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Review

Phosphoinositide 3-kinase delta (PI3Kδ) in leukocyte signaling and function

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ABSTRACT

PI3Kδ is a lipid kinase of the PI3K class IA family involved in early signaling events of leukocytes responding to a wide variety of stimuli. The leukocyte specificity of PI3Kδ is defined by its expression, whereas its signaling function is via the production of phosphoinositide 3,4,5-triphosphates at the proximity of activated receptors for recruiting other signaling molecules. The importance of PI3Kδ in B cell development and function is most apparent, and its role in other leukocyte cell types can be easily demonstrated as well. PI3Kδ participates in the development, activation and migration of T cells and NK cells. The role of PI3Kδ in myeloid cell activities, such as inflammation driven cell infiltration, neutrophil oxidative burst, immune complex mediated macrophage activation, as well as mast cell maturation and degranulation, has been well illustrated in various studies. As a result of the broad effects of PI3Kδ in leukocyte functions, the disruption of PI3Kδ expression or activity leads to decreased inflammatory and immune responses *in vivo*. The protective role of PI3Kδ inactivation in animal models of arthritis, asthma or obstructive respiratory diseases has been demonstrated. These findings suggest the potential efficacy achievable with PI3Kδ inhibitors in the treatment of autoimmune and respiratory diseases.

Contents

1. Introduction

Phosphoinositide 3-kinase delta (PI3Kδ) is a member of the PI3K lipid kinase family that phophorylates phosphoinositides at the 3′ OH position. There are three different classes of PI3K categorized by their subunit property and substrate specificity [1,2]. Class I PI3Ks generate phosphoinositide 3,4,5-triphosphates (PIP3) from phosphoinositide 4,5-diphosphates, whereas classes II and III PI3Ks preferentially produce phosphoinositide 3-phosphates from phosphoinositide. Members of the class I PI3K family are heterodimers of a catalytic subunit and a regulatory subunit, and they are subdivided into classes IA and IB families. There are three PI3K members in class IA, namely

Abbreviations: PI3Kδ, phosphoinositide 3-kinase delta; PIP3, phosphoinositide 3,4,5-triphosphates; SH2, Src homology-2; PH, pleckstrin homology; KD, kinase-dead; KO, knockout; BCR, B cell receptor; GPCR, G protein-coupled receptor; TCR, T cell receptor; FcεRI, high affinity IgE receptor; IBD, inflammatory bowel disease; BMMC, bone marrow derived mast cell; DTH, delayed type hypersensitivity; COPD, chronic obstructive pulmonary disease; PCA, passive cutaneous anaphylaxis; HDAC2, histone deacetylase.

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PI3K alpha, beta, and delta, with their catalytic isoforms being p110α, p110β and p110δ respectively, and they are coupled with one of the five regulatory subunits p85α, p55α, p50α, p85β, or p55γ. PI3Kγ is the only member in the class IB subset with its catalytic subunit P110γ coupled with either the p101 or the p84 regulatory subunit. In contrast to other PI3K members, PI3Kδ and PI3Kγ are expressed mainly in the cells of hematopoietic lineage. The cell type specific expression of PI3Kδ and PI3Kγ suggests that they have distinct functions in leukocytes. The role of PI3Kδ in signaling and biological functions is the main focus of discussion in this review.

2. PI3Kδ in leukocyte signaling

The PI3Kδ catalytic subunit p110δ carries a regulatory subunit binding site at the N-terminal, followed by a Ras-binding domain, a C2 domain, and a kinase catalytic domain at the C-terminal. All the class IA regulatory subunits possess two conserved Src homology-2 (SH2) domains for interaction with motifs containing phosphorylated tyrosines [1]. As a typical class IA PI3K member, PI3Kδ is recruited to the receptor complex through the recognition of phosphorylated tyrosine motifs with its SH2 domain, or by direct binding to Ras with its Ras-binding region. At the receptor complex, PI3K catalyzes the generation of PIP3 at the inner leaflet of the plasma membrane. PIP3 is produced in minute amounts that are highly localized at the proximity of receptor complex in a transient manner and served as a docking site for signaling molecules bearing the pleckstrin homology (PH) domain. PDK1 and Akt are the two typical PH domain containing signaling proteins brought to the signaling complex to mediate downstream signaling events. In the activation of T or B cell receptors, PI3Kδ signaling is upstream of PLCγ and it mediates MAPK activation and calcium flux [3].

The role of PI3Kδ in signaling involves its lipid kinase activity and its adaptor function in forming protein complexes. The importance of PI3Kδ catalytic function has been demonstrated in studies using kinase-inactive mutants such as the D910A mutation in the catalytic subunit p110δ. PI3Kδ D910A kinase-dead (KD) knock-in mice have been generated and results from mutant studies confirm that the PI3Kδ catalytic activity is indispensable for its signaling events and its biological functions [3]. When PI3Kδ is inactivated, signaling defects are observable in multiple cell types including B, T and mast cells.

B cells from PI3Kδ KD mice are impaired in B cell receptor (BCR) signaling [3,4]. Signaling events mediated by BCR, including the phosphorylation of Akt, Erk, FOXO3a and p70 S6K are all compromised and the calcium flux response is reduced. Similar signaling defects are shown in B cells either treated with PI3Kδ specific inhibitor IC87114, or derived from PI3Kδ knockout (KO) mice [4,5]. The role of PI3Kδ is not restricted to BCR in that signaling events induced by IL4 and CXCL13 are also impaired in PI3Kδ KD B cells [4,6]. Although PI3Kδ is a member of the class IA PI3K family typically responding to receptor activation with tyrosine kinase activities, it is also involved in signaling events of certain G protein-coupled receptors (GPCRs) such as CXCR5 on B cells [6]. The mechanism of PI3Kδ participation in GPCR signaling is still unclear. It is possible that CXCR5 signaling involves tyrosine kinase or Ras activation and thus PI3Kδ is recruited to the receptor complex.

PI3Kδ is the main PI3K isoform responsible for PIP3 accumulation at the immune synapse upon T cell receptor (TCR) activation [3,7]. Signaling events mediated by TCR such as the phosphorylation of Akt is compromised and calcium flux response is reduced in PI3Kδ KD T cells [3,8]. The specific role of PI3Kδ in sustaining CD28 costimulatory signal at the immune synapse has been suggested [7]. PI3Kδ mediated signaling in different human T cell subsets, including CD4 and CD8 naïve T cells, as well as effector and memory T cells has been investigated. No T cell subset selectivity in PI3Kδ function can be identified and all T cell subsets are equally sensitive to the PI3Kδ inhibitor IC87114 in TCR activation, showing a reduced phosphorylation of Akt, p70S6 kinase and GSK3β [9].

Mast cells are activated by IgE-bound allergens that cross-link the high affinity IgE receptor (FcεRI) on the mast cell surface. FcεRI is a receptor complex composed of an alpha subunit for IgE binding, a beta subunit and two Fc receptor gamma chains for mediating intracellular signaling. The cross-linking of FcεRI by IgE and allergen induces Akt phosphorylation in bone marrow derived mast cells (BMMC) from wild-type, not from PI3Kδ KD mice [10]. Furthermore, these PI3Kδ KD mast cells are defective in Akt phosphorylation induced by stem cell factor (SCF) or IL3 [10]. The treatment of wild-type BMMC with the PI3Kδ inhibitor IC87114 mimics signaling defects seen in PI3Kδ KD BMMC when stimulated with IgE/allergen or SCF [10].

3. PI3Kδ in B cell development and function

B cell development takes place in the bone marrow and gives rise to different B cell subsets in the periphery. The B1 B cells in the peritoneum and the marginal zone B cells lining the marginal sinus of the spleen are the innate B cells that produce natural antibodies independent of T cell help, whereas the follicular B cells in the spleen respond to antigens with T cell help in antibody production, and differentiate into memory and plasma B cells that go into the circulation. In the absence of PI3Kδ activity, defects in B cell development and function are most noticeable. In PI3Kδ KD mice, the number of progenitor B cells in bone marrow is reduced, peritoneal B1 cells are almost undetectable, and marginal zone B cells in the spleen decrease significantly [3]. Although spleen follicular B cells appear to develop normally in PI3Kδ KD or KO mice, their numbers are reduced compared to wild-type mice [3,5].

B cells derived from PI3Kδ KD or KO mice, or wild-type B cells treated with the PI3Kδ inhibitor IC87114, all have reduced proliferative response to anti-IgM, anti-CD40 or IL4 stimulation, accompanied with an increased susceptibility to apoptosis [3–5]. In response to activation by TLR4 and TLR9 ligands, both B cell proliferation and cytokine production are diminished in PI3Kδ KD B cells with similar defects seen in wild-type B cells treated with PI3Kδ inhibitor IC87114 [11]. In addition, TLR9 mediated antibody class switch is blocked in these B cells as a result of PI3Kδ inactivation [11]. PI3Kδ is also involved in the antigen presentation function of B cells. PI3Kδ KD B cells internalize and process antigens normally, but are inefficient in forming polarized conjugates with T cells and thus resulting in defective T cell activation [12]. B cell chemotaxis to CXCL13 and S1P requires PI3Kδ to activate Rap1, a key GTPase in B cell migration [6,13]. CXCL13 is important for B2 cell entry into lymphoid follicles of the spleen, and S1P is critical for the retention of B1 cells in the spleen marginal zone. CXCL13 also allows the shuttle of B1 cells to lymphoid follicles for antigen delivery to B2 cells. A disrupted distribution of marginal zone B1 cells in the spleen is observable in mice dosed with PI3Kδ inhibitor IC87114, highlighting the importance of PI3Kδ in B cell trafficking *in vivo* [6]. The defective homing of PI3Kδ KD B cells to Peyer's patches and to splenic white pulp cords has also been shown in adoptive transfer experiments [13]. Interestingly, although PI3Kγ is expected to be involved in GPCR signaling events, CXCL13 mediated B cell migration through its receptor CXCR5 seems to largely rely on PI3Kδ rather than on PI3Kγ activity.

4. PI3Kδ in T cell development and function

Thymic T cell development and lymph node T cell population in PI3Kδ KD mice appear to be normal, but memory T cell numbers are reduced, suggesting a possible role of PI3Kδ activity in memory T cell differentiation or survival [3]. Similar to PI3Kδ KD mice, PI3Kδ KO mice do not have obvious defects in T cell development [14]. However, a profound blockade at the β chain-selection check point of thymic development is detectable in PI3Kδ and PI3Kγ double KO mice [15,16]. This defect is resulting from a lack of proliferative expansion and an increase in apoptosis accompanied by an elevated expression of pro-