Targeting the PI3Kα Pathway to Treat Proliferative Glomerulonephritis

By Abbal Koirala, Bryan Chang, and Duvuru Geetha

Glomerular diseases cause 15% of kidney failure, disproportionately affecting African American and Hispanic populations (1). Effective therapies to slow disease progression are urgently needed.

Phosphoinositide 3-kinase (PI3K)α, a lipid kinase, is stimulated by various signals such as cytokines, growth factors, and immune signals (2). This activation leads to the recruitment of 3-phosphoinositide-dependent protein kinase 1, which phosphorylates AKT at the T308 residue (3). Consequently, the mammalian target of rapamycin (mTOR) is activated, initiating signaling pathways in cell proliferation, motility, survival, and metabolism in podocytes and lymphocytes (4). Dysregulation of this pathway has been linked to glomerular diseases in both human and mouse models (5).

Recently published in *The Journal of Clinical Investigation*, Yamaguchi and colleagues reported a significant discovery related to glomerular disease and its progression to kidney failure (6). Researchers found that a somatic PI3Kα mutation causes proliferative glomerulonephritis. Using mouse models, single-cell RNA sequencing, and spatial transcriptomics, they showed that this mutation promotes podocyte proliferation, dedifferentiation, and inflammation through the activation of the AKT/mTOR pathway (Figure). These findings suggest that this pathway is a potential therapeutic target for proliferative glomerulonephritis.

Researchers demonstrated that alpelisib, a PI3Kα inhibitor, can ameliorate glomerular lesions and improve kidney function in mouse models of proliferative glomerulonephritis and lupus nephritis by targeting podocytes. Interestingly, alpelisib modulates T and B lymphocytes, reducing proinflammatory cytokines, autoantibodies, and glomerular complement deposition in lupus nephritis models. These findings are significant because PI3Kδ, not PI3Kα, is predominantly expressed in lymphocytes. Similar effects were observed in human lymphocytes from patients with lupus nephritis.

Besides apolipoprotein L1 (*APOL1*) high-risk variants, collapsing glomerulopathy can be caused by other factors, such as idiopathic causes, ischemia, and bisphosphonate toxicity. Given the unique nature of *APOL1*-associated collapsing glomerulopathy and the emergence of promising therapeutic interventions (7), the authors of a recent article have uncovered the potential role of alpelisib in reversing glomerular lesions in non-*APOL1*-mediated collapsing glomerulopathy. This should be further tested in a clinical trial setting.

This research by Yamaguchi et al. (6) suggests that PI3Kα inhibition is a potential therapeutic strategy for glomerular disease. Further investigations are warranted to validate these findings in clinical trials and to assess the long-term efficacy and safety of PI3Kα inhibitors in patients with glomerular disease. ■

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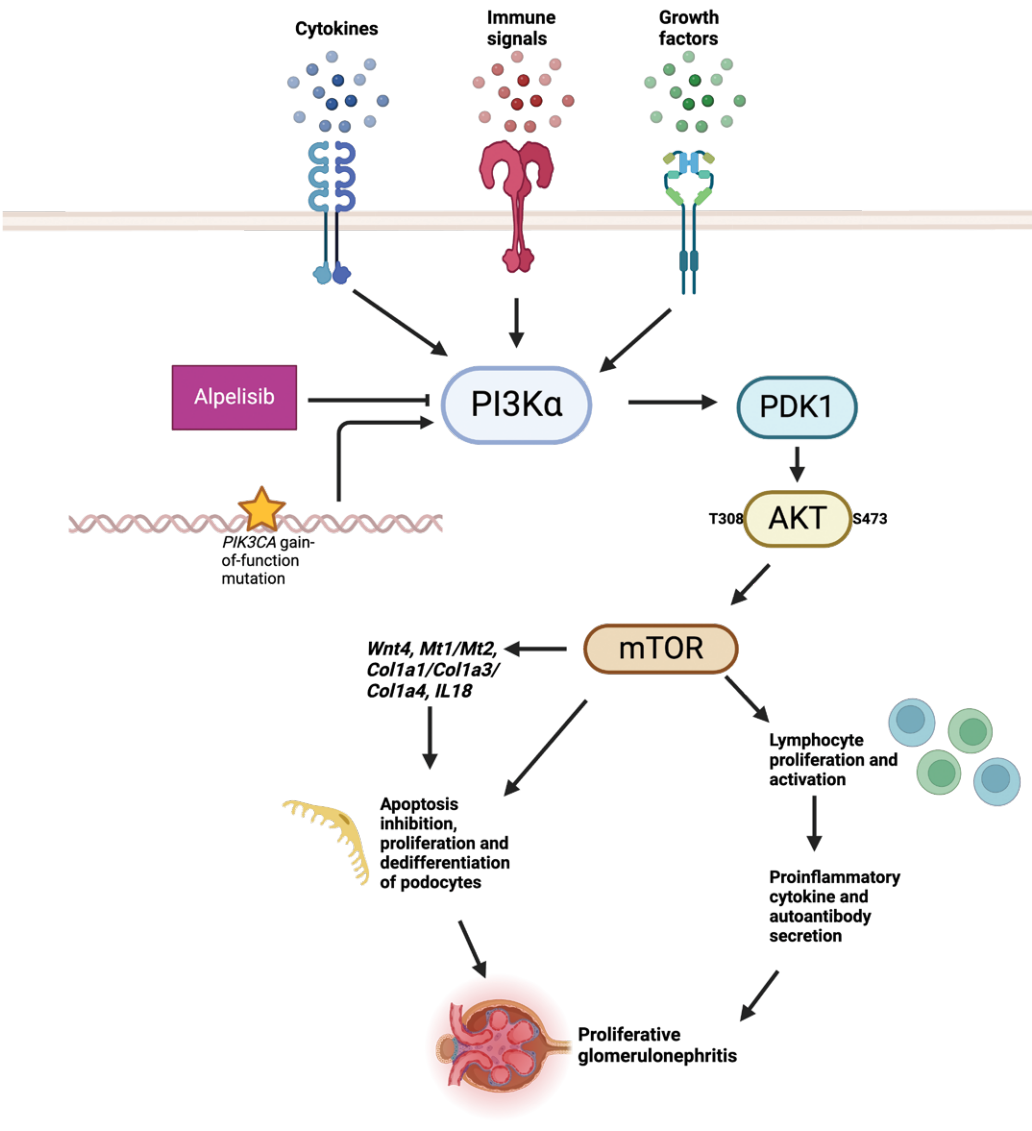
Figure. PI3Kα pathway



Activation of PI3Kα has multiple downstream effects contributing to proliferative glomerulonephritis. These effects may be inhibited by alpelisib, a PI3Kα inhibitor.
PDK1, 3-phosphoinositide-dependent protein kinase 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha. Figure created with BioRender.com.

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