

Investigating the role of PI3K γ in obesity-driven diseases

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The worldwide prevalence of obesity increased nearly 3-fold from 1975 to 2016, and obesity has become an epidemic, associated with significant comorbidities, such as cardiovascular diseases, diabetes, and cancers. At the cellular level, studies have indicated that obesity causes leukocyte cell infiltration into adipose tissue (AT), which in turn intensifies AT inflammation and the secretion of proinflammatory chemokines and adipokines, ultimately leading to systemic insulin resistance. Additionally, obesity has been associated with increased cancer risks, and inflammation may play an important role in this process.

The aim of our first study was to understand the molecular mechanisms underlying PI3K γ action in high-fat diet-induced inflammation and to understand the role of PI3K γ during the development of insulin resistance, in contexts of both diet-induced and genetically induced obesity. The objective of the second study was to investigate the role played by PI3K γ during β -cell function. The third study focused on the role played by PI3K γ during the development of hepatocellular carcinoma (HCC).

We showed that PI3K γ ablation contributes to reduce high-fat diet-induced inflammation and insulin resistance. However, we have also shown that PI3K γ activity in leukocytes promotes pro-inflammatory gene-expression and neutrophil recruitment to obese AT, which further promote the development of insulin resistance. We showed that blocking PI3K γ activity does not affect β -cell function but instead protects β -cells from apoptosis. Finally, blocking PI3K γ activity dampens the effects of obesity on the promotion of HCC by reducing the levels of tumour-promoting inflammation. Overall, our results indicate that PI3K γ is an attractive drug target for the treatment of obesity-related diseases, such as type-2 diabetes and HCC.

Jury:

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