**STRUCTURE MODELLING AND COMPARISON OF THE ACTIVE SITES OF SIK1B AND DIFFERENT ISOFORMS OF SIKS USING HOMOLOGY MODELLING.**

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Abstract— ***Salt-inducible kinases (SIKs) are critical modulators of cellular energy responses and have attracted increasing interest due to their roles in diseases like diabetes and cancer. SIKs, particularly in cancer, have been shown to act as tumor suppressors, making them promising candidates for cancer therapy. Among the SIK family, the functions and characteristics of certain isoforms, such as SIK1A, SIK1B, SIK2, and SIK3 remain poorly understood. In this review a new insight is provided on the distinct roles that these SIKs play in various cellular processes, revealing their potential as a therapeutic target for a broader range of diseases. This study could be instrumental in guiding researchers toward the development of targeted drugs that modulate SIK activity, presenting new therapeutic strategies for diseases linked to SIK dysregulation, including cancer, neurodegenerative, and metabolic disorders.***

***Keywords—*** ***Salt-inducible kinases family, cancer, neurodegenerative, therapeutics***

1. Introduction

Salt-inducible kinases (SIKs), as essential members of the AMP-activated protein kinase (AMPK) family, play crucial roles in controlling energy response mechanisms like metabolism, cell division, inflammation, sleep and cardican rythms, bone reabsorbtion, lipid metabolism and gluconeogenesis. SIK1, the founding member of the SIK family, is expressed in the adrenal cortex, adipose, and neural tissues, and in breast cancer, it promotes oxidative phosphorylation while inhibiting glycolysis .(Katoh et al., 2004). SIK2, found in adipose tissue and skeletal muscle, is overexpressed in various tumors, indicating its role in oncogenesis. SIK3 is primarily abundant in the brain (Jagannath A et al 2023). However, they remain relatively understudied in diseases such as diabetes and cancer. (Zicheng Sun) Recent attention has illuminated SIKs' role as a tumour suppressor in LKB1-mediated non-small-cell lung malignancies, suggesting their potential as targets for cancer therapy (Kei Sakamoto) (Zicheng Sun).

Mutations in the SIK1 gene result in changes in cellular distribution, leading to early infantile epileptic encephalopathy (EIEE-30) with autistic characteristics. (Moataz Badawi) Despite the limited efficacy of risperidone in treating social impairments, animal models with these mutations exhibit disruptions in synaptic balance and neuronal excitability. Moreover, SIK1 plays essential roles in cardiomyocyte plasticity, insulin resistance, and glucose homeostasis, suggesting promising avenues for therapeutic intervention in various conditions. (Mark Nixon) (Rebecca Berdeaux). Unlike sik2 and sik3, sik1 plays integral role neuronal plasticity and hence neurodegenerative disorders.

Understanding SIK2's function in lipid and glucose metabolism is critical for precision medicine in treating ovarian cancer (OC). (Dan Hu) A thorough analysis reveals SIK2's involvement in OC metabolic processes and its potential as a therapeutic target. (Dan Hu) Clinical trials support SIK2's efficacy as a target for cancer treatment, while its broader impact extends to immune response modulation, neuronal survival, and potential tumour suppression in breast cancer. (Zicheng Sun)(Jiaojiao Zhu)(Neslihan Zohrap)(Fangyu Chen).

Macrophages, crucial for innate immunity, respond to infection by releasing inflammatory chemicals upon bacterial lipopolysaccharide (LPS) activation. (Masato Sanosaka) Examining the role of salt-inducible kinase (SIK), particularly SIK3, reveals its significance in suppressing inflammatory chemicals. (Masato Sanosaka)(Suneetha Amara). In breast cancer, SIK3's involvement in adipose tissue thermogenesis and hepatic lipid metabolism, highlighting its potential as a therapeutic target for obesity and cardio metabolic diseases.(Fubiao Shi)(Tatsuya Uebi)(Siwen Liu).

Salt-inducible kinases (SIKs), comprising SIK1, SIK2, and SIK3, are implicated in various cancers, including breast, lung, liver, prostate, gastric, ovarian, and pancreatic cancers. These kinases play diverse roles in cancer progression and regulation, being expressed in multiple human tissues. SIK2 is notably expressed in adipose tissues, where it regulates cell metabolism, insulin signaling, and gluconeogenesis, while SIK3 is predominantly found in the brain, coordinating with the mTOR complex to promote cancer under inflammatory stress. Dysregulation of SIKs is linked to tumorigenesis and progression in cancers. SIK1 generally functions as a tumor suppressor, with its downregulation associated with malignancy, whereas SIK2 and SIK3 are considered oncogenes that enhance cancer cell survival and influence clinical outcomes in breast and ovarian cancers. The roles of SIKs in cancer are complex, acting as key intermediaries in molecular pathways that drive cancer progression. Understanding these intricate roles underscores their potential as therapeutic targets and prognostic indicators, highlighting the need for further research into SIKs' multifaceted involvement in cancer development. (Role of SIK)

SIK1 as a Novel Direct Target of miR-130b-3p

Through investigating Serine/Threonine-protein kinase 1 (SIK1), its novel direct target has been identified to be miR-130b-3p. For validation of miR-130b-3p binding to SIK1, dual luciferase reporter assay was used. This association is significant because it attenuates SIK1 expression which can accelerate medulloblastoma (MB) tumor formation. By inhibiting SIK1, miR-130b-3p initiates p53 signaling pathway that results in an increase in the production of pro-apoptotic proteins like BAX and p53 and decrease in anti-apoptotic protein Bcl-2. Finally, this regulatory interaction suppresses MB carcinogenesis hence suggests a potential therapeutic avenue for MB treatment (Ning et al., 2015; Crawford et al., 2007; Gajjar et al., 2006).

SIK1 and Cardiac Stress

Salt-inducible kinase 1 (SIK1) also plays an important role in cardiac stress by interacting and stabilizing histone deacetylase 7 (HDAC7) via phosphorylation. This interaction is important because phosphorylation and subsequent HDAC7 stabilization by SIK1 leads to pathological cardiac myocardial remodeling, which promotes congestive heart failure. In particular, phosphorylation of HDAC7 by SIK1 stabilizes, inhibits proteasome-mediated, and promotes its pro -hypertrophic potential is enhanced HDAC7, when immobilized, induces expression of the c-Myc gene, a key component of cardiomyocyte hypertrophy and stress response, thereby promoting cardiac remodeling These findings SIK1 in cardiomyopathy highlights the importance of the /HDAC7 signaling axis, suggesting that it is a potential therapeutic target for heart failure therapy (Hill and Olson, 2008; Zhang et al., 2002 Chang et al., 2004; Lehmann et al., 2018; Berdeaux et al., 2007).

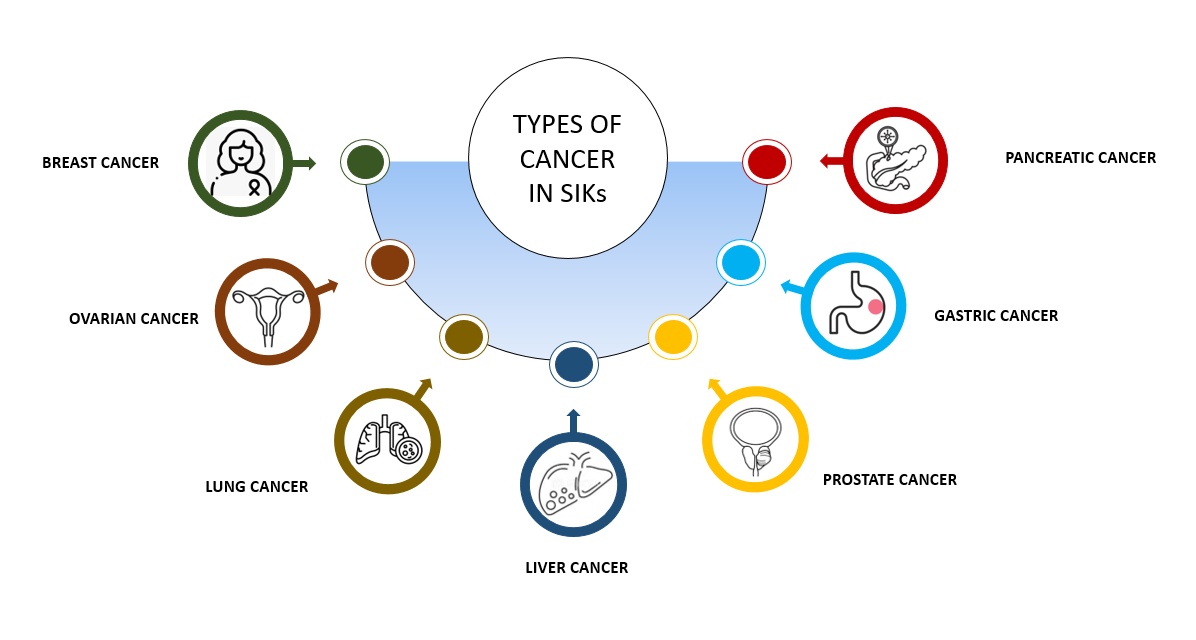
Dasatinib and SIK2 Inhibition

Dasatinib binds to SIK2 in a way that is important for its effectiveness, and this therefore leads to how the drug actually inhibits SIK2. This information could be helpful in the design of more selective and potent SIK2 inhibitors based on structural requirements of the binding interactions. Knowing the molecular mechanism of its binding, through molecular docking, molecular dynamics simulations, and binding free energy calculations, has greatly increased our knowledge of how dasatinib affects the activity of SIK2 at a molecular level. In developing pointed therapies for diseases caused by misregulation of SIK2, either in inflammatory diseases or in cancer, such knowledge is very important. Taken together, the results also give indications on how to modify dasatinib for enhanced inhibitory action against SIK2. (M. Shi)

HG-9-91-01 and SIKs

‌Above, one can see that HG-9-91-01 interacts with SIKs. HG-9-91-01 has been used previously in many studies and serves as an inhibitor targeting a family of Salt-inducible Kinases (SIKs) comprising SIK1, SIK2, and SIK3. The binding of HG-9-91-01 is especially important because it disrupts the SIKs-CRTC pathway. This interruption favors the dephosphorylation of transcriptional co-activators CRTC2/3, resulting in enhanced gene expression related to murine experimental colitis, melanin production, gluconeogenesis, and β-cell proliferation. The interaction of HG-9-91-01 with SIKs thus facilitates the modulation of these critical biological functions.(D. Huang, Wein MN, Mujahid N, Miranda F, Liang Y, Patel K)However, HG-9-91-01 was found in this study to also have an inhibiting effect on RIPK3 kinase activity, indicating a wider functional impact beyond its known targets. Such dual functionality underlines its potential as a therapeutic agent for the treatment of necroptosis-mediated inflammatory diseases by targeting the kinase activity of RIPK3 (Charbord J, Fu Y )

ROLE OF SIKs in Cancer



**ROLE OF BREAST CANCER**

SIK1, SIK2, and SIK3, play critical roles in breast cancer progression and treatment response, with each kinase displaying distinct functions and regulatory impacts on cancer cell behavior. SIK1 acts as a tumor suppressor by regulating cell polarity, promoting p53-dependent anoikis, and inhibiting metastasis. Its reduced expression is associated with increased tumor growth, metastasis, and poorer survival due to disruptions in oxidative phosphorylation, glycolysis, and key cellular signaling pathways, enhancing proliferation and invasion (Fangyu Chen, Lavanya Ponnusamy, Nathaniel Jensen, Roberta Tesch, Xin Wei, Yu-Ling Liang). In contrast, SIK2's role in breast cancer is context-dependent, functioning as both an oncogene and potential tumor suppressor. High SIK2 expression correlates with poor prognosis and aggressive tumor behavior, influencing metabolism, cell proliferation, and chemoresistance through its regulation of mitosis and the cell cycle (Lavanya Ponnusamy, Nathaniel Jensen, Xin Wei, Yu-Ling Liang). Despite its oncogenic role in promoting tumor growth and metastasis, SIK2's reduced expression is linked to decreased proliferation and better survival outcomes in certain contexts (Kimberly E. Maxfield, Neslihan Zohrap, Roberta Tesch, Zicheng Sun). SIK3, on the other hand, is highly expressed in breast cancer cells, contributing to poor survival and aggressive tumor characteristics through its impact on cell metabolism, division, and metastasis, including promoting chemoresistance via mechanisms involving ABC transporters like ABCB1 (Lavanya Ponnusamy, Nathaniel Jensen, Yu-Ling Liang, Xin Wei). Although inhibitors like emodin and berberine have shown promise in targeting SIK3 to reduce proliferation and resistance, more research is needed to fully elucidate its role in breast cancer progression and its potential as a therapeutic target (Fangyu Chen, Marc N. Wein, Roberta Tesch, Wen-Qi Du, Yue Hua, Zicheng Sun).

**ROLE OF SIKs in GASTRIC CANCER**

SIK, SIK, and SIKs play distinct but interconnected roles in gastric cancer, influencing tumor progression, cell survival, and therapeutic response. SIK1 acts as a tumor suppressor by regulating cell proliferation, apoptosis, and the epithelial–mesenchymal transition (EMT). It notably inhibits gastrin-induced migration in adenocarcinoma cells by enhancing the phosphorylation of HDACs, which influences transcriptional repression and modulates biological responses to gastrin, underscoring the need for further research into these mechanisms (Linn-Karina M. Selvik). Increased levels of SIK1 are linked to advanced tumor stages, suggesting a connection between SIK1 and gastric cancer progression, independent of metastatic status, highlighting its potential as a therapeutic target (Roberta Tesch). Downregulation of SIK1 is associated with greater tumor aggressiveness and metastasis, further reinforcing its potential as a target to mitigate cancer progression (Xin Wei). SIK2 also shows increased mRNA and protein levels in advanced tumor stages and plays a multifaceted role by influencing cell survival, progression, and chemoresistance, particularly in adipocyte-rich environments that enhance lipid synthesis and are linked to poor prognosis (Roberta Tesch). SIK2 contributes to tumor growth and EMT within the LKB1-SIK2/3-PARD3 signaling axis, promoting cancer progression. Erianin’s inhibition of SIK2 suppresses these oncogenic processes, highlighting its potential as a therapeutic target in gastric cancer treatment (Xin Wei). SIK3, though less studied, plays a significant role in tumor progression, primarily affecting the LKB1-SIK2/3-PARD3 signaling axis, which regulates EMT and tumor growth. The inhibition of SIK3 by Erianin disrupts this pathway, reducing invasion, migration, and overall tumor aggressiveness, emphasizing the need for further research into SIK3's contributions to gastric cancer development (Roberta Tesch, Xin Wei).

**ROLE OF SIK in PANCREATIC CANCER**

SIK1 (salt-inducible kinase 1) plays a complex role in pancreatic cancer, exhibiting both tumor-suppressive and tumor-promoting effects. On one hand, SIK1 acts as a potential tumor suppressor by inhibiting cell proliferation and promoting apoptosis, with higher expression levels correlating with improved prognosis, suggesting its beneficial role in restraining cancer growth (Xin Wei). However, SIK1 can also contribute to tumor progression and resistance to therapies by modulating pathways involved in cell cycle regulation and apoptosis, thereby associating its elevated levels with poorer outcomes (Yu-Ling Liang). SIK2 is implicated in pancreatic cancer by promoting cancer cell proliferation, migration, and invasion, significantly contributing to the epithelial-mesenchymal transition (EMT) and enhancing tumor aggressiveness (Xin Wei). Its elevated expression is linked to aggressive tumor behavior and poor prognosis, as it influences key signaling pathways crucial to cancer progression, highlighting SIK2 as a potential therapeutic target (Yu-Ling Liang). Similarly, SIK3 is involved in regulating cell metabolism, division, and metastasis in pancreatic cancer, acting downstream of LKB1 and influencing cancer progression and spread (Xin Wei). Studies indicate that SIK3 contributes to tumor growth and chemoresistance, affecting cancer pathways and potentially serving as both a prognostic marker and a therapeutic target (Yu-Ling Liang).

**ROLE OF SIK in OVARIAN CANCER**

SIK1, SIK2, and SIK3 play critical and distinct roles in ovarian cancer, influencing tumor progression, metastasis, and therapeutic responses. SIK1 acts as a tumor suppressor, maintaining cell homeostasis and affecting cancer cell survival under stress conditions such as chemoradiotherapy. Its downregulation is linked to poorer clinical outcomes, while inhibitors like ARN3236 show potential in reducing tumor progression and metastasis in xenograft models (Fangyu Chen; Marc N. Wein). Furthermore, SIK1’s modulation of the LKB1-p53 axis affects anoikis and metastasis, highlighting its therapeutic potential (Wen-Qi Du, S Charoenfuprasert). In contrast, SIK2 is often overexpressed in high-grade serous ovarian cancer, promoting tumor growth and metastasis by enhancing cell cycle progression and supporting metabolic processes, including fatty acid oxidation via the PI3K-AKT pathway (Marc N. Wein, Nathaniel Jensen, Yue Hua, Yu-Ling Liang). SIK2’s involvement in epithelial-mesenchymal transition (EMT) further contributes to its role in promoting aggressive tumor phenotypes, while its inhibition sensitizes cells to chemotherapy, making it a promising target (Fangyu Chen; Zicheng Sun; Nicola J. Darling; Aarti Jagannath). SIK3, acting as an oncogene, accelerates tumor growth and metastasis through pathways like c-Src PI3K and MMP9/CXCR4, and is associated with poor prognosis and increased chemoresistance (Yu-Ling Liang; Zicheng Sun ,S Charoenfuprasert). SIK3 also regulates lipid synthesis, influencing tumor progression through its interaction with the mTOR complex and contributing to poor overall survival outcomes in ovarian cancer patients (Roberta Tesch; Xin Wei; Aarti Jagannath). Collectively, these findings underscore the complex and pivotal roles of SIK1, SIK2, and SIK3 in ovarian cancer, highlighting their potential as therapeutic targets depending on their expression and functional context in the disease.

**ROLE OF SIK in PROSTATE CANCER**

SIK1 (Salt-Inducible Kinase 1) primarily functions as a tumor suppressor in prostate cancer, with its downregulation linked to increased cancer risk and disrupted circadian gene expression, such as PER1, which impacts cancer cell proliferation and tumor progression (Aarti Jagannath). It is expressed in neural and adipose tissues and plays a role in hormonal stimulation, contributing to tumor development and progression in the prostate (Fangyu Chen). SIK1 also regulates TGF signaling by forming a complex with SMAD7 and SMURF2, influencing pathways critical to cancer progression (Luke D. Hutchinson). While SIK1 generally acts as a tumor suppressor, its downregulation may lead to tumorigenesis by disrupting cell differentiation and promoting pathways like EMT and metastasis (Xin Wei). Additionally, SIK1 modulates cell cycle regulators such as p21, p27, and Cyclin D, and its low expression can impair apoptosis through ER stress and G1 cell cycle arrest, thereby inhibiting prostate cancer progression (Zicheng Sun). SIK2, on the other hand, influences prostate cancer biology by promoting tumor cell proliferation, metastasis, and chemotherapy resistance, impacting key signaling pathways. It regulates TGF-induced transcriptional responses related to apoptosis, with its inhibition potentially affecting cancer cell survival (Luke D. Hutchinson). SIK2 also controls cell cycle regulators, facilitating G1/S phase transition and inhibiting apoptosis via CREB-mediated ER stress responses (Zicheng Sun). Its overexpression is associated with poor prognosis, enhancing F-actin expression and MYL2 phosphorylation, which contribute to ovarian cancer metastasis (Xin Wei ,Aarti Jagannath). SIK3, although less studied in prostate cancer, has a broader role in oncogenesis, metabolism, and circadian rhythms, potentially influencing prostate cancer progression. It is known to support cancer cell proliferation in AML by inhibiting HDAC4 (Fangyu Chen). SIK3’s upregulation is linked to enhanced cell growth, proliferation, and metastasis, contributing to tumor aggressiveness and poor prognosis, acting as an oncogene by modulating cell cycle processes such as CDK2 activity (Xin Wei; Zicheng Sun; Luke D. Hutchinson).

**ROLE OF LUNG CANCER**

SIK1, SIK2, and SIK3 play multifaceted roles in lung cancer, influencing various cellular processes that impact tumor progression and therapeutic outcomes. SIK1 acts predominantly as a tumor suppressor and is highly expressed in lung adenocarcinoma, regulating the cell cycle, metastasis, and anoikis by linking LKB1 to p53-mediated anoikis, thereby restraining metastatic spread (Wen-Qi Du). The loss of SIK1 promotes metastasis in mouse models and correlates with distant metastasis in humans (Yu-Ling Liang). Its depletion accelerates tumor growth, invasion, and epithelial-mesenchymal transition (EMT), while overexpression reduces proliferation and stem cell formation, indicating poor prognosis when SIK1 levels are low (Zicheng Sun). In non-small cell lung cancer (NSCLC), SIK1 disruption accelerates tumor growth, highlighting its critical role in inhibiting cancer progression (Nicola J. Darling). Conversely, SIK1 may overexpress in lung tissues, acting as an oncogenic signaling transmitter during lung tumor development (Fangyu Chen). SIK2, overexpressed in lung tumors, regulates the PI3K-Akt-mTOR pathway, impacting tumorigenesis and development (Fangyu Chen). SIK2's dysregulation can act as both a tumor promoter and suppressor, enhancing therapy sensitivity, particularly to paclitaxel, and correlating with poor prognosis in various cancers (Wen-Qi Du ,Nicola J. Darling). It promotes cancer progression through regulation of cell metabolism, division, and EMT, contributing to cancer cell survival and migration (Xin Wei, Zicheng Sun). SIK3, especially in NSCLC, is involved in cancer proliferation, EMT, and tumor growth, where its dysregulation affects cell cycle progression and tumorigenesis by interacting with the mTOR complex (Wen-Qi Du, Xin Wei). Elevated SIK3 levels are associated with poor prognosis, contributing to malignancy and promoting cancer cell proliferation (Zicheng Sun). Overall, the roles of SIK1, SIK2, and SIK3 in lung cancer underscore their therapeutic potential, warranting further exploration of their regulatory mechanisms (Nicola J. Darling).

**ROLE OF LIVER CANCER**

SIK1, SIK2, and SIK3 play significant yet complex roles in liver cancer, impacting various metabolic and tumor suppression mechanisms. SIK1 is involved in regulating hepatic metabolism and tumor suppression, notably through the modulation of hepatic steatosis via p300 phosphorylation linked to ChREBP, and interaction with LKB1, triggering p53-dependent anoikis to suppress metastasis (Fangyu Chen). SIK1's role in regulating hepatic glucose and lipid metabolism, including gluconeogenesis and lipogenesis, highlights its potential influence on liver cancer progression through metabolic dysregulation (Kei Sakamoto). Disruption of SIK1, particularly alongside mutations such as LKB1 and KRAS, accelerates liver tumor growth, suggesting its tumor-suppressive effects in cellular differentiation and growth control pathways (Nicola J. Darling). Reduced SIK1 expression correlates with increased metastasis, making it a target for liver cancer treatment and prevention (Wen-Qi Du), though its functions can vary, as its loss is linked to tumor development, highlighting a complex, context-dependent role in liver cancer (Xin Wei). SIK2 also plays a multifaceted role, mediating hepatic steatosis prevention through p300 phosphorylation and linking with ChREBP and LKB1 to induce p53-dependent anoikis, illustrating its complex functions in cancer (Fangyu Chen). While generally a tumor promoter, SIK2 influences insulin signaling, adipogenesis, and gluconeogenesis, linking it to metabolic dysregulation in liver cancer (Kei Sakamoto). It is crucial in hepatic glucose metabolism and tumorigenesis, with inhibition shown to alter gluconeogenic gene expression, affecting glucose homeostasis and pointing to its therapeutic potential (Nicola J. Darling). SIK2 also regulates lipid metabolism, impacts cancer cell proliferation, and delays the G1/S transition upon depletion, highlighting its potential as a therapeutic target (Wen-Qi Du). High SIK2 levels correlate with aggressive liver cancer, making it a promising target for therapy (Xin Wei). SIK3, identified as a critical player in various cancers, supports cancer cell proliferation through the LKB1-HDAC axis and plays a significant role in liver metabolism, influencing gluconeogenesis and lipid metabolism, which may affect liver cancer development (Fangyu Chen, Kei Sakamoto). SIK3’s role in liver cancer is complex, with functions varying by cancer type; it is often upregulated in liver cancer, promoting tumor growth by enhancing cell proliferation and metastasis, marking it as a potential therapeutic target (Wen-Qi Du, Xin Wei ,Nicola J. Darling,).

**ROLE OF DIABETIC IN SIKs**

The role of Salt Inducible Kinases (SIKs) in diabetes and metabolic regulation has garnered significant attention due to their involvement in essential cellular processes, particularly glucose and lipid metabolism. The importance of SIK isoforms, especially SIK2, in regulating gluconeogenesis and glucose metabolism. While some studies indicate that SIK2 is crucial for hepatic gene expression and blood glucose regulation, conflicting findings exist; some suggest no significant effects upon SIK2 inactivation. Notably, SIK inhibitors could enhance gluconeogenesis, with cancer drugs like bosutinib and dasatinib showing potential to promote an anti-inflammatory macrophage phenotype. Clinical observations suggest that dasatinib improves glucose control in chronic myeloid leukemia patients suffering from type 2 diabetes, hinting at a direct correlation between SIK inhibition and glycemic improvement. This underlines the necessity for further investigation focused on isoform-specific SIK inhibitors to elucidate both the acute and chronic impacts of SIKs on metabolic functions in vivo (Kei Sakamoto). The molecular mechanisms underpinning type 2 diabetes, pointing to the dysregulated gene expression that influences gluconeogenesis and lipogenesis as key contributors to the disease's pathophysiology. In this context, SIK1 and SIK2 emerge as vital proteins regulating these metabolic processes. For instance, SIK1 inhibits lipogenesis by phosphorylating Srebp1c, thereby mitigating hepatic triglyceride accumulation. Her research also underscores the role of CREB-dependent transcription in modulating glucose output during fasting, indicating its dysregulation in diabetic livers. Restoring SIK activity in diabetic patients may decrease excessive lipogenesis and hyperglycemia, positioning SIK kinases as promising therapeutic targets for addressing metabolic complications associated with diabetes (Rebecca Berdeaux). This explores the SIK2 p35 PJA2 complex within pancreatic cells, essential for maintaining insulin secretion and glucose homeostasis. His study reveals that SIK2 phosphorylates p35, leading to its ubiquitylation by PJA2, thereby enhancing insulin secretion in response to glucose stimulation. In metabolic syndrome models, SIK2 accumulation facilitates compensatory insulin secretion, whereas SIK2 knockout results in p35 accumulation and impaired insulin release. This intricate interaction among p35, CDK5, and AMPK is vital for regulating insulin release, offering significant insights into the cellular mechanisms influencing insulin secretion, especially in prediabetic conditions (Jun-Ichi Sakamaki). SIKs’ influence on hepatic glucose production, positing that their dysregulation may impair glycemic control in diabetes. His findings suggest that targeting SIK inhibition could serve as a viable therapeutic strategy for managing hyperglycemia in diabetic patients. The activities of SIK1 and SIK2 are directly linked to blood glucose levels, reinforcing the potential of SIK regulation in therapeutic approaches aimed at enhancing glycemic control in type 2 diabetes (Marc N. Wein). Lastly, the critical role of SIK2 in regulating lipid homeostasis and adipogenesis, key factors influencing glucose levels and insulin tolerance. His study illustrates the interaction between CREB-regulated transcription factor CRTC2 and its negative regulator, SIK2, in metabolic pathways within adipocytes. SIK2 knockout mice exhibit elevated blood glucose levels, shedding light on the metabolic pathways associated with glucose and insulin tolerance. The interplay of SIK2 and adiponectin in hepatic lipogenesis and gluconeogenesis further emphasizes the significance of SIK regulation within broader metabolic landscapes (Jinyoung Park). Together, these studies present compelling evidence supporting SIKs not only as crucial players in metabolic regulation but also as potential therapeutic targets for diabetes management, indicating a need for ongoing research in this domain.

**NEURODEGENERATIVE DISORDERS**

Salt-Inducible Kinases (SIKs) have gained prominence as crucial regulators of various cellular pathways relevant to neurodegenerative disorders. Their involvement spans critical processes such as inflammation, metabolism, and oxidative stress, which are central to the pathogenesis of diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy. This review delves into the intricate roles of SIKs in these disorders, synthesizing findings from recent research to elucidate their potential as therapeutic targets.

**SIKs and the CREB Signaling Pathway**

SIKs, particularly SIK2 and SIK3, are involved in the regulation of the CREB (cAMP-response element-binding protein) signaling pathway. CREB plays a critical role in neuronal function, and its dysregulation is implicated in various neurodegenerative conditions, including depression and epilepsy. SIK2's increased activity in the hippocampus has been associated with depressive behavior, suggesting that alterations in SIK2 function can contribute to mood disorders (Nicola J. Darling).

Genetic mutations in SIK1 have also been identified in developmental epilepsy patients, further linking SIK dysregulation to epileptic disorders. The role of SIKs in modulating CREB activity and subsequent gene expression highlights their potential as targets for novel therapeutic strategies. Inhibition of SIKs has been shown to produce antidepressant-like effects, indicating that targeting the SIK-CREB-BDNF pathway could offer new avenues for treating neurodegenerative disorders (Aarti Jagannath).

**The Role of SIKs in Neurodevelopment and Epilepsy**

Recent advancements in genetic research have highlighted the significance of SIKs, particularly SIK1, in neurodevelopmental disorders such as epilepsy. Exome sequencing studies have identified mutations in the SIK1 gene associated with developmental epilepsies (Hansen et al., 2015). These findings emphasize the role of SIK1 in neurodevelopment and epilepsy pathogenesis, linking it to critical targets such as MEF2C (myocyte enhancer factor 2C) and CRTC1 (CREB-regulated transcription coactivator 1). MEF2C and CRTC1 are integral to synaptic function and neuronal morphology, and their regulation by SIK1 is crucial for maintaining synaptic activity (Proschel et al., 2023).

Moreover, Brain-Derived Neurotrophic Factor (BDNF), a key player in neuronal development and survival, has been shown to upregulate SIK1 expression in primary rat cortical neurons. This interaction enhances MEF2 transcription and highlights the role of SIK1 dysregulation in neurodegenerative conditions. The dysregulation of this pathway underscores the importance of SIK1 in synaptic function and its potential impact on neurodevelopmental and neurodegenerative disorders (Badawi et al., 2021).

**SIK1 in Neuroinflammation**

SIK1 has been found to play a protective role in alcohol-induced neuroinflammation. Increased SIK1 expression following alcohol treatment correlates with reduced levels of pro-inflammatory cytokines and decreased apoptosis in microglial cells. This suggests that SIK1's ability to modulate inflammatory responses could be harnessed as a therapeutic target for alcohol-induced neuroinflammation (Yu Zhang). The protective effects of SIK1 in mitigating neuroinflammatory responses emphasize its potential utility in managing neurodegenerative conditions associated with chronic inflammation.

**SIK2 and Parkinson's Disease**

The role of SIK2 in Parkinson's disease has garnered significant attention due to its impact on mitochondrial function and energy metabolism. Mitochondrial dysfunction is a hallmark of Parkinson's disease, and SIK2's involvement in regulating mitochondrial activity is crucial for dopaminergic neuronal survival. Studies have shown that SIK2 affects mitochondrial dynamics and energy metabolism, which are essential factors in the progression of Parkinson's disease (Waleed Hassan Almalki).

Inhibition of SIK2 has been linked to reduced neurobehavioral deficits and improved neuronal survival in models of neurodegenerative diseases. Research involving SIK2 knockout mice demonstrated enhanced neuronal survival following ischemic brain injury, indicating that SIK2's role in neuroprotection could be leveraged for therapeutic purposes (Tsutomu Sasaki). The findings suggest that targeting SIK2 may offer therapeutic benefits in neurodegenerative diseases through its effects on neuronal survival and inflammation.

**SIKs and Inflammation**

SIKs influence inflammation through pathways such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). SIKs, particularly SIK1 and SIK3, can suppress inflammatory responses by inhibiting NF-κB, a key transcription factor in promoting pro-inflammatory gene expression. Disruption in SIK function can lead to unchecked activation of inflammatory pathways, contributing to chronic inflammation and neurodegeneration (Waleed Hassan Almalki).

The ability of SIKs to modulate NF-κB activity highlights their potential as therapeutic targets for managing chronic inflammatory conditions associated with neurodegenerative diseases. Research into SIKs' role in regulating inflammation underscores their significance in the context of neurodegeneration and offers insights into potential treatment strategies.

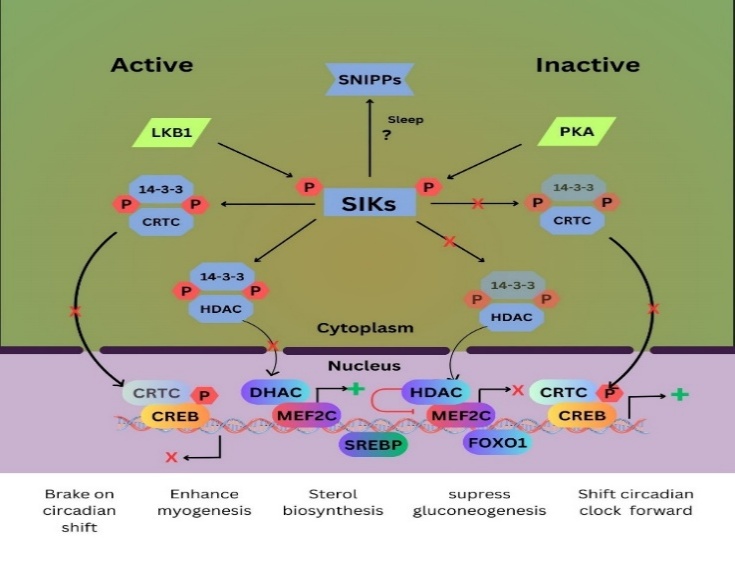
**SIKs in Alzheimer's Disease**

SIK1 and SIK3 have been implicated in Alzheimer's disease through their regulation of the cholinergic system and calcium pathways. Dysregulation in these pathways can exacerbate oxidative stress and inflammation, contributing to the progression of Alzheimer's disease. SIKs' involvement in modulating oxidative stress and inflammatory responses highlights their potential role in managing Alzheimer's disease and other neurodegenerative conditions (Waleed Hassan Almalki).

Similarly, SIK2's role in metabolic regulation and synaptic function is crucial in Parkinson's disease. Mitochondrial dysfunction and altered energy metabolism are central to Parkinson's disease pathogenesis, and SIK2's involvement in these processes underscores its potential as a therapeutic target (Waleed Hassan Almalki).

SIKs are emerging as critical regulators in neurodegenerative disorders, influencing pathways related to inflammation, oxidative stress, and metabolism. Their roles in these processes make them promising targets for novel therapeutic interventions. As research continues, understanding the multifaceted functions of SIKs in neurodegeneration could lead to effective treatments and improved management of neurodegenerative diseases. The growing body of evidence highlighting SIKs' involvement in various neurodegenerative conditions underscores their potential as therapeutic targets and calls for further investigation into their mechanistic roles and therapeutic applications.

**Targets of Salt-Inducible Kinases**



When SIKs are active, they affect the phosphorylation state of a number of substrates by acting at the LxB(S/T)xS xxxL motif (where X is any amino acid and B is a basic amino acid), as determined by in vitro research ([Robert A Screaton](https://pubmed.ncbi.nlm.nih.gov/?term=Screaton+RA&cauthor_id=15454081)). Two of these families the class IIA histone deacetylases (HDAC4/5/7/9) and the cyclic AMP-response-element binding protein (CREB)-regulated transcriptional coactivators (CRTC1/2/3) have been the subject of substantial research. Class IIa HDACs and CRTC proteins are phosphorylated by SIK, which causes their cytoplasmic retention ( [Donald R Walkinshaw](https://pubmed.ncbi.nlm.nih.gov/?term=Walkinshaw+DR&cauthor_id=23393134)), changing downstream transcription (FIGURE 2). Transcription is inhibited by class 2A HDACs because they remove acetylation marks from both histone and nonhistone proteins. Myocyte enhancer factor 2 (MEF2) and other transcription factors that class 2A HDACs would normally be bound to are released by the phosphorylation and sequestration of these enzymes, which in turn promotes MEF2-dependent gene transcription. MEF2 promotes the survival and growth of skeletal and other myocytes by stimulating the production of muscle-specific genes. The function of SIK1 as a class 2A HDAC in this system has been extensively investigated ([Randi Stewart](https://pubmed.ncbi.nlm.nih.gov/?term=Stewart+R&cauthor_id=23256157), [Pablo E Hollstein](https://pubmed.ncbi.nlm.nih.gov/?term=Hollstein+PE&cauthor_id=31350328), 1[Rebecca Berdeaux](https://pubmed.ncbi.nlm.nih.gov/?term=Berdeaux+R&cauthor_id=17468767)), whereby the phosphorylation of HDAC4/5/9 releases MEF2 to transcribe progrowth genes. This finally results in myocardial hypertrophy ([Austin Hsu](https://pubmed.ncbi.nlm.nih.gov/?term=Hsu+A&cauthor_id=32106109)) and calcification ([Alon Abend](https://pubmed.ncbi.nlm.nih.gov/?term=Abend+A&cauthor_id=28588072)), under pathological settings. The activity of SIK1 on HDAC7, on the other hand, was recently demonstrated to stabilize HDAC7 and promote MYC-mediated transcription ([Austin Hsu](https://pubmed.ncbi.nlm.nih.gov/?term=Hsu+A&cauthor_id=32106109)), indicating that the pathways may be more intricate than is currently understood. Furthermore, a broad range of effects on the development and differentiation of various cell types are downstream of MEF2 activity. These effects include the regulation of DLX5/6 or SOST with subsequent sclerostin expression ([Michael P Verzi](https://pubmed.ncbi.nlm.nih.gov/?term=Verzi+MP&cauthor_id=17420000), Collette NM, [Michael A Arnold](https://pubmed.ncbi.nlm.nih.gov/?term=Arnold+MA&cauthor_id=17336904)), the differentiation of the musculoskeletal system through interactions with mastermind-like protein 1 (MAML1) ([Huangxuan Shen](https://pubmed.ncbi.nlm.nih.gov/?term=Shen%20H%5BAuthor%5D)) and bHLH transcription factors like BMAL1 in regulating circadian rhythmicity ([Mickaël Di-Luoffo](https://pubmed.ncbi.nlm.nih.gov/?term=Di-Luoffo+M&cauthor_id=26019261), ([Maria M Mihaylova](https://pubmed.ncbi.nlm.nih.gov/?term=Mihaylova+MM&cauthor_id=21565617)). HDACs also control glucose homeostasis by activating transcription factors belonging to the forkhead family, such as forkhead box O (FOXO) ([Maria M Mihaylova](https://pubmed.ncbi.nlm.nih.gov/?term=Mihaylova+MM&cauthor_id=21565617)).

CRTC phosphorylation by SIK functions as a brake on this system because, in contrast, dephosphorylated CRTCs enhance the transcription of CREB and associated basic leucine zipper family (bZip) transcription factor-dependent gene transcription. Through an association with 14-3-3 that is reliant on phosphorylation, CRTCs are trapped in the cytoplasm. CRTC is initiated by the concomitant signaling of calcium and cAMP. On the other hand, dephosphorylated CRTCs support CREB and the associated basic leucine zipper family. Transcription of genes depending on transcription factors (bZip); Consequently, CRTC's cytoplasmic relocalization upon phosphorylation serves as a brake on this system through SIK. In the cytoplasm, CRTCs are trapped by a phosphorylation- interdependent relationship with 14-3-3. The occurrence CRTC dephosphorylation by the phosphatase calcineurin and cAMP signaling is initiated by the suppression of SIK activity, which permits CRTC nuclear entrance ([Robert A Screaton](https://pubmed.ncbi.nlm.nih.gov/?term=Screaton+RA&cauthor_id=15454081)), as CRTCs encourage CREB-dependent transcription of genes. PKA subsequently deactivates SIK, phosphorylating CRTC to cause cytoplasmic relocalization ([Emma Henriksson](https://pubmed.ncbi.nlm.nih.gov/?term=Henriksson%20E%5BAuthor%5D)). This mechanism has been shown in a variety of cell types, including pancreatic cells ([Robert A Screaton](https://pubmed.ncbi.nlm.nih.gov/?term=Screaton+RA&cauthor_id=15454081)) and hepatic cells ([Seung-Hoi Koo](https://pubmed.ncbi.nlm.nih.gov/?term=Koo+SH&cauthor_id=16148943)) that regulate fasting glucose metabolism, as well as the SCN (A. Jagannath, [Kensuke Sakamoto](https://pubmed.ncbi.nlm.nih.gov/?term=Sakamoto+K&cauthor_id=23699513)). The target genes of the transcription factor CREB have a variety of functions and CRE motifs in their promoters; they are covered in depth in sect. 2. The targets are, in short, several interleukins (2/6/10), TNF-a, and NF-κB, all important players in controlling immunity ([Andy Y. Wen](https://pubmed.ncbi.nlm.nih.gov/?term=Wen%20AY%5BAuthor%5D)), Period (PER1/2/3), which is important in the photoentrainment of the circadian cycle (A. Jagannath), and phosphoenolpyruvate carboxykinase (PEPCK) and cytochrome c, which assist cellular metabolism and respiration, respectively ([B Mayr](https://pubmed.ncbi.nlm.nih.gov/?term=Mayr+B&cauthor_id=11483993)).

The proteome comprises at least 100,000, if not more, phosphorylation sites, thanks to the recent development of trustworthy mass spectrometry-based techniques for quantitative phosphoproteomics analysis ([Elise J. Needham](https://www.science.org/doi/10.1126/scisignal.aau8645#con1)). Nevertheless, only a small portion of these sites are covered by the phosphosites' functional analysis and the kinases facilitating these modifications, hence the moniker "the dark phosphoproteome" ([Elise J. Needham](https://www.science.org/doi/10.1126/scisignal.aau8645#con1)). These methods have been used in the investigation of SIKs, where the effects of the SIK inhibitor HG-9-91-01 and the phosphoproteome resulting from SIK3 gain of function (S551 mutation that eliminates PKA inactivation) were profiled on the whole brain extract ([Zhiqiang Wang](https://pubmed.ncbi.nlm.nih.gov/?term=Wang+Z&cauthor_id=29899451)). This study found that the inhibition of SIKs caused several changes in phosphorylation, but the majority of these changes were caused by a cascade of kinases/phosphatases, among which MPK and a few others were proposed to play a substantial role ([Zhiqiang Wang](https://pubmed.ncbi.nlm.nih.gov/?term=Wang+Z&cauthor_id=29899451), [Franziska Brüning](https://pubmed.ncbi.nlm.nih.gov/?term=Br%C3%BCning+F&cauthor_id=31601740)). Instead of being directly attributable to SIK itself. It is crucial to remember that the kinases responsible for phosphosite modifications are only those whose targets have been thoroughly studied. As such, any annotations of these kinases should be done carefully. However, an entirely new target of SIK2 was recently discovered by phosphoproteomic analysis of host cell responses to Salmonella infection: surprisingly, SIK2 directly associates with actin filaments under basal conditions but is recruited to the protective Salmonella-containing vacuole with elements of the actin polymerization machinery upon Salmonella infection ([Marcel Hahn](https://pubmed.ncbi.nlm.nih.gov/?term=Hahn+M&cauthor_id=33947818)).

VII. CONCLUSION

Finally, the Progression and comparison of the active sites of SIK1B and different isoforms of SIKs were made easier by homology modelling. Through evaluation of the modelled structures, information on possible ligand interactions and SIK1B's biological roles was attained. Sequence and function-wise, SIK1 and SIK1B are analogous, but their unique structural characteristics point to potential variations in regulatory mechanisms and tissue-specific activities. Understanding SIK1B's role in cellular processes and determining potential treatment targets may be possible with more research on the protein's active sites and ligand interactions. In summary, this research aids in clarifying the functional importance of SIK1B in both biological and pharmacological settings.

VIII. FUTURE SCOPE

The future scope of research on **Salt-Inducible Kinases (SIKs)** lies in advancing our understanding of their isoform-specific roles in cancer, neurodegenerative, and metabolic diseases to enable **precision-targeted therapeutics**. With their dual functions as tumor suppressors (SIK1) and oncogenes (SIK2/3), as well as their involvement in energy metabolism, circadian regulation, and inflammation, SIKs represent a promising yet underexplored therapeutic axis. Future studies should focus on **developing selective SIK inhibitors or activators**, integrating **structural biology, AI-driven drug discovery, and clinical trials** to evaluate their translational potential. Such efforts could pave the way for innovative therapies in oncology, cardiometabolic diseases, diabetes, and neurodegeneration, positioning SIKs as central molecular targets for next-generation precision medicine.

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