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EDITORIAL

PI3Kβ moonlights as a protein kinase: driving fatty acid metabolism and histone acetylation in cancer

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Phosphoinositide 3-kinase (PI3K) catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3), a key second messenger that orchestrates downstream signaling by recruiting and activating effector proteins, such as protein kinase B (AKT). PI3Ks are categorized into four classes (IA, IB, II, and III) based on structural characteristics and substrate preferences[1]. Class IA PI3K enzymes are heterodimeric complexes composed of a catalytic subunit (p110α, p110β, or p110δ) and a regulatory subunit (p85α, p55α, p50α, p85β, or p55γ)[2]. Although the catalytic isoforms p110α and p110β, are ubiquitously expressed across tissues, p110δ is predominantly found in leukocytes[3]. Notably, p85α functions as the primary regulatory subunit.

The *PIK3CA* gene, encoding the p110α catalytic subunit of PI3K, represents one of the most frequently altered oncogenes across multiple cancer types. Recurrent mutations and amplifications have been identified in breast, gastric, colon, prostate, cervical, and lung cancers[4]. In contrast, the *PIK3CB* gene, which encodes the p110β subunit, exhibits relatively few mutations in human malignancies. However, experimental evidence demonstrates that overexpression of wild-type p110β can drive oncogenic transformation in cultured cells, suggesting that its tumorigenic potential is independent of mutations[5]. The p110β subunit has a critical role in promoting tumor cell growth and immune evasion, especially in phosphatase and tensin homolog (PTEN)-deficient tumors[6,7]. PTEN, a well-established antagonist of PI3K, functions by dephosphorylating PIP_3 to regenerate PIP_2, thereby terminating downstream signaling[8].

PI3K activation is initiated through various mechanisms. PI3K can be activated by diverse extracellular stimuli in normal physiologic settings, such as growth factors and cytokines[9]. Upon activation, PI3K facilitates the synthesis of PIP_3. The subsequent accumulation of PIP_3 at the plasma membrane brings phosphoinositide-dependent kinase-1 (PDK1) and AKT to the plasma membrane, where PDK1 phosphorylates AKT at T308, a critical step in AKT activation (**Figure 1**). Activated AKT subsequently phosphorylates various downstream targets, thereby promoting cell proliferation, metabolism, motility, and survival[9]. Mutation or overexpression of growth factor receptors and alterations in key oncogenes and tumor suppressor genes, such as Ras and PTEN, also activate PI3K[10]. Aberrant PI3K signaling is observed in numerous human cancers, underscoring a fundamental contribution to carcinogenesis.

In addition to these classical roles, PI3Ks exert a range of non-canonical functions, especially within the nucleus. Nuclear PI3K activity, through both kinase-dependent and -independent mechanisms, has been implicated in the regulation of DNA replication and repair, transcription, chromatin architecture, cell cycle control, and ribosome biogenesis[11]. However, whether PI3K possesses functions independent of the conversion of PIP_2 to PIP_3, which is critical for tumor progression, has not been established.

He et al.[12] performed co-immunoprecipitation of the p110β catalytic subunit from glioblastoma (GBM) U251 cells, followed by mass spectrometry analysis to investigate the potential non-canonical functions of PI3K independent of lipid kinase activity. This methodology identified O-GlcNAc transferase (OGT) as a novel p110β-interacting protein. This

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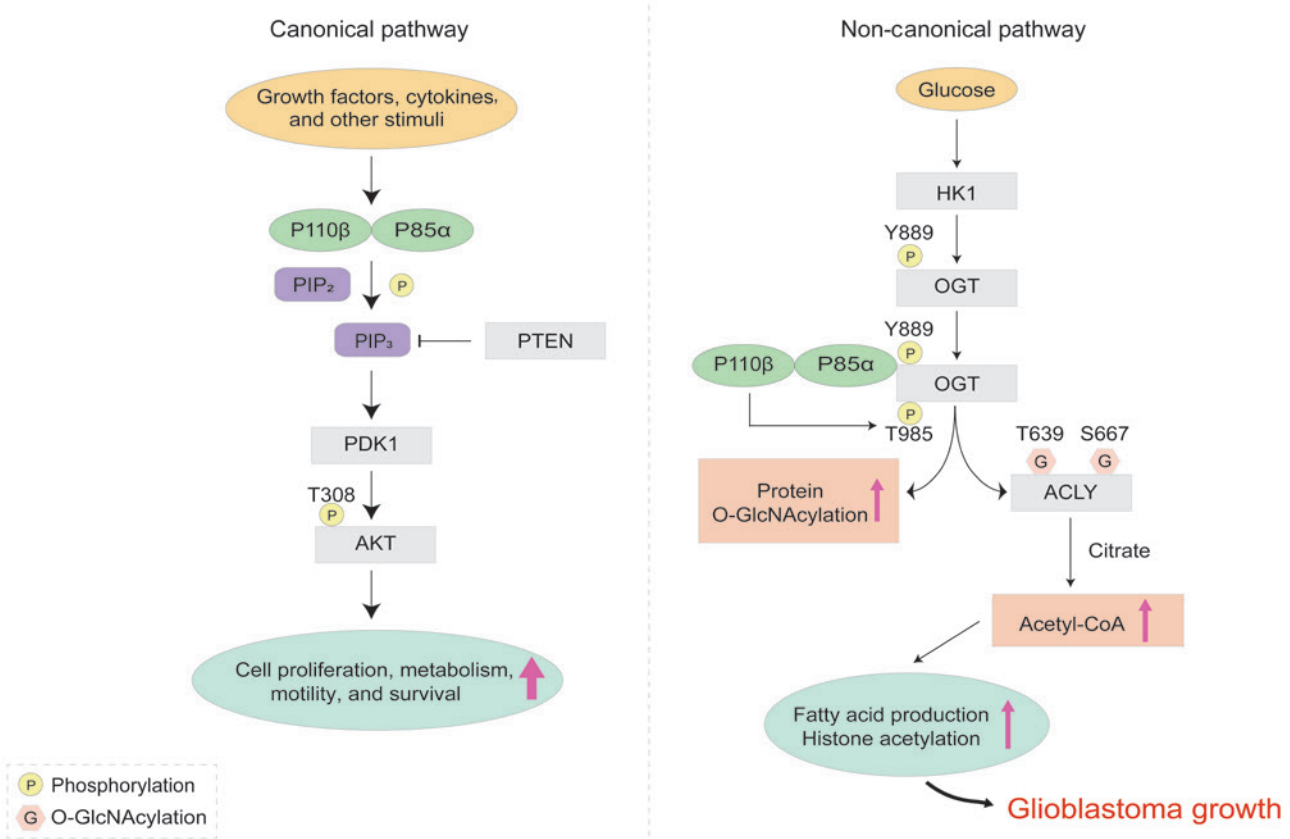


Figure 1 Canonical and non-canonical PI3K signaling pathways in the regulation of tumor progression. Growth factors, cytokines and other stimuli activate PI3K to generate PIP_3 in the canonical PI3K pathway. PIP_3 recruits PDK1 and AKT to the plasma membrane, where PDK1 phosphorylates and activates AKT, promoting cell proliferation, metabolism, motility and survival. HK1 phosphorylates OGT at Y889 in the non-canonical PI3K pathway under high-glucose conditions, creating a docking site for the p85α regulatory subunit. This interaction facilitates phosphorylation of OGT at T985 by the p110β catalytic subunit, leading to OGT activation and a significant increase in global protein O-GlcNAcylation, including specific ACLY O-GlcNAcylation at T639 and S667. PI3Kβ/OGT-mediated ACLY O-GlcNAcylation activates ACLY, leading to enhanced acetyl-CoA production, fatty acid synthesis, and histone H3 acetylation, ultimately promoting GBM progression. ACLY, ATP-citrate lyase; GBM, glioblastoma; HK1, hexokinase 1; OGT, O-GlcNAc transferase; PDK1, phosphoinositide-dependent kinase-1; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog.

finding is particularly significant because p110β is the only PI3K catalytic isoform exhibiting a strong correlation with GBM incidence[13]. Importantly, the interaction between p110β and OGT is enhanced in a glucose concentration-dependent manner. Elevated glucose levels enhance OGT-mediated protein O-GlcNAcylation[14]. O-GlcNAcylation is a dynamic post-translational modification catalyzed by OGT that modulates key metabolic enzymes and transcription factors, thereby promoting cancer metabolic reprogramming and adaptation to microenvironmental stress[15]. O-GlcNAcylation concurrently regulates chromatin dynamics through modification of histones and epigenetic regulators, which influences gene expression and tumor progression[16]. The authors observed that genetic ablation of p110β significantly reduces global protein O-GlcNAcylation levels, whereas overexpression of p110β markedly increases this modification, suggesting that glucose-stimulated O-GlcNAcylation requires p110β. Intriguingly, p110β regulates protein O-GlcNAcylation independent of PIP_2-binding, indicating a lipid kinase activity-independent, non-canonical function of PI3Kβ in the regulation of protein O-GlcNAcylation. High-glucose concentrations potentiate OGT enzymatic activity and enhanced protein O-GlcNAcylation relies on the interaction between p110β and OGT. He et al. further demonstrated that p110β

phosphorylates OGT at T985, a process that is facilitated by high-glucose concentrations. p110β-mediated phosphorylation of OGT T985 activates OGT and enhances cellular protein O-GlcNAcylation.

Building upon the initial discovery, He et al.[12] further elucidated the molecular mechanism by which p110β regulates OGT activity under high-glucose conditions. He et al.[12] reported that the glucose-stimulated binding of p110β to OGT and OGT T985 phosphorylation depended on the p85α subunit. Hexokinase 1 (HK1) translocates from the mitochondrial compartment to the cytosol upon stimulation with a high-glucose concentration, where HK1 associates with OGT and acts as a protein kinase to phosphorylate OGT at Y889. HK1 phosphorylates OGT, then recruits p85α, which facilitates p110β-mediated OGT T985 phosphorylation and activation.

High glucose-stimulated and PI3Kβ-activated OGT binds ATP-citrate lyase (ACLY), the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA, and mediates O-GlcNAcylation of ACLY at T639 and S667, which leads to increased ACLY activity and acetyl-CoA production. Notably, OGT-dependent acetyl-CoA production is independent of acetyl-CoA synthetase 2 activity. AKT induces ACLY S455 phosphorylation, which activates ACLY[17]. He et al. found that a high-glucose concentration did not enhance AKT-induced ACLY S455 phosphorylation and that ACLY activation is modulated independently by O-GlcNAcylation (mediated by OGT) and phosphorylation (dependent on AKT). Acetyl-CoA serves as a precursor for fatty acid synthesis and is required for histone acetylation, which is important for gene transcription[18]. He et al. showed that a high-glucose concentration enhances cellular fatty acid levels and histone H3 acetylation at K9 and K27. These processes are regulated by PI3Kβ-induced OGT T985 phosphorylation and OGT-mediated ACLY T639 and S667 O-GlcNAcylation. The investigators systematically explored the functional implications of the PI3Kβ-OGT-ACLY axis in GBM, demonstrating that PI3Kβ-mediated OGT phosphorylation and subsequent ACLY O-GlcNAcylation collectively enhanced tumor cell proliferation *in vitro* and xenograft growth *in vivo*. Furthermore, the authors assessed the clinical relevance of these findings using immunohistochemical (IHC) analysis of human GBM tumors. The results indicated that OGT T985 and Y889 phosphorylation exhibit interdependent upregulation, paralleling heightened overall protein O-GlcNAcylation and H3K9/K27 acetylation. Moreover, OGT T985 and OGT Y889 phosphorylation levels are inversely correlated with survival in patients with GBM, suggesting the importance of PI3Kβ-mediated OGT activation and acetyl-CoA production in GBM progression.

He et al. proposed a novel combination therapy strategy for GBM using PI3K inhibitor (GSK2636771) and OGT inhibitor (OSMI-4) in a murine GBM model. The treatment yielded promising synergistic effect, underscoring the potential clinical value of the novel combination therapy strategy for GBM. This effect is mediated by a coordinated inhibition of the PI3Kβ–OGT–ACLY axis, a critical driver of metabolic reprogramming in tumors. By disrupting tumor-specific metabolic processes, this approach presents a potential precision therapeutic strategy for GBM and other malignancies.

Collectively, He et al. elucidated the novel PI3Kβ-OGT signaling axis as follows: (1) elevated glucose levels facilitate HK1-mediated phosphorylation of OGT at Y889, thereby enhancing OGT's affinity for the PI3Kβ subunit p85α; (2) subsequent p110β-dependent phosphorylation of OGT at T985 amplifies global protein O-GlcNAcylation, including ACLY modifications at T639 and S667; (3) ACLY O-GlcNAcylation drives the production of acetyl-CoA, fatty acids synthesis, and histone H3 acetylation, ultimately supporting GBM growth (**Figure 1**). This study revealed a novel non-canonical function of PI3Kβ in regulating protein O-GlcNAcylation, thereby expanding our understanding of PI3Kβ involvement in GBM progression. PI3K has a critical role in regulating fundamental cellular processes, such as growth, survival, and proliferation, the dysregulation of which contributes to carcinogenesis. This finding has driven the development of PI3K inhibitors as targeted cancer therapeutics. PI3K inhibition has emerged as a therapeutic strategy for multiple malignancies with several agents already gaining Food and Drug Administration (FDA) approval[19,20]. Most PI3K inhibitors are ATP-competitive and the high homology of class I PI3K ATP-binding sites poses challenges in developing isoform-specific inhibitors. Discovery of PI3Kβ non-canonical function may pave the way for the development of novel and specific inhibitors of PI3K.

Although this study offers significant insights, several fundamental questions warrant investigation in future studies. Do other class IA PI3K isoforms (p110α and p110δ) have similar capabilities to phosphorylate and activate OGT or is this function exclusive to p110β? Beyond OGT, what additional protein substrates might be phosphorylated by the HK1-PI3Kβ cascade, and how do these modifications contribute to tumorigenesis? Is the HK1-PI3Kβ-OGT axis relevant to

malignancies other than GBM? Is the HK1-PI3Kβ-OGT axis specific to oncogenic processes or does the HK1-PI3Kβ-OGT axis represent a conserved metabolic regulatory mechanism that is active in other pathophysiologic contexts (e.g., diabetes mellitus and cardiovascular disorders)? Addressing these questions is essential for understanding the broader biological implications of this pathway, developing targeted therapeutic strategies, and determining the potential off-target effects of PI3K inhibitors for clinical use.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yixin Duan, Juanjuan Liu, Jianxin Xu.
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