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## Review Article

# GSK-3-mediated regulation of cellular functions and signaling pathways

Lingaraj Anawal\*, Sanjay Havaragi, Chandrashekhar V. M.

Department of Pharmacology, B. V. V. Sangha's Hanagal Shri Kumareswar, College of Pharmacy, Bagalkote, Karnataka, India

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### \*Correspondence:

Lingaraj Anawal,

Email: [lingarajanawal@gmail.com](mailto:lingarajanawal@gmail.com)

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### ABSTRACT

Glycogen synthase kinase-3 (GSK-3) is a highly conserved serine/threonine kinase that has emerged as a central regulator of diverse cellular signaling networks and physiological processes. Originally recognized for its role in glycogen metabolism, GSK-3 is now known to participate in the regulation of gene expression, metabolism, proliferation, differentiation, development, apoptosis, cellular adhesion, migration, and neuronal function. Its activity is controlled through multiple regulatory mechanisms, including inhibitory phosphorylation and modulation of protein complexes, enabling GSK-3 to respond dynamically to extracellular and intracellular signals. The two paralogues, GSK-3 $\alpha$  and GSK-3 $\beta$ , share considerable structural similarity but may exhibit distinct and sometimes overlapping biological functions. Dysregulated GSK-3 signaling has been associated with neurological and neurodegenerative disorders, metabolic and inflammatory diseases, and cancer. Although pharmacological inhibition of GSK-3 has therefore attracted considerable therapeutic interest, clinical translation remains challenging because of limited isoform selectivity, context-dependent biological effects, and the complex physiological functions of this kinase. Recent findings further demonstrate that GSK-3 can regulate central cellular processes through distinct isoform-dependent mechanisms, emphasizing the importance of understanding its spatial, temporal, and substrate-specific regulation. A comprehensive characterization of GSK-3 $\alpha$  and GSK-3 $\beta$  may consequently facilitate the development of more selective and clinically effective therapeutic strategies.

**Keywords:** Glycogen synthase kinase-3, GSK-3 $\alpha$ , GSK-3 $\beta$ , Cellular signaling, Cellular homeostasis, Neurodegeneration

### INTRODUCTION

#### ***GSK3: A multifunctional regulator of cellular and pathophysiological processes***

Glycogen synthase kinase-3 (GSK3) was initially identified and characterized as a kinase that suppresses glycogen synthase activity.<sup>1</sup> Subsequent studies established the existence of two closely related paralogues, GSK3 $\alpha$  and GSK3 $\beta$ , which share substantial structural and functional similarity.<sup>2</sup> Since then, GSK3 has emerged as a highly versatile regulatory kinase involved in a broad spectrum of intracellular processes through interactions

with numerous substrates and signaling networks.<sup>3-5</sup> Rather than functioning as a simple metabolic enzyme, GSK3 acts as an important signaling hub that integrates diverse extracellular and intracellular cues to regulate cellular responses. The activity of GSK3 is controlled through several regulatory mechanisms. In many cellular contexts, stimulation by insulin, tumor necrosis factor (TNF), and various growth factors promotes inhibitory phosphorylation of GSK3, thereby reducing its kinase activity.<sup>6</sup> In contrast, regulation of GSK3 by the Wnt signaling pathway can occur through mechanisms that do not depend solely on phosphorylation. Wnt stimulation has been associated with sequestration of GSK3 within

intracellular vesicular compartments<sup>7</sup> and alterations in the composition and activity of GSK3-containing protein complexes.<sup>7,8</sup>

These mechanisms highlight the considerable complexity of GSK3 regulation and demonstrate that its activity can be modified through multiple interconnected pathways. Both GSK3 $\alpha$  and GSK3 $\beta$  participate in a wide range of physiological functions, including transcriptional regulation, cellular metabolism, proliferation, differentiation, development, apoptosis, cell adhesion, and migration.<sup>6</sup> Consequently, abnormalities in GSK3 signaling have been associated with numerous pathological conditions. These include neurological and neurodegenerative disorders, metabolic and inflammatory diseases, and several forms of cancer, in which GSK3 may also influence angiogenesis and metastatic progression.<sup>4</sup>

In many of these disorders, pathological effects have been linked either to altered GSK3 activity or to inappropriate interactions between GSK3 and its downstream substrates.<sup>9</sup> Because excessive or dysregulated GSK3 activity has been implicated in several diseases, pharmacological inhibition of the kinase initially appeared to represent an attractive therapeutic strategy. Numerous GSK3 inhibitors have consequently been developed. Nevertheless, clinical translation has proven challenging, and several therapeutic approaches have produced less favorable outcomes than anticipated. Some small-molecule GSK3 inhibitors remain under investigation, but their development has been complicated by the high structural similarity between GSK3 $\alpha$  and GSK3 $\beta$ .<sup>6</sup>

The lack of sufficient selectivity between the two isoforms may contribute to unwanted biological effects. More recently, efforts have produced compounds capable of preferentially targeting individual GSK3 paralogues, potentially allowing more precise manipulation of their distinct biological functions.<sup>10</sup> An additional challenge arises from the context-dependent nature of GSK3 signaling. Depending on the cellular environment, disease state, and signaling network involved, GSK3 may produce beneficial, neutral, or detrimental effects.<sup>6</sup>

Consequently, its contribution to particular pathological conditions, including infection and cancer, cannot always be predicted solely from its enzymatic activity. The apparently contradictory functions of GSK3 emphasize the importance of understanding isoform-specific regulation, cellular localization, substrate selection, and interactions with other signaling pathways. These considerations have stimulated continued investigation into the mechanisms governing GSK3 $\alpha$  and GSK3 $\beta$  and their contributions to physiological and pathological processes.

## METHODS

A structured narrative literature search was conducted using PubMed, Scopus, and Google Scholar to identify relevant literature on the biological functions, regulatory

mechanisms, pathological roles, and therapeutic targeting of glycogen synthase kinase-3 (GSK-3). The search strategy employed combinations of keywords and phrases including “glycogen synthase kinase-3,” “GSK-3 $\alpha$ ,” “GSK-3 $\beta$ ,” “GSK-3 signaling,” “GSK-3 regulation,” “GSK-3 inhibitors,” “neurodegenerative diseases,” “inflammation,” “cancer,” “metabolism,” and “therapeutic targeting.” The primary search focused on studies published between 2015 and 2025 to capture recent advances in GSK-3 biology and therapeutic research. However, seminal studies published before 2015 were also considered where necessary to establish the historical development, fundamental mechanisms, and key biological functions of GSK-3. Additional relevant studies were identified through citation tracking of retrieved articles. Publications that did not substantially address GSK-3 $\alpha$ /GSK-3 $\beta$  regulation, biological functions, disease mechanisms, or therapeutic implications were excluded. The selection process involved preliminary screening of titles and abstracts, followed by detailed assessment of relevant full-text articles. The retrieved evidence was critically synthesized to provide an updated overview of the isoform-specific functions, regulatory mechanisms, physiological and pathological significance, and therapeutic potential of GSK-3 $\alpha$  and GSK-3 $\beta$ , while highlighting current challenges and emerging opportunities for selective GSK-3-targeted interventions.

## Regulation of GSK3 activity and neuroinflammation

One of the best-characterized mechanisms regulating GSK3 is inhibitory phosphorylation. Under appropriate cellular conditions, phosphorylation at Ser21 in GSK3 $\alpha$  and Ser9 in GSK3 $\beta$  reduces their kinase activity. However, additional inhibitory phosphorylation sites have also been identified, indicating that regulation of GSK3 is more complex than previously appreciated. Ser389, for example, has been described as another site capable of negatively regulating GSK3 $\beta$  activity.<sup>11</sup> The functional importance of Ser389 phosphorylation has particular relevance to neuroinflammation, a process increasingly recognized as an important contributor to cognitive and mood-related disorders.<sup>12</sup>

Calvo and colleagues investigated this regulatory mechanism using a genetically modified mouse model in which Ser389 of GSK3 $\beta$  was replaced with alanine, preventing phosphorylation at this site.<sup>13,14</sup> Their findings indicated that the inability to suppress GSK3 $\beta$  through Ser389 phosphorylation altered inflammatory signaling within the hippocampus. Interestingly, the phosphorylation-deficient animals displayed impaired activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), whereas signaling associated with signal transducer and activator of transcription 3 (STAT3) was not similarly affected.<sup>13</sup> These mice also exhibited evidence of persistent basal neuroinflammation, including increased activation of microglia and astrocytes together with greater infiltration of neutrophils into the brain. Thus, the inability to appropriately inhibit GSK3 $\beta$

through Ser389 appears to disturb the normal regulation of neuroimmune responses. The response to systemic inflammatory stimulation provided additional evidence for an altered inflammatory phenotype.

Administration of lipopolysaccharide (LPS), a commonly used experimental stimulus for inducing neuroinflammation, did not produce the expected additional increase in immune-cell activation or infiltration in the mutant animals.<sup>15</sup> This finding suggests that chronic basal inflammation may have been accompanied by an impaired capacity to respond appropriately to subsequent inflammatory challenges.<sup>13</sup> Importantly, these alterations appeared to be largely restricted to the central nervous system. Peripheral immune-cell populations and responses to LPS in the spleen remained comparatively normal, suggesting that Ser389-dependent regulation of GSK3 $\beta$  has a particularly important role in maintaining immune homeostasis within the brain.

### ***GSK3 isoforms in endothelial function and atherosclerosis***

The contribution of GSK3 $\alpha$  and GSK3 $\beta$  to vascular pathology has also received considerable attention, particularly in relation to atherosclerosis and vascular calcification. Two studies have provided evidence that the two paralogues may exert distinct effects in endothelial and vascular cells. Cai and colleagues investigated the involvement of endothelial GSK3 $\beta$  in vascular calcification associated with atherosclerotic lesions. Vascular calcification is a complex pathological process involving phenotypic changes in endothelial cells, including endothelial-to-mesenchymal transition.<sup>16</sup> Their findings demonstrated that pharmacological suppression of GSK3 activity reduced vascular calcification in experimental atherosclerosis.<sup>17</sup> In apolipoprotein E-deficient (Apoe-KO) mice, GSK3 inhibition was associated with reductions in aortic calcium accumulation and calcified lesion burden, together with decreased expression of osteogenic and mesenchymal markers within atherosclerotic plaques.

Comparable effects were obtained using endothelial-specific deletion of GSK3 $\beta$  following tamoxifen administration.<sup>17</sup> The protective influence of GSK3 $\beta$  inhibition was also observed in diabetic Ins2Akita/+ mice, in which suppression of GSK3 $\beta$  reduced vascular calcification.<sup>18</sup> Collectively, these findings indicate that endothelial GSK3 $\beta$  may contribute to the molecular processes underlying vascular calcification and suggest that its inhibition could have beneficial effects in specific atherosclerotic settings. In contrast, Mastrogiacomo and colleagues investigated the individual contributions of GSK3 $\alpha$  and GSK3 $\beta$  in endothelial cells and macrophages during atherogenesis.<sup>19</sup> Their experiments initially used Tie2Cre-based genetic approaches to produce cell-specific GSK3 deletion. However, Tie2Cre-mediated recombination occurs in both endothelial and myeloid cell

populations, meaning that these models resulted in simultaneous GSK3 deletion in endothelial cells and macrophages.<sup>19,20</sup> Most systemic parameters examined, including circulating lipid concentrations and body weight, were not substantially influenced by GSK3 deletion.

Nevertheless, mice lacking GSK3 $\alpha$  in endothelial and macrophage populations exhibited a significant reduction in atherosclerotic plaque volume, endothelial activation, and recruitment of monocytes and macrophages compared with control animals. Similar effects were not observed following deletion of GSK3 $\beta$ , indicating that GSK3 $\alpha$  and GSK3 $\beta$  cannot necessarily be considered functionally interchangeable in vascular disease. To distinguish endothelial effects from those originating in myeloid cells, bone marrow transplantation was subsequently performed to restore GSK3 expression within the hematopoietic compartment.

The resulting experiments demonstrated that selective loss of endothelial GSK3 $\alpha$  reproduced the beneficial effects observed in the dual endothelial/myeloid knockout model. Conversely, deletion of endothelial GSK3 $\beta$  failed to generate comparable changes.<sup>19</sup> These findings strongly support a specific pro-atherogenic role for endothelial GSK3 $\alpha$ . They are also consistent with previous evidence demonstrating protective effects associated with whole-body GSK3 $\alpha$  deficiency and myeloid-specific GSK3 $\alpha$  deletion.<sup>21,22</sup> Together, these studies emphasize that the two GSK3 paralogues can exert distinct and sometimes opposing effects depending on the cell type and pathological context.

### ***GSK3 in cell-cycle regulation and cancer-cell adaptation***

Beyond vascular biology and inflammation, GSK3 participates in fundamental cellular processes such as cell-cycle control, adaptation to nutrient deprivation, and metabolic regulation.<sup>23-25</sup> Shenker and colleagues examined the mechanisms through which cytolethal distending toxin produced by *Aggregatibacter actinomycetemcomitans* (AaCdt) affects cell-cycle progression.<sup>23</sup>

AaCdt is a bacterial toxin composed of three subunits and possesses both DNase and lipid phosphatase activities. The toxin is known to interfere with cell-cycle progression and can promote apoptosis in susceptible cells.<sup>26</sup> To investigate its effects independently of extensive DNA damage and apoptosis, the researchers used oral keratinocytes, which are comparatively resistant to Cdt-induced cell death.

Exposure of cell lines and primary human gingival keratinocytes to AaCdt resulted in a persistent and concentration-dependent arrest at the G2/M transition. This effect depended on the phosphatase activity of the toxin rather than its DNase activity and occurred without clear evidence of DNA damage or increased apoptosis. Similar phosphatase-dependent effects had previously

been reported in lymphocytes and HeLa cells.<sup>27</sup> At the molecular level, toxin exposure was associated with reduced cyclin-dependent kinase 1 (CDK1) and Akt activity together with increased GSK3 $\beta$  activity. Importantly, pharmacological inhibition of GSK3 reduced the G2/M arrest induced by AaCdt.<sup>23</sup> These observations indicate that activation of GSK3 $\beta$  forms an important component of the signaling cascade through which the bacterial toxin interferes with cell-cycle progression. GSK3 $\alpha$  has also been implicated in the ability of malignant cells to survive under conditions of amino-acid deprivation.

Nutrient limitation is an important stress encountered by cancer cells and can influence their response to therapeutic strategies such as asparaginase treatment. Previous evidence suggested that GSK3 $\alpha$  contributes to cellular adaptation to amino-acid deficiency by promoting degradation of proteins and thereby facilitating the release and recycling of protein-associated amino acids.<sup>28</sup> Loxha and colleagues examined this mechanism in T-cell acute lymphoblastic leukemia and colorectal cancer models.<sup>24</sup> Suppression of GSK3 $\alpha$  markedly decreased cellular viability and protein ubiquitination when cells were exposed to arginase, while simultaneously increasing cell death.

In colorectal cancer cells, however, the classical pro-apoptotic GCN2-eIF2 $\alpha$ -ATF4-CHOP pathway associated with amino-acid deficiency, as well as major cell-cycle alterations, did not appear to account for the observed phenotype.<sup>29</sup> Transcriptomic analysis provided additional insight into the mechanism. GSK3 $\alpha$ -deficient cells that survived asparagine depletion exhibited reduced expression of multiple ribosomal proteins. Furthermore, experimental suppression of selected ribosomal proteins in GSK3 $\alpha$ -deficient cells was sufficient to improve resistance to asparaginase-associated cell death.<sup>24</sup> These observations suggest that ribosomal protein regulation may form part of the mechanism through which GSK3 $\alpha$  supports cancer-cell survival during amino-acid deprivation. The findings further illustrate how GSK3 signaling can influence tumor-cell adaptation to metabolic stress.

### **GSK3 and metabolic regulation**

Metabolic regulation represents one of the most established biological functions associated with GSK3. Evidence from diverse organisms indicates that GSK3-related proteins influence carbohydrate, lipid, and other metabolic pathways. Zhang and colleagues identified a GSK3 homolog, designated DcGSK3, in *Diaphorina citri* Kuwayama, commonly known as the Asian citrus psyllid.<sup>25</sup> This hemipteran insect serves as a vector for *Candidatus Liberibacter asiaticus*, the bacterial pathogen associated with citrus greening disease.<sup>30</sup>

DcGSK3 showed broad expression across the tissues and developmental stages examined, with particularly high expression in the head and during the egg stage. To

determine its biological function, researchers introduced double-stranded RNA targeting DcGSK3 into fifth-instar nymphs to trigger RNA interference. Reduction of DcGSK3 transcript levels produced pronounced developmental abnormalities, including defective molting, morphological malformations, and increased mortality. GSK3 suppression also altered several important metabolic pathways. Specifically, knockdown of DcGSK3 was associated with reductions in glucose, trehalose, glycogen, and fatty-acid levels, together with altered expression of genes involved in lipid and chitin metabolism.

These findings indicate that DcGSK3 participates in the regulation of carbohydrate, lipid, and structural metabolism during insect development. Transcriptome profiling further demonstrated that differentially expressed genes were enriched in metabolic, transport, and structural processes, as well as in pathways identified through Kyoto Encyclopedia of Genes and Genomes analysis.<sup>25</sup> Thus, DcGSK3 appears to function as an important regulator linking metabolism with growth and development in *D. citri*.

### **GSK3 $\beta$ in behavioral regulation and psychostimulant responses**

The influence of GSK3 $\beta$  extends beyond cellular metabolism and inflammatory signaling to include the regulation of neuronal function and behavior. Cho and colleagues investigated the involvement of GSK3 $\beta$  in the ability of cocaine- and amphetamine-regulated transcript (CART) to modulate amphetamine-induced hyperlocomotion.<sup>31,32</sup> Systemic administration of amphetamine produced a marked increase in locomotor activity in rats. Consistent with earlier observations, bilateral administration of the CART 55–102 peptide into the nucleus accumbens (NAcc) before amphetamine treatment substantially attenuated this hyperlocomotor response.<sup>31</sup>

Biochemical analysis of the NAcc core revealed that amphetamine treatment reduced phosphorylation of Akt at Thr308, decreased inhibitory phosphorylation of GSK3 $\beta$  at Ser9, and increased phosphorylation of the AMPA receptor subunit GluA1 at Ser845. These molecular changes were prevented when animals received the CART peptide before amphetamine exposure. Further experiments demonstrated that suppression of GSK3 $\beta$  activity was necessary for the behavioral effects of CART.

Administration of CART together with the S9 peptide, which interferes with Ser9-dependent inhibitory regulation of GSK3 $\beta$ , abolished the ability of CART to reduce amphetamine-induced locomotor activity.<sup>33</sup> This intervention was accompanied by reduced GSK3 $\beta$ -Ser9 phosphorylation and enhanced GluA1-Ser845 phosphorylation. Based on these findings, the proposed mechanism involves a signaling cascade in which CART peptide suppresses amphetamine-induced Akt inhibition,

thereby maintaining inhibitory phosphorylation of GSK3 $\beta$ . Reduced GSK3 $\beta$  activity subsequently limits GluA1 phosphorylation and ultimately attenuates the locomotor response to amphetamine.<sup>32</sup> These observations provide further evidence that GSK3 $\beta$  serves as an important molecular link between intracellular kinase signaling and complex behavioral responses.

## CONCLUSION

Collectively, the findings discussed above demonstrate the remarkable functional diversity of GSK3 $\alpha$  and GSK3 $\beta$  across cellular, tissue, and organismal levels. Although originally characterized primarily as regulators of glycogen metabolism, GSK3 proteins are now recognized as important signaling hubs involved in inflammation, vascular disease, cancer-cell survival, metabolism, cell-cycle regulation, neuronal signaling, and behavior<sup>3-6</sup>. An important emerging concept is that the two GSK3 paralogues should not necessarily be regarded as functionally redundant enzymes. GSK3 $\alpha$  and GSK3 $\beta$  may produce distinct biological effects depending on cellular identity, subcellular localization, regulatory phosphorylation, interacting proteins, and disease context.

The contrasting observations obtained in vascular disease, for example, demonstrate that selective manipulation of one paralogue can produce effects that are not reproduced by targeting the other. The complex nature of GSK3 signaling also helps explain the difficulties encountered in translating GSK3 inhibitors into successful clinical therapies. Broad inhibition may interfere with physiological functions that are essential for normal cellular homeostasis, while inadequate selectivity may produce undesirable effects by simultaneously targeting both paralogues. Future therapeutic strategies may therefore need to move beyond generalized GSK3 inhibition toward approaches that selectively regulate individual isoforms, signaling complexes, substrates, or disease-specific GSK3 functions. Overall, GSK3 should be viewed as a highly context-dependent molecular regulator rather than simply an enzyme that promotes or suppresses a single biological pathway.

Its ability to integrate signals from metabolic, inflammatory, growth-factor, neuronal, and stress-responsive pathways places it at a critical intersection of normal physiology and disease. A deeper understanding of the mechanisms controlling GSK3 $\alpha$  and GSK3 $\beta$ , together with clarification of their isoform-specific functions, may facilitate the development of more precise therapeutic strategies for neurological, inflammatory, metabolic, cardiovascular, and malignant disorders.

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