GSK-3β and Non-Small Cell Lung Cancer: A Review of Its Role in Disease Mechanisms and Treatment Strategies

Erna Kristiani[1]

[1]*Department of Pathological Anatomy, Universitas Pelita Harapan, Tangerang, Indonesia*
Correspondece to: Ena Kristiani (erna.kristani@uph.edu).

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ABSTRACT

Introduction
Recent molecular docking studies have identified potential inhibitors targeting GSK-3β, offering promising avenues for therapeutic intervention. These inhibitors could potentially disrupt the oncogenic signaling pathways mediated by GSK-3β, thereby halting or reversing tumor progression. This literature review seeks to deliver a thorough examination of the current knowledge regarding GSK-3β influence on NSCLC.
Methods
The author carried out an extensive literature review utilizing various electronic databases such as PubMed, Scopus, and Europe PMC. The search keywords included "GSK-3β," "glycogen synthase kinase-3 beta," "non-small cell lung cancer," "NSCLC," "prognosis," "apoptosis," "cell proliferation," "autophagy," "radiosensitivity," "tumor differentiation," and "molecular docking." The findings from the included studies were integrated into a narrative review, emphasizing GSK-3β role in NSCLC pathogenesis, its potential as a therapeutic target, and its utility as a prognostic biomarker.
Results
GSK-3β is a multifunctional serine/threonine kinase involved in various cellular processes, including proliferation, differentiation, motility, and survival. Its expression is associated with NSCLC differentiation, with GSK-3β-negative tumors showing better prognosis. Preclinical studies have identified potential GSK-3β inhibitors with favorable docking scores and ADME profiles for NSCLC treatment. However, targeting GSK-3β for NSCLC treatment faces several significant challenges. One major issue is the broad role of GSK-3β in various cellular processes, including metabolism and cell survival, which increases the risk of off-target effects and toxicity.
Conclusions
GSK-3β has emerged as a critical biomarker in NSCLC, exerting a significant impact on disease progression, treatment response, and prognosis.

1. Introduction

Non-small cell lung cancer (NSCLC) continues to be a predominant cause of cancer-related deaths globally, underscoring the critical need for persistent research into its molecular pathways and potential treatment targets.[1] Glycogen synthase kinase-3 beta (GSK-3β) has become a noteworthy factor in the development and progression of NSCLC.[2,3] Research consistently indicates that elevated levels of GSK-3β correlate with unfavorable prognoses in NSCLC patients.[4–6] This association underscores the potential of GSK-3β as a prognostic biomarker, offering crucial insights into patient outcomes and informing therapeutic strategies.[6]

GSK-3β expression levels have been linked to tumor differentiation and the advanced stages of NSCLC, highlighting its significance in disease progression. Elevated GSK-3β expression is frequently associated with more aggressive tumor behavior and worse clinical outcomes, positioning it as a potential marker for assessing disease severity.[7,8] This association underscores the importance of understanding the regulatory mechanisms governing GSK-3β expression and activity in NSCLC, as it could lead to the development of novel diagnostic and therapeutic strategies.[8]

Experimental evidence indicates that the inhibition of GSK-3β has profound effects on NSCLC cell lines.[9,10] Inhibiting GSK-3β suppresses cell proliferation, induces apoptosis, and reduces cell motility, indicating its crucial role in sustaining the malignant phenotype of NSCLC cells. These observations suggest that targeting GSK-3β could be a promising therapeutic strategy to limit tumor growth and progression.[7] Furthermore, GSK-3β has been found to inhibit autophagy and enhance radiosensitivity in NSCLC cells, thereby affecting the efficacy of existing treatments and opening avenues for combination therapies that could improve patient outcomes.[11]

Recent molecular docking studies have identified potential inhibitors targeting GSK-3β, offering promising avenues for therapeutic intervention. These inhibitors could potentially disrupt the oncogenic signaling pathways mediated by GSK-3β, thereby halting or reversing tumor progression.[2] Additionally, the significant association between GSK-3β and PTEN expression in NSCLC tumors suggests a complex interplay that could be pivotal in understanding tumor biology and response to treatment. The PTEN tumor suppressor gene is known to play a crucial role in regulating cell growth and survival, and its interaction with GSK-3β may provide further insights into the molecular underpinnings of NSCLC.[12,13]

This literature review seeks to deliver a thorough examination of the current knowledge regarding GSK-3β influence on NSCLC. By delving into its role as both a therapeutic target and a prognostic biomarker, this review aims to illuminate the potential of GSK-3β-targeted therapies in enhancing outcomes for NSCLC patients. Through a detailed analysis of existing research, we aspire to clarify the mechanisms through which GSK-3β affects NSCLC progression and to highlight prospective directions for future investigations in this domain.

2. Method

The author carried out an extensive literature review utilizing various electronic databases such as PubMed, Scopus, and Europe PMC. The search keywords included "GSK-3β," "glycogen synthase kinase-3 beta," "non-small cell lung cancer," "NSCLC," "prognosis," "apoptosis," "cell proliferation," "autophagy," "radiosensitivity," "tumor differentiation," and "molecular docking." The author implemented specific inclusion and exclusion criteria to ensure the studies selected were relevant and methodologically rigorous. The inclusion criteria stipulated that the studies must be published in peer-reviewed journals and include research articles, reviews, or meta-analyses that investigated the role of GSK-3β in non-small cell lung cancer. Furthermore, the studies were required to involve experimental models such as cell lines, animal studies, or clinical samples, and be written in English. Conversely, studies were excluded if they did not focus on NSCLC, lacked primary data or detailed methodologies, or were not published in English. Data were extracted from the selected studies using a standardized form, which captured key details such as the authors, year of publication, journal, and study design, including in vitro, in vivo, and clinical study types. For information specifically related to GSK-3β, we collected data on its expression levels in NSCLC, its correlation with clinical outcomes such as prognosis, tumor stage, and differentiation, and the impact of GSK-3β inhibition on various aspects of NSCLC, including cell proliferation, apoptosis, motility, autophagy, and radiosensitivity. The study investigated the molecular mechanisms by which GSK-3β affects non-small cell lung cancer and explored potential therapeutic strategies, with a focus on GSK-3β inhibitors and the interaction between GSK-3β in the context of NSCLC.

Data Analysis

The author analyzed the extracted data to uncover patterns, trends, and gaps in the existing research. Descriptive statistics helped the author summarize how frequently key findings appeared and their distribution across the studies. The qualitative synthesis involved comparing and contrasting these results to offer a thorough understanding of GSK-3β role in NSCLC.

Synthesis of Findings

The findings from the included studies were integrated into a narrative review, emphasizing GSK-3β role in NSCLC pathogenesis, its potential as a therapeutic target, and its utility as a prognostic biomarker. The review also pinpointed areas requiring further research and explored the possible clinical applications of GSK-3β inhibitors in the treatment of NSCLC.

3. Results

GSK-3β Role and NSCLC Pathogenesis

Numerous studies have documented the potent effects of GSK-3β inhibitors when combined with radiation and chemotherapy across a range of cancer contexts, highlighting the critical role of this kinase in cancer treatment approaches.[14–16] Furthermore, GSK-3β suppresses autophagy and heightens the sensitivity of NSCLC cells to radiation. Tumors deficient in GSK-3β exhibit a more favorable prognosis. The link between GSK-3β and ANXA1 has been clarified, with ANXA1 acting to decrease GSK-3β phosphorylation, thus preventing epithelial-mesenchymal transition and, as a result, reducing the migration and invasion of NSCLC cells.[15] Researchers have found that the GSK-3 protein kinase exhibits increased activity in 41% of human NSCLC samples. When GSK-3 is inhibited, a decrease in proliferation is observed in NSCLC cell lines. This suggests that certain NSCLC tumors may be dependent on GSK-3 for their continuous growth.[17] Owing to the connection

between GSK-3β expression levels and tumor progression, it is crucial to understand the regulatory mechanisms governing this protein. GSK-3β levels correlate with NSCLC differentiation and progression.[18] Inhibiting GSK-3β signaling impairs cell proliferation, promotes apoptosis, and reduces motility in NSCLC cell lines. Additionally, computational studies have identified potential GSK-3β inhibitors as promising therapeutic options for NSCLC.[16] The observed association between GSK-3β and PTEN levels in NSCLC samples emphasizes the potential of targeting this relationship for therapeutic purposes.[3,19,20] The findings suggest that GSK-3β may serve as a potential biomarker for assessing prognosis and therapeutic response in non-small cell lung cancer. While these significant findings have been made, the function of GSK-3β in the progression of non-small cell lung cancer is complex and may be influenced by specific contexts. This underscores the need for further research to thoroughly understand its role in lung cancer development and to improve targeted therapeutic strategies. GSK-3β stimulates the proliferation and survival of tumor cells, and inhibiting its activity reduces cell growth while inducing apoptosis.[21–23] Notably, GSK-3β exerts an inhibitory effect on autophagy, thereby enhancing the sensitivity of NSCLC cells to radiation. Furthermore, GSK-3β participates in regulating the epithelial-mesenchymal transition process by phosphorylating Slug, a protein that suppresses the transcription of E-cadherin.[24,25] The phosphorylation process facilitates Slug degradation through the CHIP-mediated ubiquitin-proteasome pathway, potentially suppressing metastasis.[25]

Molecular Mechanisms of GSK-3β in NSCLC

High levels of the enzyme GSK-3β are linked to poor clinical outcomes in non-small cell lung cancer patients. In contrast, blocking the activity of GSK-3β results in reduced tumor cell growth, increased cell death, and decreased cell movement.[26,27] Additionally, GSK-3β suppresses the cellular process of autophagy, resulting in enhanced sensitivity of NSCLC cells to radiation therapy. In contrast, NSCLC tumors that lack GSK-3β demonstrate improved clinical outcomes. Furthermore, the epithelial-mesenchymal transition induced by the Snail transcription factor in NSCLC involves the Smad1/Akt/GSK-3β signaling pathway, which modulates the expression of Nanog and enhances stem cell-like properties within the tumor.[28–30] NSCLC cells that demonstrate resistance to cisplatin exhibit heightened activation of the Wnt/β-catenin signaling pathway due to suppression of the cytoplasmic form of glycogen synthase kinase-3 beta (GSK-3β). This elevated signaling cascade results in increased expression of the proteins β-catenin and survivin, which collectively contribute to enhanced resistance to cisplatin therapy.[31,32] The multifaceted function of GSK-3β in NSCLC underscores its potential as a compelling therapeutic target. Understanding the multifaceted roles of GSK-3β is crucial for a thorough grasp of its impact on cancer progression and therapy. GSK-3β, a multifunctional serine/threonine protein kinase, is implicated in regulating diverse cellular functions, encompassing cell proliferation, differentiation, motility, and survival.[33] GSK-3β is critical in regulating cell cycle progression and apoptosis through the control of proteolysis and the subcellular localization of key proteins. Its role in tumorigenesis and cancer progression is complex and context-dependent, as it can act as either a tumor suppressor or promoter, depending on the specific type of cancer.[18,34] GSK-3β is a key regulator of important signaling pathways like Wnt and NF-κB, which are vital for blood cell formation and the onset of leukemia.[35,36] Additionally, GSK-3β influences drug sensitivity and resistance in cancer chemotherapy. While GSK-3β inhibitors show potential for treating a range of diseases, their impact on tumorigenesis and cancer therapy requires comprehensive evaluation and careful consideration.

The varying effects of GSK-3β inhibition across different cancer types highlight the need for context-specific research. In pancreatic cancer cells, GSK-3β inhibition has been shown to enhance radioresistance through a mechanism that relies on β-catenin.[37,38] On the contrary, in NSCLC, inhibiting GSK-3β can enhance autophagy and decrease radiosensitivity.[39,40] GSK-3β is a crucial regulator in several signaling pathways, including Wnt/β-catenin and PI3K/PTEN/AKT, and it also plays a role in DNA repair mechanisms.[41] The expression of GSK-3β is associated with the differentiation status of NSCLC, with tumors deficient in GSK-3β showing a more favorable prognosis.[26] The effects of GSK-3β inhibitors used in conjunction with radiation and chemotherapy have been reported across various cancer types, underscoring the importance of GSK-3β in cancer treatment strategies.[41–45] Continued investigation into the complicated interactions between GSK-3β and crucial signaling pathways holds the potential to unveil novel therapeutic prospects. GSK-3β has been linked to cancer progression, such as in colon cancer, via its interplay with Notch signaling.[46] Additionally, GSK-3β interacts directly with p53 in response to DNA damage, facilitating cellular reactions like elevated p21 levels and caspase-3 activity.[47,48] Additionally, GSK-3β collaborates with casein kinase 2 to phosphorylate PTEN, a tumor suppressor that inhibits cell growth and survival. This interaction between GSK-3β and PTEN suggests a possible feedback regulatory mechanism. In hematopoiesis and the development of leukemia, GSK-3β engages with several pathways, such as Wnt/β-catenin, PI3K/PTEN/Akt/mTOR, and Ras/Raf/MEK/ERK.[47,49,50] Due to

its involvement in critical signaling pathways and interactions with hematopoietic and leukemia-related factors, GSK-3β emerges as a promising therapeutic target for different cancers. It holds particular potential in tackling leukemia stem cell pathophysiology and overcoming treatment resistance.[47]

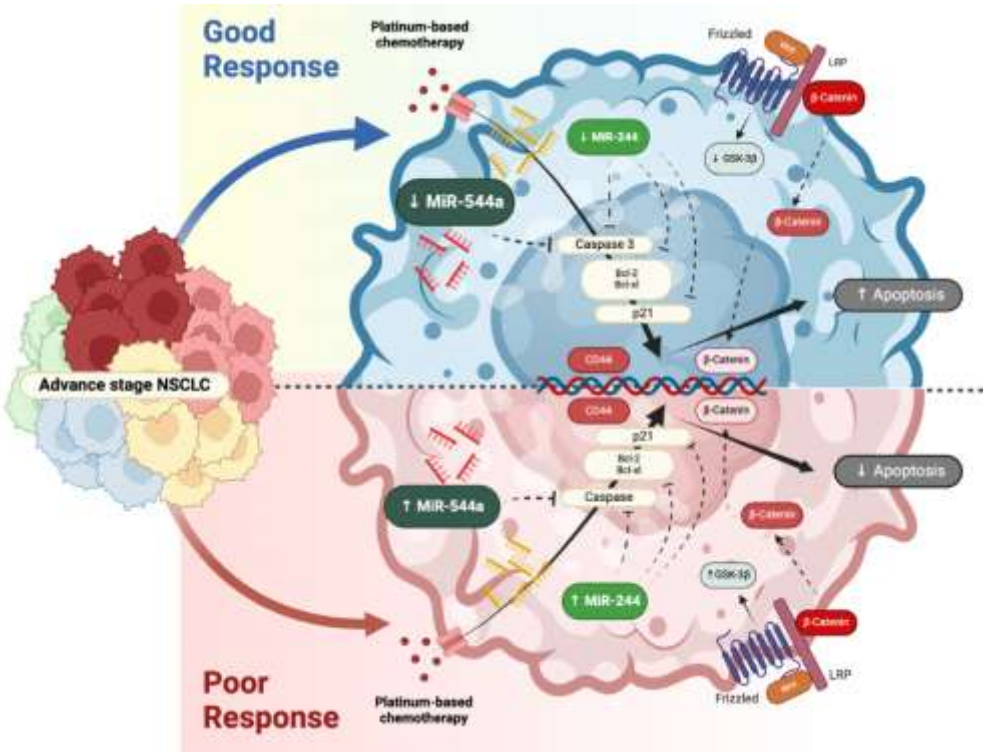

Figure 1. Chemoresistance to Platinum Chemotherapy in Advance-Stage NSCLC.

Therapeutic Approaches Aiming at the Inhibition of GSK-3β

Indeed, GSK-3β is a versatile enzyme with roles in multiple biological processes, making it a promising therapeutic target for a range of diseases such as Alzheimer's disease (AD), diabetes melitus (DM), and cancer.[51–54] The development of GSK-3β inhibitors has rapidly expanded, with lithium being the first inhibitor utilized therapeutically.[55] However, most inhibitors exhibit poor selectivity and off-target effects, limiting their clinical potential. Recent research has focused on improving selectivity and reducing adverse effects, with non-ATP competitive inhibitors, such as allosteric inhibitors, showing promise in reducing side effects compared to ATP-competitive inhibitors.[56–58] The exploration of GSK-3β drug-binding cavities and the development of diverse chemical structures have contributed to the ongoing efforts to create more effective and selective GSK-3β inhibitors for various human diseases.[58] In cancer therapy, GSK-3β has emerged as a highly promising target, especially in the treatment of NSCLC.[59] GSK-3β plays a critical role in a variety of cellular functions, such as regulating cell growth, differentiation, and programmed cell death. Promising inhibitors of GSK-3β have been identified in preclinical investigations, demonstrating favorable docking characteristics and pharmacokinetic properties for the potential treatment of non-small cell lung cancer.[60–62] The clinical development of GSK-3β inhibitors has demonstrated promise across multiple cancer types, with ongoing studies examining their efficacy and safety.[57] These inhibitors modulate key signaling pathways involved in cancer progression, such as Wnt/β-catenin and NF-κB. Additionally, GSK-3β inhibitors may enhance antitumor immune responses, presenting opportunities for combination therapies.[57] As research advances, GSK-3β inhibitors persist in showing potential as innovative cancer treatments, particularly for NSCLC.

In addition to their applications in cancer treatment, GSK-3β inhibitors have shown significant potential as versatile therapeutic agents for various diseases, notably AD.[53] These inhibitors exhibit promise in regulating crucial pathways associated with tau hyperphosphorylation, neuroinflammation, and neuronal plasticity in AD. In oncology, GSK-3β inhibitors have shown antitumor efficacy by affecting cell proliferation, apoptosis, and metastasis. Recent research underscores the synergistic benefits of combining GSK-3β inhibitors with standard chemotherapies or targeted therapies, suggesting new directions for cancer treatment.[63,64] Additionally, GSK-3β inhibitors hold potential for enhancing anticancer immune responses, possibly providing a dual therapeutic

benefit. Despite the known difficulties of developing new GSK-3β inhibitors, such as problems with selectivity and brain penetration, my ongoing research and participation in clinical trials are exploring the effectiveness of these novel compounds with improved pharmacokinetic characteristics.[53,58] However, targeting GSK-3β for the treatment of NSCLC presents several substantial challenges. A primary concern is the extensive involvement of GSK-3β in numerous cellular processes, such as metabolism and cell survival, which heightens the potential for off-target effects and toxicity.[65,66] Moreover, cancer cells can adapt to GSK-3β inhibition by activating compensatory pathways or modifying signaling networks, which complicates the treatment's efficacy. The intricate nature of GSK-3β pathways adds to the challenge, as GSK-3β can function as both a tumor suppressor and a tumor promoter, depending on the context.[66]

Pharmacokinetic challenges, including drug stability, bioavailability, and targeted delivery, further complicate the development of GSK-3β inhibitors. Additionally, non-selective inhibition may lead to potential side effects. The development of effective GSK-3β inhibitors is also impeded by limitations in preclinical models and difficulties in clinical validation, such as patient stratification and dose optimization.[57,67] Furthermore, the tumor microenvironment can significantly impact drug responses, introducing another layer of complexity to treatment strategies. Addressing these challenges necessitates innovative approaches in drug design, the exploration of combination therapies, and the development of personalized treatment plans.

GSK-3β as a Prognostic Biomarker

Research has shown that GSK-3β expression levels can predict patient outcomes and responses to therapy across different types of cancer. In breast cancer, higher GSK-3β levels are associated with worse survival rates, indicating it may serve as a potential biomarker for poor prognosis.[68,69] Similarly, in NSCLC, high GSK-3β expression is associated with reduced overall survival, positioning GSK-3β as a significant prognostic marker.[68] Research in hepatocellular carcinoma has also highlighted the prognostic value of phosphorylated Ser9-GSK-3β, particularly in patients with type 2 DM.[70,71] GSK-3β has established itself as a crucial biomarker, with the potential to shape disease prognosis and guide targeted therapeutic interventions. Research indicates that GSK-3β levels affect radiosensitivity in NSCLC cells; specifically, inhibiting GSK-3β leads to increased expression of AMPK and LC3 proteins following X-ray irradiation.[72,73] Moreover, GSK-3β is involved in cisplatin resistance through the GSK-3β/MCL-1 pathway, underlining its role in treatment response.[74,75] Investigations have examined the association between GSK-3β expression and other molecular characteristics of non-small cell lung cancer, including PDL1 score, PTEN levels, and driver mutations, underscoring the pivotal role of GSK-3β in the molecular profile of this disease.[76] Further studies have revealed that GSK-3β contributes to overcoming radioresistance through the DcR3/AKT/GSK-3β pathway, suggesting its potential as a target for enhancing treatment efficacy.[77]. GSK-3β multifaceted involvement in NSCLC highlights its potential as both a prognostic marker and a therapeutic target. Unlike other biomarkers like tumor mutational burden (TMB), which predict responses to immune checkpoint inhibitors, GSK-3β role extends to regulating pathways involved in cell proliferation, invasion, and metastasis.[78] GSK-3β inhibitors demonstrate a promising potential in heightening the sensitivity of NSCLC cells to radiation therapy, thereby providing a viable therapeutic approach to enhance treatment effectiveness. In contrast to biomarkers like CNPY2 and FAM110B, which primarily impact epithelial-mesenchymal transition and cell proliferation, the involvement of GSK-3β in NSCLC is comprehensive and crucial.[79–82]. Targeting GSK-3β could offer new treatment options and potentially improve responses when used alongside existing therapies. Additionally, GSK-3β levels could be monitored to track disease progression and adjust treatment strategies accordingly. In clinical trials, GSK-3β expression can help select patients most likely to benefit from specific treatments, improving trial efficiency and outcomes.

Future Directions and Research Gaps

Understanding GSK-3β role in NSCLC faces several unresolved questions and gaps. The precise mechanisms by which GSK-3β influences NSCLC progression, treatment response, and resistance remain unclear, necessitating further research to elucidate its specific pathways and molecular interactions. While GSK-3β shows promise as a biomarker, more extensive validation across diverse patient populations is needed to confirm its reliability. The efficacy and safety of GSK-3β inhibitors in clinical applications necessitate thorough examination through extensive clinical trials to mitigate potential adverse effects and refine treatment approaches. To advance the clinical utility of GSK-3β, future research should focus on several key areas. Combining GSK-3β inhibitors with other treatment modalities, such as immune checkpoint inhibitors or targeted therapies, could reveal new strategies for enhancing NSCLC treatment outcomes.[83,84] Personalized medicine approaches should aim to identify patient subsets most likely to benefit from GSK-3β-targeted therapies,

integrating genetic and molecular profiles into tailored treatment plans. Furthermore, exploring GSK-3β role in the tumor microenvironment and conducting longitudinal studies could provide deeper insights into its dynamic role and guide treatment adjustments. Emerging technologies offer promising methods for studying GSK-3β in NSCLC. Single-cell omics, including RNA sequencing and proteomics, can reveal detailed expression patterns and heterogeneity within tumors. Advanced gene-editing technologies like CRISPR/Cas9 can help validate therapeutic strategies by manipulating GSK-3β expression in model systems.[85,86] Molecular imaging techniques, such as PET imaging with GSK-3β-specific tracers, could enable non-invasive monitoring of GSK-3β activity in vivo. Additionally, high-throughput screening methods can accelerate the discovery of novel compounds targeting GSK-3β, advancing our understanding and therapeutic options.

4. Conclusions

GSK-3β has emerged as a critical biomarker in NSCLC, exerting a significant impact on disease progression, treatment response, and prognosis. Elevated levels of GSK-3β are associated with poorer survival outcomes and resistance to therapies such as cisplatin and radiation, underscoring its potential as both a prognostic marker and a therapeutic target. Integrating GSK-3β into clinical practice could enhance patient stratification and personalize treatment approaches, potentially improving therapeutic efficacy and overcoming resistance mechanisms. As ongoing research continues to validate its clinical utility, GSK-3β holds promise for advancing the management of NSCLC through targeted therapies and more tailored treatment strategies.

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