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Review

The role of SRC-3 in prostate cancer progression and implications for therapeutic targeting: A systematic review

[El papel de SRC-3 en la progresión del cáncer de próstata y las implicaciones para la orientación terapéutica: Una revisión sistemática]

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Abstract

Context: Prostate cancer remains a significant global health concern, and understanding the molecular drivers of this disease is crucial for developing effective diagnostic and therapeutic strategies. Steroid receptor coactivator-3 (SRC-3), a member of the SRC family, has emerged as a key player in prostate cancer pathogenesis.

Aims: To examine the role of SRC-3 in prostate cancer, encompassing molecular mechanisms, clinical implications, and therapeutic opportunities.

Methods: A systematic literature search following PRISMA guidelines was conducted in PubMed, PMC, and other relevant databases to identify studies that investigate SRC-3 in prostate cancer.

Results: 785 articles were retrieved from databases using specific keywords and MeSH terms related to SRC-3 and Prostate Cancer. After removing 461 duplicates, 260 articles were excluded based on title and abstract review. Subsequently, a comprehensive screening by three researchers resulted in 47 relevant articles for this systematic review. Evidence suggests that SRC-3 expression correlates with prostate cancer aggressiveness, disease recurrence, and poor patient outcomes. Its potential as a diagnostic biomarker and therapeutic target if explored, offers insights into personalized medicine approaches.

Conclusions: SRC-3 plays a pivotal role in prostate cancer, influencing disease progression and clinical outcomes. Understanding the molecular intricacies of SRC-3 in prostate cancer offers new opportunities for precision medicine and innovative therapeutic approaches. This review provides a comprehensive overview of SRC-3's involvement in prostate cancer, emphasizing its clinical relevance and potential as a therapeutic target, ultimately contributing to improved patient care in the era of personalized oncology.

Keywords: androgen receptor; signaling; prostate cancer; SRC-3; therapeutics.

Resumen

Contexto: El cáncer de próstata sigue siendo un importante problema de salud mundial, y la comprensión de los impulsores moleculares de esta enfermedad es crucial para el desarrollo de estrategias diagnósticas y terapéuticas eficaces. El coactivador del receptor de esteroides 3 (SRC-3), miembro de la familia SRC, se ha revelado como un agente clave en la patogénesis del cáncer de próstata.

Objetivos: Examinar el papel de SRC-3 en el cáncer de próstata, abarcando mecanismos moleculares, implicaciones clínicas y oportunidades terapéuticas.

Métodos: Se realizó una búsqueda bibliográfica sistemática siguiendo las directrices PRISMA en PubMed, PMC y otras bases de datos relevantes para identificar estudios que investiguen SRC-3 en cáncer de próstata.

Resultados: Se recuperaron 785 artículos de bases de datos utilizando palabras clave específicas y términos MeSH relacionados con SRC-3 y cáncer de próstata. Tras eliminar 461 duplicados, se excluyeron 260 artículos basándose en la revisión del título y el resumen. Posteriormente, un cribado exhaustivo realizado por tres investigadores dio como resultado 47 artículos relevantes para esta revisión sistemática. Las pruebas sugieren que la expresión de SRC-3 se correlaciona con la agresividad del cáncer de próstata, la recurrencia de la enfermedad y los malos resultados de los pacientes. Su potencial como biomarcador de diagnóstico y diana terapéutica, si se explora, ofrece ideas sobre enfoques de medicina personalizada.

Conclusiones: SRC-3 desempeña un papel fundamental en el cáncer de próstata, influyendo en la progresión de la enfermedad y en los resultados clínicos. La comprensión de los entresijos moleculares de SRC-3 en el cáncer de próstata ofrece nuevas oportunidades para la medicina de precisión y los enfoques terapéuticos innovadores. Esta revisión ofrece una visión global de la implicación de SRC-3 en el cáncer de próstata, destacando su relevancia clínica y su potencial como diana terapéutica, contribuyendo en última instancia a mejorar la atención al paciente en la era de la oncología personalizada.

Palabras Clave: cáncer de próstata; receptor de andrógenos; señalización; SRC-3; terapéutica.

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Abbreviations: AD: Transcriptional Activation Domains; ADT: Androgen Deprivation Therapy; AIB1: Amplified in Breast Cancer 1; AR: Androgen Receptor; ARSI: Androgen Receptor Signaling Inhibitor; bHLH: Basic-Helix-Loop-Helix; CBP: Cyclic Adenosine Monophosphate Response Element Binding Protein; CRPC: Castration-Resistant Prostate Cancer; DHT: Dihydrotestosterone; HAT: Histone Acetyltransferase; MIF: Migration Inhibitory Factor; NCOA: Nuclear Receptor Coactivator; PCa: Prostate Cancer; PTM: Post-Translational Modification; RID: Receptor-Interaction Domain; SRC-3: Steroid receptor coactivator 3; PTMs: Post-translational Modifications.

INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men worldwide, representing a substantial health burden (ACS, 2023). Although there has been significant advancements in our understanding of this disease, its etiology, progression, and therapeutic management remain complex and multifaceted (Barnard et al., 2020; Bernasocchi and Theurillat, 2022; Chen et al., 2023; Crona and Whang, 2017). Despite these advancements in diagnosis and treatment, PCa mortality remains significant. A key challenge lies in identifying novel therapeutic targets that specifically address the complex molecular mechanisms driving disease progression and resistance to current therapies (Cleanclay et al., 2023). A deeper comprehension of the molecular mechanisms underpinning PCa is imperative for the development of effective diagnostic tools and targeted therapies. In this context, the steroid receptor coactivator-3 (SRC-3), also known as amplified in breast cancer 1 (AIB1), has emerged as a crucial player in PCa biology (Szwarc et al., 2014).

SRC-3 is a member of the steroid receptor coactivator (SRC) family, which includes SRC-1 and SRC-2 (Xu and Li, 2003). These coactivators serve as pivotal intermediaries in the intricate regulatory networks governing transcriptional events in response to hormonal and growth factor signaling (Li et al., 2021). Among the SRC family members, SRC-3 has garnered increasing attention for its diverse roles in various cancers, including breast, ovarian, and PCa. While initially recognized for its involvement in hormone-dependent breast cancer, SRC-3's significance in PCa is becoming increasingly evident (Maurya et al., 2022). PCa's progression is intricately linked to the androgen receptor (AR) signaling pathway (Zakari et al., 2024). AR is a central player in PCa development and progression, and its aberrant activation is a hallmark of this disease (Mohler et al., 2021; Zakari et al., 2024). However, due to the unique properties and diverse functions of SRC-3 as a coactivator beyond androgen receptors, it has emerged as a promising therapeutic target for PCa. Studies suggest it can regulate AR signaling, cell proliferation, and metabolic reprogramming in cancer cells, potentially contributing to disease progression and therapeutic (Li et al., 2021). This review aims to investigate the role of SRC-3 (I) in PCa progression (O) in patients diagnosed with the disease (P). We compared and analyzed the current knowledge on SRC-3's various functions, its interactions with the androgen receptor pathway, and its potential as a therapeutic target, highlighting existing uncertainties and gaps in knowledge (C).

SRC-3, also known as steroid receptor coactivator-3, has been implicated in PCa progression (Li et al., 2021). Its established functions in PCa include promoting cell proliferation, survival, invasion, and metastasis. SRC-3 is known to interact with various transcription factors and coactivators, influencing gene expression related to cancer growth and progression (Ma et al., 2011). However, there are key areas where knowledge remains limited or uncertain. One such area is the specific mechanisms by which SRC-3 contributes to PCa progression. While its role in promoting cancer growth is acknowledged, the detailed molecular pathways through which SRC-3 exerts its effects are not fully understood. Understanding how SRC-3 functions in various contexts of the disease could lead to the development of targeted therapies that could be more effective in specific patient populations. The limitations of current research on SRC-3 in PCa highlight the need for further investigation. More studies are required to elucidate the precise mechanisms of SRC-3 action, identify potential therapeutic targets within these pathways, and explore the feasibility and efficacy of targeting SRC-3 in different stages or subtypes of PCa. This ongoing research is crucial for advancing our understanding of SRC-3's role in PCa and developing more effective treatment strategies for patients.

This review aims to comprehensively explore the multifaceted role of SRC-3 in PCa progression, specifically focusing on its interactions with AR signaling, its impact on key cancer hallmarks, and its potential as a therapeutic target. By elucidating this relationship, we hope to demonstrate the potential for SRC-3-based interventions to improve current treatment strategies and patient outcomes. Furthermore, we delve into the emerging therapeutic prospects centered around targeting SRC-3, shedding light on the promising avenues for precision medicine in the management of this complex disease. By addressing these facets, we endeavor to consolidate current knowledge and offer insights into the future directions of SRC-3 research in the context of PCa.

MATERIAL AND METHODS

Study registration

The research study was conducted following 2020 protocols and guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews (Page et al., 2021) . The study was prospectively registered with the recognized research registry (Prospero International Prospective Register of Systematic Reviews) with the I.D: CRD42023471034 (Zakari et al., 2023) to ensure transparency and adherence to best practices.

Eligibility criteria

The eligibility criteria for this systematic review were established to include studies that investigated the role of SRC-3 in PCa progression. Studies were required to focus on SRC-3's interaction with androgen receptor signaling, its impact on cancer hallmarks like proliferation and metastasis, and its potential as a diagnostic biomarker and therapeutic target. Only studies reported in English and published within the last 10 years were included. *In vitro* studies, *in silico* studies, clinical studies, review papers, meta-analyses study designs were included. Further, reports with multiple studies were included, but reports with multiple studies in which the mechanism of action was centered on the other studies and animal studies in which insufficient data was extracted were excluded.

Information sources

A comprehensive search strategy was devised to retrieve relevant articles from electronic databases, including PubMed, PMC, and other relevant sources. On November 21, 2023, the reviewers reached a consensus and checked the databases for the last time, but narrowed the search to reports in the English language, published within the last 10 years, as shown in Table 1. Boolean operators (OR and AND) were utilized to broaden and refine search results, ensuring comprehensive coverage of relevant literature. Additionally, reference lists of identified articles and reviews were screened for potentially eligible studies. The results of each search and search term used were sent to three reviewers (SZ, GO, and KNN) to validate the search term and identify studies.

Search strategy

A comprehensive search strategy was developed using relevant keywords related to SRC-3, PCa, and the key aspects of interest. The search strategy included appropriate keywords, Medical Subject Headings (MeSH) terms, and Boolean operators to ensure the thorough identification of pertinent literature. The PubMed search strategy was designed to comprehensively identify relevant studies pertaining to the research topic. The three search categories used were: (1) "Steroid Receptor Coactivator-3" OR "SRC-3" OR "Amplified in Breast Cancer 1" OR "AIB1" (2) "Prostate Cancer" OR "Prostatic Neoplasms" OR "Prostate Carcinoma" (3) "Molecular Mechanisms" OR "Androgen Receptor Signaling Pathways" OR "Cellular Signaling". These categories were combined using the AND operator as follows: (1) AND (2) AND (3). This combined search strategy aimed to retrieve articles that specifically address the molecular mechanisms, biochemical pathways, and cellular signaling involving SRC-3 in the context of PCa. The search strategy aimed to identify all relevant studies published up to the date of the search. Details of the search strategy are outlined in Table 1.

Table 1. The search term used for this study.

Database	Search term	Filters
PUBMED	#1: "Steroid Receptor Coactivator-3" OR "SRC-3" OR "Amplified in Breast Cancer 1" OR "AIB1" #2: "Prostate Cancer" OR "Prostatic Neoplasms" OR "Prostate Carcinoma" #3: "Molecular Mechanisms" OR "Androgen Receptor Signaling Pathways" OR "Cellular Signaling" These categories were combined using the AND operator as follows: (#1) AND (#2) AND (#3)	English, 10 years, and others
PMC	Role of Steroid Receptor Coactivator-3" OR "SRC-3" OR "Amplified in Breast Cancer 1" OR "AIB1" in "Prostate Cancer" OR "Prostatic Neoplasms" OR "Prostate Carcinoma" "Molecular Mechanisms" OR "Androgen Receptor Signaling Pathways" OR "Cellular Signaling"	English, 10 years, and others
WOS	Role of Steroid Receptor Coactivator-3" OR "SRC-3" OR "Amplified in Breast Cancer 1" OR "AIB1" in "Prostate Cancer" OR "Prostatic Neoplasms" OR "Prostate Carcinoma". "Molecular Mechanisms" OR "Androgen Receptor Signaling Pathways" OR "Cellular Signaling"	English, 10 years, and others
Google Scholar	Role of Steroid Receptor Coactivator-3" OR "SRC-3" OR "Amplified in Breast Cancer 1" OR "AIB1" in "Prostate Cancer" OR "Prostatic Neoplasms" OR "Prostate Carcinoma". "Molecular Mechanisms" OR "Androgen Receptor Signaling Pathways" OR "Cellular Signaling"	Since 2019

Selection process

Two experienced researchers, denoted as SZ and HZ, independently conducted the initial screening of identified articles based on the predefined inclusion and exclusion criteria. Any discrepancies in their selections were resolved through discussion and consensus or negotiated with a third researcher (OOO). Subsequently, these researchers performed data extraction from the selected studies. The use of three researchers ensured the accuracy and reliability of the extracted data. The following inclusion and exclusion criteria were established to ensure that the selected studies were pertinent to the research objectives and maintained a high level of scientific rigor:

Inclusion criteria: (1) Studies published in peer-reviewed journals, (2) Studies conducted on human subjects, (3) Studies investigating the role of steroid receptor coactivator-3 (SRC-3 or AIB1) in PCa, (4) Studies examining molecular mechanisms, biochemical pathways, or cellular signaling related to SRC-3 in PCa, (5) Studies available in English language.

Exclusion criteria**:** (1) Non-peer-reviewed articles, such as conference abstracts and posters, (2) Studies conducted solely on animals or *in vitro* experiments without relevance to human subjects, (3) Studies not directly related to the molecular mechanisms or cellular signaling of SRC-3 in PCa. Studies not available in the English language.

Data items and collection process

Data extraction was performed independently by two reviewers using a standardized data extraction form. The extracted data included study characteristics, participant demographics, SRC-3-related outcomes, and other relevant data items as specified in the data extraction form. Key data items extracted from included studies included study design, sample size, patient characteristics, SRC-3 expression levels, outcomes related to PCa progression, and any relevant statistical measures.

Study risk of bias assessment

A rigorous quality assessment of the included studies was conducted to evaluate the methodological soundness and risk of bias. The assessment considered various aspects, such as study design, sample size, data collection methods, and statistical analysis. The quality assessment was performed to determine the strength of evidence and potential sources of bias in the selected. The risk of bias in individual studies was assessed using established tools appropriate for different study designs, such as the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. The certainty of evidence was assessed using established frameworks such as Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to evaluate the quality of evidence and strength of recommendations based on the findings of included studies.

Ethical approval

This systematic review adhered to PRISMA guidelines and other applicable ethical standards. Since this study did not involve human or animal subjects, formal ethical approval was not required. However, ethical considerations related to data usage, citation, and transparency were upheld throughout the research process.

RESULTS

Study selection

The literature screening process aimed to systematically identify and select relevant articles for inclusion in this systematic review.

The process was conducted in multiple stages to ensure the comprehensive capture of pertinent literature. A total of 785 articles were initially retrieved from various electronic databases, including PubMed, PMC, and other relevant sources. These articles were identified based on the comprehensive search strategy that incorporated specific keywords and Medical Subject Headings (MeSH) terms related to SRC-3 and PCa

Risk of bias in studies

To eliminate redundancy, 461 duplicate articles were identified and removed using reference management software. This step ensured that each unique article was considered only once in the screening process. Subsequently, a detailed review of the titles and abstracts of the remaining articles was conducted. Based on the predefined inclusion and exclusion criteria, 260 articles were excluded during this stage. Articles that did not align with the research focus or did not provide sufficient information in their titles and abstracts were excluded.

Quality assurance

The remaining articles underwent a comprehensive layer-by-layer screening process. Two experienced researchers (SZ and HZ) independently assessed the full texts of the articles to determine their relevance to the research objectives.

Results of synthesis

The literature screening process and results are shown in Fig. 1. After the thorough literature screening process, a total of 47 articles met the predefined inclusion criteria and were included in this systematic review. Also, further search on researchrabbit database for Links between our collection and 50 papers gave the output below (Fig. 2). Accessible here; https://www.researchrabbitapp.com

The systematic screening process ensured that only the most relevant and high-quality studies were considered for the synthesis and analysis in this review. The articles were also filtered according to year and those deemed to provide valuable insights into the molecular mechanisms, biochemical pathways, and cellular signaling involving SRC-3 in the context of PCa using researchrabbit web-based platform for getting connected papers (Fig. 3). The selected articles collectively contribute to a comprehensive understanding of the role of SRC-3 in PCa.

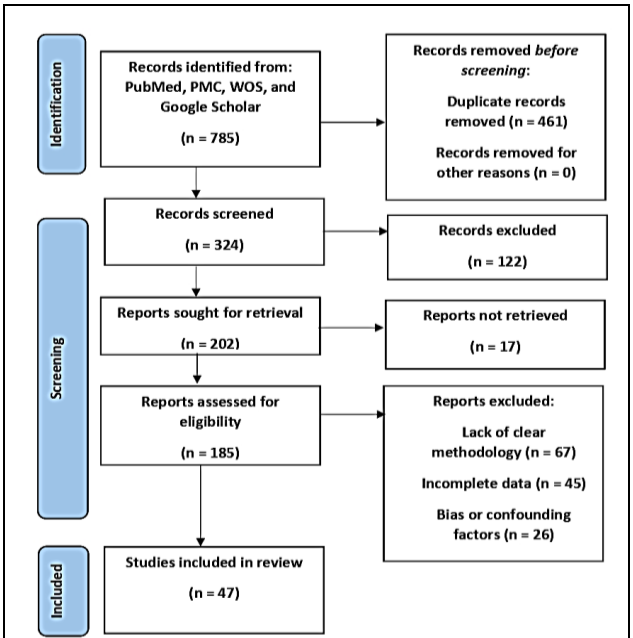

Figure 1. Study flow chart showing search results.

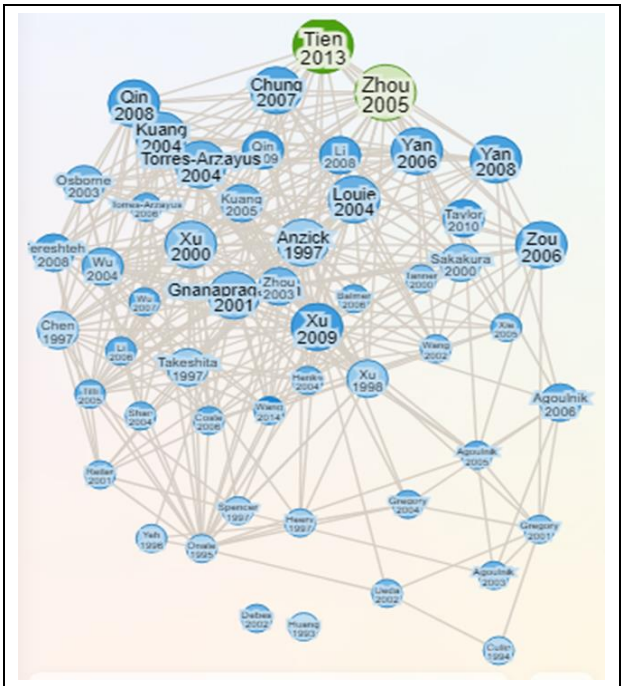

Figure 2. General paper graph search output using researchrabbit platform.

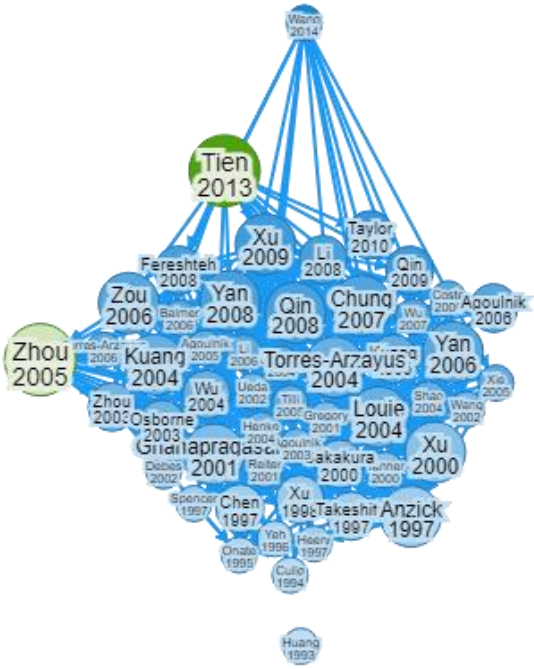

Figure 3. Paper graph search output showing relevance to two key articles using researchrabbit web platform.

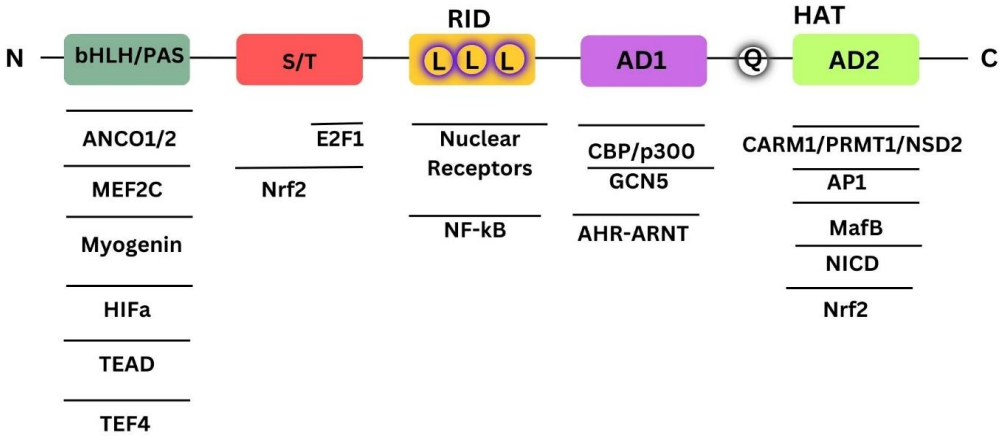

Figure 4. SRC-3 protein structure.

bHLH: Basic Helix-Loop-Helix; PAS: Per-Arnt-Sim; AD1: Activation Domains 1; RID: Receptor-Interaction Domain; AD1 and AD2: Transcriptional Activation Domains; Q: Polyglutamate sequence; HAT: Histone Acetyltransferase. Modified from (Li et al., 2021).

DISCUSSION

The discussion section provides a platform for the interpretation of the findings from the selected 47 articles, which collectively shed light on the role of SRC-3 in the context of PCa. This section aims to synthesize and analyze the key insights and implications of the reviewed literature.

SRC-3 protein

The molecular structure of SRC-3, also known as amplified in AIB1, is a complex and multifunctional protein that plays a crucial role in transcriptional regulation (Li et al., 2021). SRC-3 consists of several distinct structural and functional domains, each contributing to its diverse functions in gene expression modulation (Fig. 4). SRC-3's molecular structure is characterized by its basic helix-loop-helix (bHLH), Per/ARNT/ Sim (PAS), receptor-interaction domain (RID) with LXXLL motifs, transcriptional activation domains (AD1, AD2) with a polyglutamate sequence (Q), and histone acetyltransferase (HAT) activity. These structural features enable SRC-3 to interact with transcription factors and coregulators, facilitating its role as a coactivator in the regulation of gene

expression, including genes involved in PCa and other physiological processes.

SRC-3 contains the following domains:

bHLH and PAS domain: SRC-3 contains a bHLH domain, which is involved in DNA binding and protein-protein interactions. The PAS domain contributes to the regulation of transcription by sensing changes in cellular signals and responding accordingly.

RID: The RID of SRC-3 is crucial for its role as a coactivator. Within this domain are three LXXLL motifs (L represents leucine and X represents any amino acid), which are responsible for the interaction of SRC-3 with nuclear receptors, including the AR. These motifs serve as binding sites for nuclear receptors, allowing SRC-3 to coactivate these receptors and enhance their transcriptional activity.

Transcriptional activation domains (AD1 and AD2): SRC-3 possesses two transcriptional activation domains, AD1 and AD2. These domains are responsible for activating the transcription of target genes. Additionally, SRC-3 contains a polyglutamate sequence (Q) within these domains, which contributes to its transcriptional activation function.

HAT activity: SRC-3 has HAT activity, which enables it to acetylate histone proteins within chromatin. Histone acetylation is a crucial epigenetic modification that relaxes chromatin structure, making it more accessible to transcriptional machinery and promoting gene expression.

Interactions with transcription factors and coregulators: SRC-3 is a versatile coactivator that interacts with multiple transcription factors and coregulators. It forms complexes with nuclear receptors, such as the androgen receptor, estrogen receptor, and others. Additionally, SRC-3 interacts with various other coregulators, and proteins involved in transcriptional regulation, creating a network of interactions that modulate gene expression.

SRC-3 as a key player in PCa progression

The reviewed studies consistently highlight the pivotal role of SRC-3 in PCa progression. SRC-3, also known as amplified in AIB1, or nuclear receptor coactivator 3 (NCOA3) emerges as a critical coactivator that directly interacts with the AR and plays a significant role in AR-driven transcriptional activity in PCa cells (Dahiya and Heemers, 2022). SRC-3's role in enhancing the chromatin accessibility at AR-binding sites and recruiting transcriptional machinery to target genes underscores its importance in the regulation of AR-dependent gene expression. The AR directly interacts with SRC-3, a member of steroid receptor coactivator family proteins and boosts its transcriptional activity. The SRC family, which comprises SRC-1 (also known as NCOA-1), SRC-2 (NCOA-2), and SRC-3 (NCOA-3), is a group of three evolutionarily conserved coregulators of transcription. These coregulators play a crucial role in mediating the interaction between AR and the transcriptional machinery, ultimately influencing gene regulation.

SRC-1 expression is associated with PCa aggressiveness and suppressing SRC-1 expression reduced growth and altered AR target gene regulation in PCa cells. However, in a murine PCa model, SRC-1's role differs from that of SRC-3, which is essential for PCa progression and metastasis in mice (Tien et al., 2013). SRC-2 is amplified in both primary and metastatic PCa. Androgen deprivation induces SRC-2, activating PI3K signaling and promoting PCa metastasis and castration-resistant PCa (CRPC) development (Qin et al., 2022). SRC-2 also stimulates reductive carboxylation of alpha-ketoglutarate, supporting lipogenesis and metabolic reprogramming, which is strongly increased in metastatic PCas (Dasgupta et al., 2015). Compared with SRC-1 and SRC-2, markedly less is known concerning the individual functional role of SRC-3 in endometrial biology and dysfunction; this knowledge-gap is significant because expression studies indicate that this coregulator may have important roles in both endometrial contexts. SRC-3 expression is elevated in advanced PCa, particularly in CRPC. It negatively correlates with PTEN expression and recurrence-free survival in PCa patients. SRC-3 is essential for CRPC development by enhancing Akt activity and S6K1 expression (Tien et al., 2013). SPOP, a tumor suppressor in PCa, promotes SRC-3 turnover via ubiquitination. PCa-associated SPOP mutants lose the ability to interact with SRC-3, impairing its ubiquitination (Geng et al., 2013).

Androgen receptor signaling in PCa cells is augmented by the AR coactivator p300, which transactivates and acetylates the AR in the presence of dihydrotestosterone (DHT) (Gong et al., 2006). Cyclic adenosine monophosphate response element binding protein (CBP) and p300 are other known AR coactivators with oncogenic roles in PCa. Androgen deprivation upregulates CBP/p300 proteins in PCas. Inhibition of the CBP/p300 bromodomain suppresses AR activity at the chromatin level, leading to the downregulation of proliferative gene expression and inhibiting CRPC tumor growth *in vitro* and *in vivo* (Debes et al., 2003). SRC-3 acts by enhancing the transcriptional activity of AR, leading to increased expression of genes involved in PCa progression. These coactivator complexes related to AR have the effect of enhancing the accessibility of the chromatin structure at the AR-binding sites. This increased accessibility facilitates the recruitment of the transcriptional machinery

required for gene expression. SRC-3 was also found to be a critical regulator of PCa cell proliferation and survival. Studies suggest that it is required for the proliferation of PCa cells, highlighting its role in promoting cancer growth (Zhou et al., 2005). SRC-3 is amplified in both primary and metastatic PCa, indicating its importance in the disease progression (Fujita and Nonomura, 2019). SRC-3 acts as a co-activator, enhancing the activity of the AR in PCa. This interaction contributes to the androgen signaling pathway, which is pivotal for PCa development and progression (Gnanapragasam et al., 2001). SRC-3's involvement in PCa highlights its potential as a therapeutic target in the treatment of this disease. Understanding its role in AR signaling and cancer growth may lead to the development of targeted therapies for PCa patients.

Furthermore, our analysis revealed that SRC-3's contribution to PCa extends beyond its interaction with AR. The interplay between estrogen signaling and transcriptional coregulator activity has been extensively explored in hormone-dependent models of PCa. In particular, the upregulated expression and heightened activity of SRC-3 play a pivotal role in driving the initiation and progression of breast cancers. SRC-3 gene amplification is observed in 5% to 10% of breast cancers, and the SRC-3 mRNA or protein is overexpressed by approximately 60% in various cohorts of breast cancer patients (Kiliti et al., 2023). Notably, SRC-3 overexpression is linked to more aggressive forms of breast cancer and poorer survival rates. Clinical data from breast cancer patients further reveal that high SRC-3 expression is associated with reduced disease-free survival (Yao et al., 2019). Genetic mouse models have demonstrated that the loss of SRC-3 reduces breast tumor incidence and delays tumor growth (Watters et al., 2021).

SRC-3 has been shown to coactivate non-nuclear receptor transcription factors (TFs) such as PEA3, leading to the upregulation of matrix metalloproteinases (He et al., 2019). This highlights SRC-3's involvement in cancer invasion and metastasis, emphasizing its multifaceted role in disease progression. SRCs play a crucial role in modifying chromatin structure, facilitating transcription. They achieve this by directly or indirectly recruiting other coactivators, leading to chromatin remodeling, de-condensation, and the creation of a transcriptionally favorable environment at gene promoters. Additionally, SRCs possess histone-acetyltransferase activity, enabling them to directly acetylate histones and other chromatin regulators, thus promoting transcriptional activation (Tanizaki et al., 2021). These coactivators participate in a complex gene regulatory network, influenced by various post-translational modifications (PTMs) like phosphorylation, ubiquitination, sumoylation, acetylation, and methylation. PTMs on SRCs impact their stability, function, and ability to recruit proteins for transcriptome complex formation. Specific PTM patterns are critical for hormone-dependent tumor growth, proliferation, and metastasis. Phosphorylation of SRC-3, for instance, is associated with prognosis in ER-positive breast cancer and resistance to tamoxifen. Dysregulation of SRCs has been observed in various cancers, emphasizing the significance of coactivators in carcinogenesis (Takayama, 2018). SRCs notably drive the progression of breast and PCa, and their elevated expression is common in patient samples. Targeting coactivators like SRCs with small molecule inhibitors has shown promise in preclinical models, indicating potential therapeutic benefits. Clinical studies are needed to evaluate their efficacy in treating advanced breast and PCa.

SRC-3 in the context of metabolic reprogramming

Another intriguing aspect illuminated by the reviewed literature is SRC-3's involvement in metabolic reprogramming in PCa (Shrestha, 2022). Metabolic reprogramming is a characteristic feature of cancer, describing the alteration of metabolic pathways and gene expression patterns to fuel increased cell proliferation and growth (Iheagwam et al., 2022). This metabolic adaptation is crucial for the survival and spread of aggressive cancers. Even in the presence of oxygen, tumor cells utilize glucose as an energy source through a heightened rate of glycolysis, a phenomenon known as aerobic glycolysis or the Warburg effect (Xu et al., 2015). Although glycolysis is less efficient in terms of ATP production compared to oxidative phosphorylation, it generates additional metabolites that support the synthesis of large molecules required for rapid cell division. Enzymes within the glycolytic pathway, such as glucose-6 phosphate and fructose-6 phosphate, produce glycolytic intermediates that are redirected into the pentose phosphate pathway. This pathway is responsible for synthesizing nucleotides and regenerating dihydronicotinamide adenine dinucleotide phosphate, which is essential for supporting tumor growth and metastasis (Lu et al., 2015).

In addition to glucose, proliferating tumors exhibit an increased reliance on glutamine consumption, highlighting its critical role in metabolic reprogramming (Yoo et al., 2020). Glutamine is converted into glutamate and eventually into α-ketoglutarate, which enters the citric acid cycle via anaplerotic reactions. This process provides energy and supports the synthesis of fatty acids, further fueling the demands of rapidly growing cancer cells. SRC-3 promotes reductive carboxylation of alpha-ketoglutarate, facilitating

lipogenesis and the reprogramming of glutamine metabolism (Sawant Dessai et al., 2023). The SRC-3-driven metabolic signature is particularly pronounced in metastatic PCas. This metabolic rewiring may play a crucial role in sustaining uncontrolled growth and survival in advanced PCa. SRC-3 plays a pivotal role in metabolic reprogramming in castration-resistant PCa, contributing to the altered metabolism observed in CRPC (Kishore and Zi, 2023). Targeting SRC-3 and its associated metabolic pathways holds promise as a potential therapeutic strategy to combat this aggressive form of PCa. SRC-3 is known to stimulate reductive carboxylation of alpha-ketoglutarate, a key metabolic process that promotes lipogenesis (Blundon and Dasgupta, 2019). This process provides cancer cells with the necessary lipids for membrane synthesis and energy storage. Additionally, SRC-3 is involved in the reprogramming of glutamine metabolism, which can provide an alternative source of energy and biosynthetic precursors for rapidly proliferating CRPC cells (Tang et al., 2021).

Studies have shown that the metabolic signature associated with SRC-3 is strongly increased in metastatic PCas (Wang et al., 2020). This suggests that SRC-3-dependent transcriptional reprogramming may play a crucial role in resetting the metabolic pathways of tumors to support uncontrolled growth and survival. These metabolic adaptations are essential for CRPC cells to thrive even in the absence of androgen signaling. Given its involvement in metabolic reprogramming, SRC-3 has emerged as a potential therapeutic target in CRPC. Inhibiting SRC-3 activity may disrupt the metabolic adaptations that fuel tumor growth and progression. Researchers are actively exploring the development of SRC-3 inhibitors as a strategy to target the metabolic vulnerabilities of CRPC cells. Understanding the role of SRC-3 in metabolic reprogramming provides valuable insights into the molecular mechanisms underlying CRPC. It also opens up new avenues for the development of targeted therapies that can complement existing treatments for advanced PCa.

Implications for therapeutic strategies

The insights gained from the reviewed literature have significant implications for therapeutic approaches in PCa. Dysregulation of SRC-3 in PCa has significant implications for therapeutic strategies. SRC-3 dysregulation offers a potential target for therapeutic interventions. Developing drugs that specifically inhibit SRC-3 activity or expression can be a promising approach to treat PCa (Qin et al., 2021). Such targeted therapies aim to disrupt the oncogenic functions of SRC-3 and inhibit its contribution to tumor progression. Combining SRC-3-targeted therapies with existing treatments like androgen deprivation therapy (ADT) or chemotherapy could enhance therapeutic outcomes. SRC-3 dysregulation often occurs alongside other molecular changes in PCa, and combination therapies may address multiple pathways driving cancer progression. Targeting SRC-3 and its coactivation mechanisms, particularly in the context of AR-driven transcription, may hold promise as a therapeutic strategy. Strategies to disrupt SRC-3-AR interactions or inhibit SRC-3 expression and activity could be explored to potentially mitigate the progression of PCa. In a comparative investigation conducted by Gilad et al. (2021), they identified SRC-3 as a unique target within the realm of endocrine therapies. Apart from its role as a significant regulator of estrogen receptor transcriptional functions, SRC-3 also acts as a coactivator for a diverse array of other transcription factors, indicating that inhibiting SRC-3 could have potential advantages in hormone-independent cancers. The recent unveiling of a potent small molecule inhibitor of SRC-3, known as SI-2, has paved the way for the advancement of related compounds. SI-12 represents an enhanced iteration of SI-2 and, much like its predecessor, exhibits anti-proliferative properties across various cancer types.

The coactivator role of SRC-3 on AR signaling in PCa and its opportunity for targeting in CRPC are pivotal aspects of this review. In CRPC, the activation of the AR signaling pathway initiates with the intratumoral synthesis of testosterone and DHT, a process catalyzed by AKR1C3 (Fujita and Nonomura, 2019). Subsequently, DHT binds to AR, which is initially sequestered by Hsp90 in the cytosol. This binding leads to the translocation of the dimerized AR to the nucleus, where it interacts with androgen response elements in the promoters of responsive genes. Fig. 5 illustrates the sites of action for two androgen receptor signaling inhibitor (ARSI) therapies, abiraterone and enzalutamide. Additionally, it highlights alternative forms of AR, denoted as AR-SV, which are transcriptionally active even in the absence of ligands, and phosphorylated forms of AR (Asangani et al., 2021). The recruitment of coregulatory; SRC-3 to the transcriptional complex is also depicted. Notably, within the context of eradicating AR signaling, the review identifies specific protein targets highlighted in red boxes. These targets are crucial in understanding and potentially disrupting the AR signaling pathway in the context of PCa and CRPC.

A study demonstrated that Bufalin effectively targets the SRC-3 protein to reduce the release of macrophage migration inhibitory factor (MIF) in chemoresistant cells (Chen et al., 2021). This reduction in MIF plays a crucial role in regulating the polarization of M2 macrophages, which are known to contribute

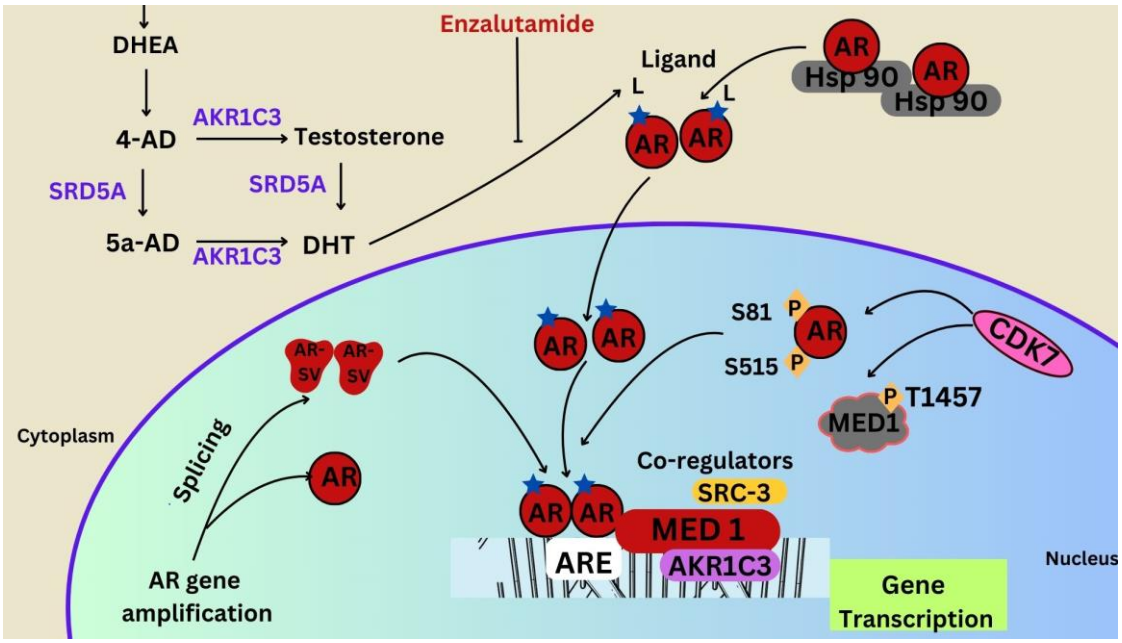

Figure 5. Androgen receptor (AR) signaling and targets.
Modified from (Asangani et al., 2021).

significantly to tumor chemoresistance. Previous research has indicated that bufalin possesses notable anti-tumor properties, including the ability to decrease the polarization of M2 macrophages *in vivo*. However, the precise mechanisms underlying this effect have remained unclear. It was observed that Bufalin successfully reduced the polarization of M2 macrophages induced by chemo-resistant cells, both in laboratory settings (*in vitro*) and within living organisms (*in vivo*). Notably, the study also revealed that cinobufacini, a medicinal product containing bufalin as its primary active component, could effectively regulate M2 macrophage polarization. This regulation enhanced the anti-tumor efficacy of oxaliplatin, a chemotherapy agent, both in experimental settings and in clinical applications. This research provides valuable insights into the potential clinical use of bufalin-containing drugs, particularly in combination with established chemotherapy, for the treatment of colorectal cancer (Chen et al., 2021).

In ovarian cancer cell lines, both SRC-3 and TRAF4 exhibited increased expression levels. Investigations unveiled that the interplay between SRC-3 and TRAF4 plays a pivotal role in promoting various aspects of ovarian cancer progression, including cell growth, migration, invasion, and the maintenance of stemness properties (Wang et al., 2023). These effects are primarily mediated through the activation of the PI3K/AKT signaling pathway. When SRC-3 was silenced, there was a notable reduction in TRAF4 expression. Consequently, the silencing of either SRC-3 or TRAF4 resulted in the inhibition of cell proliferation, migration, invasion, as well as the expression of key stem cell-related factors. Moreover, another study demonstrated that the suppression of SRC-3 or TRAF4, along with the use of LY294002 (an inhibitor of the PI3K/AKT pathway), effectively hindered the phosphorylation of Akt and PI3K. This inhibition subsequently repressed the activation of the PI3K/AKT signaling pathway in ovarian cancer cell lines. The overexpression of TRAF4 counteracted the effects of SRC-3 silencing, thereby reinstating cell proliferation, migration, invasion, and stemness properties. These findings underscore the intricate interplay between SRC-3 and TRAF4 and their significant roles in modulating ovarian cancer progression through the PI3K/AKT pathway (Wang et al., 2023).

Additionally, SRC-3 plays a significant role in clinical resistance to tamoxifen and aromatase inhibitors (Osborne et al., 2003). This resistance is attributed to SRC-3's involvement downstream of growth factor signaling pathways, enabling it to circumvent the inhibition of ER in breast cancer cells. Genomic changes have also been identified that contribute to endocrine therapy resistance, including mutations in the ligand-binding domain of the ER gene, allowing receptor activation in the absence of estrogen signaling (Rotimi et al., 2021). Upstream signaling, including metabolic cues impacting SRC-3, is crucial for inducing hormone-independent activation of target genes. Promisingly, drugs targeting SRC-3, such as phospho-bufalin and SI-2, have shown favorable effects in mouse models of Breast Cancer (Song et al., 2016). These findings collectively underscore the sig-

nificance of SRC activity in the context of Breast Cancer and its potential as a therapeutic target. Assessing the status of SRC-3 dysregulation in PCa patients can serve as a valuable biomarker. Identifying patients with elevated SRC-3 expression or activity could help tailor treatment strategies. Patients with SRC-3 dysregulation might benefit more from SRC-3-targeted therapies. SRC-3 dysregulation has been linked to resistance to endocrine therapies like ADT (Axlund et al., 2010). Understanding how SRC-3 contributes to treatment resistance can inform the development of strategies to overcome this resistance. This could involve combination therapies or novel approaches to target SRC-3-driven resistance mechanisms. The study of SRC-3 dysregulation in PCa underscores the importance of personalized medicine. Tailoring treatments based on the specific molecular characteristics of a patient's tumor, including SRC-3 status, can improve treatment efficacy while minimizing side effects. Clinical trials evaluating SRC-3-targeted therapies are essential. These trials can provide critical data on the safety and efficacy of novel treatments. The results can guide the development of approved therapies for PCa patients. SRC-3 dysregulation in PCa offers both challenges and opportunities for therapeutic strategies. Targeting SRC-3 and understanding its role in treatment resistance can potentially lead to more effective and personalized treatments for PCa patients. However, rigorous clinical testing and ongoing research are necessary to translate these findings into improved clinical outcomes.

Future directions

By pursuing the following future directions, the scientific and medical communities can harness the potential of SRC-3 as a key player in PCa and pave the way for more effective, personalized, and tailored approaches to diagnosis and treatment:

Targeted therapies: Building on the insights gained from the role of SRC-3 in PCa, future research should focus on developing targeted therapies that specifically inhibit SRC-3. These therapies may include small molecules, antibodies, or gene-based approaches aimed at modulating SRC-3 activity.

Combination therapies: Investigate the potential synergistic effects of combining SRC-3-targeted therapies with existing treatments for PCa, such as ADT or immunotherapies. Combinatorial approaches may enhance treatment efficacy and overcome resistance mechanisms.

Biomarker development: Further explore SRC-3 as a diagnostic and prognostic biomarker for PCa. Develop standardized assays and diagnostic tools that can accurately measure SRC-3 expression levels in patient samples, aiding in risk stratification and treatment decisions.

Personalized medicine: Expand research into personalized medicine approaches that consider SRC-3 status along with other genetic and molecular markers. Tailor treatment plans based on the individual patient's SRC-3 profile to maximize therapeutic outcomes.

Understanding resistance mechanisms: Investigate the mechanisms underlying resistance to SRC-3-targeted therapies. Identifying why some patients do not respond to these treatments will be crucial in refining therapeutic strategies. Continuing fundamental research to unravel the intricate molecular pathways involving SRC-3 in PCa. This includes elucidating its interactions with other co-regulators, transcription factors, and signaling pathways.

Clinical trials: Encourage and support clinical trials specifically designed to evaluate the safety and efficacy of SRC-3-targeted therapies in PCa patients. Collaborate with pharmaceutical companies and regulatory agencies to advance these therapies to the clinical setting.

Long-term outcomes: Assess the long-term effects of SRC-3 inhibition on PCa patients, including survival rates, quality of life, and potential side effects. Longitudinal studies will provide a comprehensive understanding of the impact of SRC-3-targeted therapies.

Exploration of comorbidities: Investigate the potential associations between SRC-3 dysregulation and comorbidities frequently observed in PCa patients, such as metabolic syndrome and cardiovascular diseases. Understanding these links may provide new avenues for intervention.

Patient education and support: Develop educational resources and support networks for PCa patients and their families to raise awareness about SRC-3 and the evolving landscape of targeted therapies. Informed patients can actively participate in shared decision-making regarding their treatment.

CONCLUSION

This systematic review comprehensively explores SRC-3's multifaceted role in prostate cancer progression, highlighting its key functions in androgen receptor signaling, tumor growth, and metastasis. Our findings confirm SRC-3's importance in disease pathogenesis and its potential clinical relevance, demonstrating correlations with aggressiveness, recurrence, and poor patient outcomes. Importantly, the review emphasizes the promise of SRC-3 as a diagnostic biomarker and therapeutic target, paving the way for

personalized medicine approaches in prostate cancer management. Future research and clinical trials guided by these insights could lead to improved diagnostic accuracy, novel therapeutic strategies, and ultimately, better patient outcomes. This comprehensive analysis contributes significantly to our understanding of SRC-3, offering a valuable resource for clinicians, researchers, and healthcare professionals seeking to advance more effective strategies for prostate cancer diagnosis and treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contribution	Zakari S	Cleanclay WD	Omunagbe MB	Zakari H	Ogbu CO	Uti DE	Ogunlana OO
Concepts or ideas	x						
Design	x						x
Definition of intellectual content		x					
Literature search			x	x			
Experimental studies	x				x		
Data acquisition					x		
Data analysis					x	x	
Statistical analysis			x		x		
Manuscript preparation	x						
Manuscript editing		x		x			x
Manuscript review	x	x	x	x	x	x	x

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