Insight Medical Publishing

INSIGHTS IN IMMUNOLOGY

The effects of p110 synthetic inhibitors in mouse neutrophils and macrophages

Samira Khaliq

University of Balochistan, Pakistan

Abstract

Phosphatidylinositol 3-Kinases (PI3Ks) are a family of lipid kinases that synthesize PtdIns(3,4,5)P3, and in doing so, relay signals from external cues, regulating multiple signaling pathways such as cell proliferation, growth, survival, motility, and metabolism. Hyperactivation of PI3K signaling cascades is one of the most common events in human cancers. Tremendous efforts have been devoted to the development of effective PI3K inhibitors for cancer therapy. Initial PI3K-directed drugs in clinical trials, consisting largely of non-isoform-selective pan-PI3K inhibitors, have not yielded exciting results. However, recent preclinical studies have demonstrated that different PI3K isoforms play divergent roles in cellular signaling and cancer, suggesting that inhibitors targeting individual isoforms may be able to achieve greater therapeutic efficacy. Isoform-selective inhibitors are now emerging in the clinic, and have had promising success. Class I PI3K catalytic isoforms share a conserved domain structure. They utilize the same lipid substrates and generate the same lipid products. Despite their similarities, accumulating evidence indicates these isoforms have distinct roles in mediating PI3K signaling in physiological and oncogenic contexts.PI3K has been reported to be either pro- or anti-inflammatory in different model systems. We hypothesized that this could be due to different activities of the p110 and isoforms of PI3K.

The role of class I PI3kinase isoforms is well studied in processes like chemotaxis, cell differentiation, apoptosis, and ROS production in myeloid cells. However, little is known about their involvement in phagocytosis and the exact mechanism underlying the regulation of this process.

This study was aimed at investigating the involvement of p110 isoforms in Fc-mediated phagocytosis of IgG tagged SRBC in mouse neutrophils, macrophages and RAW cell line.

p110γ-/- neutrophils, p110γ-/- macrophages, p110γ KD in Raw cells or Inhibition of p110γ by AS-603 (p110γ specific inhibitor) all showed significant reduction of uptake of IgG tagged SRBCs as compared to untreated cells. RFP-tagged p110γ localized at the base of protrusions forming the phagosome, within 25 seconds of the initial contact between the particle and the cell surface but re-localized away from the phagosome within the next 30 seconds in wild type RAW cells. Since p110γ is known to have a RBD, when these cells were incubated with Ras activation inhibitor specific to act downstream of RTK signalling, it was observed that in 57% of the cells p110γ did not localize to the phagosome whereas in 20% of the cells it did localize initially but did not relocate and move away.

On the other hand, when primary neutrophils, macrophages and RAW cells, were treated with Ras activation inhibitor, they showed a comparable decrease in phagocytic uptake to the cells which were treated with LY294002 or AS-603 alone. Phagocytic uptake did not show any significant reduction when a combination of LY294002 and Ras activation Inhibitor or AS604-850 and Ras activation inhibitor was used.

Biography

Khaliq S completed her PhD from University of Birmingham, England. She is currently working as an Assistant Professor, and M.Phil/PhD program coordinator in the University of Balochistan, Pakistan. She held a postdoctoral position in the University of Toronto and has 3 publications. She has an active participation in numerous conferences, workshops and symposia that she attended.

2nd World Congress on Stem Cell Research and Regenerative Medicine | July 29-30, 2020.

Citation: Samira Khaliq, The effects of p110 synthetic inhibitors in mouse neutrophils and macrophages, Stem Cell Research 2020, 2nd World Congress on Stem Cell Research and Regenerative Medicine| July 29-30,2020, 06.