways, the most important of which is the AR pathway. Therefore, the combined targeting of these two pathways constitutes a possible treatment approach for PCa.[14]

The epidermal growth factor receptor (EGFR) is a 170 kDa proto-oncogene and transmembrane receptor that is commonly overexpressed in a variety of cancers, including PCa. Ligand binding to EGFR causes dimerisation, phosphorylation, and internalisation of the EGFR, which activates a network of intracellular signalling pathways that result in DNA synthesis, cell proliferation, migration, and adhesion.[15] It has been demonstrated that almost 30% of PCa patients overexpress EGFR, and that dysregulation of EGFR-mediated signalling pathways is related to poor clinical outcomes. Although EGFR has been discovered as an essential anti-tumour target, therapy targeting EGFR with modest tyrosine kinase inhibitors such as Gefitinib, Lapatinib, and Erlotinib has demonstrated little efficacy in PCa.[15]

Recent research indicates that stimulation of Receptor tyrosine-protein kinase ErbB-2 signalling promotes CR PCa cell proliferation via downstream effector pathways such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K).[16] Furthermore, the autocrine growth factor loop containing ErbB-1, ErbB-2, and ErbB-3 can activate AR and accelerate CR PCa development. In addition to AKT, active ErbB-2 triggers the MAPK pathway, which includes ERK1/2. These proteins are frequently found to be activated in aggressive PCa and are important regulatory kinases for processes involved in PCa genesis and progression. Thus, because it promotes the metastatic phenotype and induces AR signalling, ERK is a potential therapeutic target for CR PCa therapy.[16]

The phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) signalling cascade is an important carcinogenic signalling pathway that plays a role in various cellular processes important for cancer progression. In many malignancies, receptor tyrosine kinases improperly activate the PI3K-AKT pathway.[17] The PI3K/AKT/mTOR pathway inhibits apoptosis, increases cancer cell proliferation, and confers resistance to anticancer medicines that act on cellular differentiation and metabolism. Recently, multiple studies have shown that activation of the PI3K/AKT/mTOR pathway is closely linked to PCa progression. Furthermore, it has been proposed that this signalling system may serve as a novel target for therapeutic intervention in PCa.[17]

5. CONCLUSION

In this *Insilico* analysis, we ranked druggable targets associated with PCa in descending order by disease score, including AR, FOLH1, TMPRSS2, PIK3CA, PIK3CB, PIK3CG, PIK3CD, EGFR, ERBB2, and MTOR. In drug discovery or systems biology, the emphasis is on nodes with higher disease scores to identify the most promising targets for validation or trial. As a result, targeting two or more of these proteins together could be a promising treatment approach for PCa.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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