Review

Status of PI3K/Akt/mTOR Pathway Inhibitors in Lymphoma

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Abstract

The phosphatidylinositol-3-kinase (PI3K) pathway is well known to regulate a wide variety of essential cellular functions, including glucose metabolism, translational regulation of protein synthesis, cell proliferation, apoptosis, and survival. Aberrations in the PI3K pathway are among the most frequently observed in cancer, and include amplifications, rearrangements, mutations, and loss of regulators. As a net result of these anomalies, the PI3K pathway is activated in many malignancies, including in Hodgkin and non-Hodgkin lymphomas, and yields a competitive growth and survival advantage, increased metastatic ability, and resistance to conventional therapy. Numerous inhibitors targeting various nodes in the PI3K pathway are undergoing clinical development, and their current status in lymphoma will be the focus of this review.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Akt, Lymphoma, mTor, PI3K, Review, Signalling, Targeted, Therapy

Introduction

The phosphatidylinositol-3-kinase (PI3K) family consists of a number of serine/threonine and lipid kinases, including those that phosphorylate the membrane-bound phosphatidylinositol-3 (PIP3). These enzymes, and the downstream Akt (also referred to as protein kinase B) and mammalian target of rapamycin (mTOR), have a profound role in multiple critical cellular processes, including growth, differentiation, metabolism, survival, and cellular proliferation (Fig. 1).[1-3] Recently, many novel inhibitors of various portions of the PI3K pathway have entered clinical trials for patients with lymphomas. Because inhibition of this pathway preliminarily appears to be a promising strategy for other malignancies, there is a high degree of interest regarding the current and future therapeutic relevance of the PI3K pathway and lymphoma.

PI3K/Akt/mTOR Pathway Biology

The PI3K enzymes consist of 3 classes with variable primary structure, function, and substrate specificity. Class I PI3Ks, the class most widely implicated as aberrant in cancers, consist of heterodimers of regulatory and catalytic subunits, and are subdivided into 1A and 1B based on their mode of activation (Fig. 1).

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Submitted: Nov 14, 2013; Revised: Jan 21, 2014; Accepted: Jan 23, 2014

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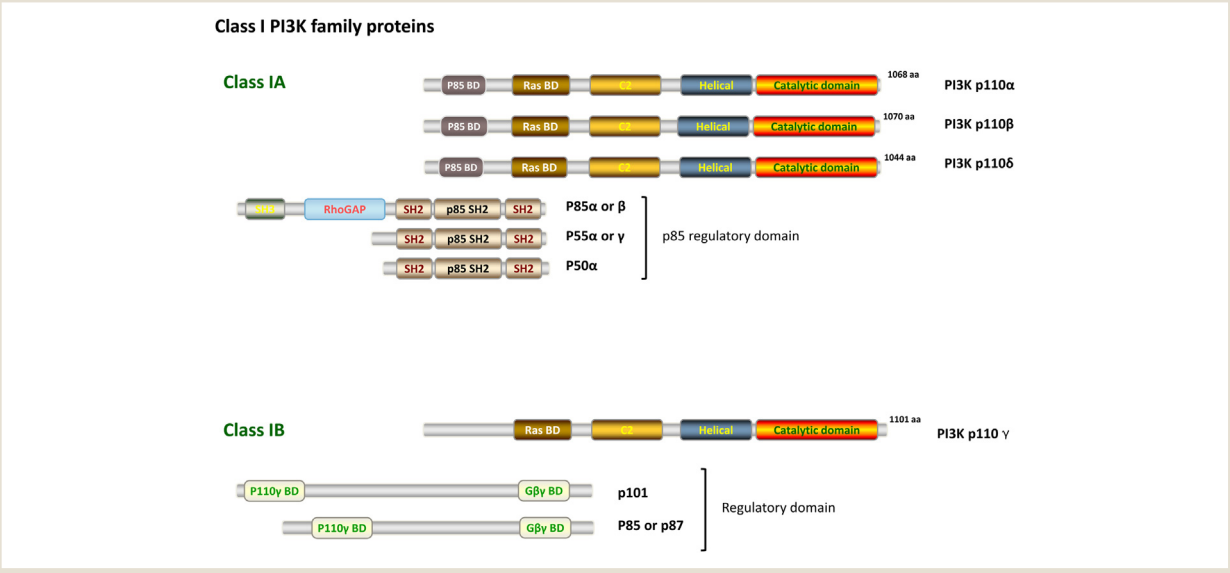
Class 1A PI3Ks are activated by various cell surface tyrosine kinases, and consist of the catalytic p110 and regulatory p85 subunits. The 3 known isoforms of Class 1A p110 are p110α, p110β, and p110δ, which all contain an amino terminal regulatory interacting region (which interfaces with p85), a Ras binding domain, and a carboxy terminal catalytic domain.[3-5] Class 1B PI3Ks consist of the catalytic (p110γ) and regulatory (p101) subunits and are activated by G-protein coupled receptors. The 4 p110 isoforms have variable tissue distribution and different physiologic functions (Table 1).[6-11] p110α is expressed ubiquitously, including leukocytes, is encoded by the frequently mutated gene *PIK3CA*, and is lethal when removed in embryonic mouse models with decreased proliferation.[12-14] p110β is also expressed ubiquitously, including leukocytes, and is important in cancer cell motility, insulin signaling, and platelet adhesion. p110β can signal downstream of G-protein coupled receptors, and is also lethal when removed in embryonic mouse models.[15-19] p110δ is expressed in leukocytes, thymus, and breast tissue, and is essential for B- and T-cell development and B-cell receptor signaling. Mouse embryonic knockout of p110δ is nonlethal but results in a substantial decrease in B cell number and function.[20,21] As a result, p110δ is preferentially targeted in B-cell malignancies. p110γ is expressed in leukocytes, thymus, cardiac, and endothelial tissue, and is involved in physiologic and pathologic immune function. The nonlethal embryonic knockout mouse model has a severe T cell and neutrophil chemotaxis impairment, with essentially normal B cells.[11,21-23] If p110δ and p110γ are both knocked out, the T cell and natural killer cell populations are significantly diminished in number and function.[10,24]

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.01.007

Figure 1 Class I PI3K Family Proteins



Abbreviations: aa = amino acid; BD = binding domain; PI3K = phosphatidylinositol-3-kinase.

Class II and class III PI3K are ubiquitously expressed, are essential for normal cellular function, and do not appear to have an oncogenic function. Class II PI3K consists of 3 classes: PI3K-C2α and PI3K-C2β are ubiquitously expressed and PI3K-C2γ is only expressed in hepatocytes. The function of the membrane-bound class II PI3Ks is not yet known, but likely is involved in protein-membrane lipid interactions.[25] Class III PI3Ks are ubiquitously expressed and essential for survival, as evidenced by the nonviable mouse embryonic knockout model.[26] Class II PI3Ks (α and β isoforms) and class III PI3Ks also play a critical role in the regulation of autophagy.[27] Because class II and III PI3K are essential and are not oncogenic, for clarity, "PI3K" will refer to class I for the remainder of this review.

The main product of PI3K is PIP3, the phosphorylated form of membrane-bound phosphoinositides, which initiates a widely active signaling cascade. A main downstream target of PI3K is the serine-threonine kinase Akt, the major oncogenic effector of the PI3K/Akt pathway (Fig. 2). The primary negative regulator of Akt activation is phosphatase and tensin homolog (PTEN), which functions to dephosphorylate PIP3.[28] Loss of the tumor suppressor PTEN via somatic mutation or epigenetic silencing is a frequent event in many cancers, but uncommon in lymphoma, and allows for increased PI3K signaling.[29] Cell membrane-bound PIP3 allows docking of Akt in proximity to numerous kinase targets, including the mTOR inhibitor tuberous sclerosis complex (TSC)1/2. Additional targets include the oncogenically-relevant MDM2, IKKα, p21, and p27.[30] MDM2 promotes cell survival and progression by inhibition of the p53 tumor suppressor, which is reversible by PI3K/Akt inhibition.[31] IKKα is a critical regulator of nuclear factor−κB (NFκB) activity, a therapeutically relevant target in many lymphomas, that is activated in part by Akt.[32] Activity of Akt can also inhibit the function of the cell cycle inhibitors p21 and p27, thus leading to unchecked growth.[33-35]

Akt indirectly activates mTOR, a complicated checkpoint of cellular growth influenced by growth factor signaling, adenosine monophosphate levels, and nutrient and O_2 availability.[1] mTOR refers to 2 distinct multimolecular complexes, mTOR complex 1 (mTORC1) and complex 2 (mTORC2). When TSC2 is phosphorylated at Ser939 by activated Akt, it dissociates from TSC1 leading to mTORC1 activation.[36] mTORC1, which activates translational repressor eukaryotic translation initiation factor 4EBP1 and S6K1, is sensitive to rapaymycin-like mTOR inhibitors.[37,38] mTORC1 activity leads to increased mRNA translation, protein synthesis, and cellular proliferation. mTORC2 is

Table 1 Expression Pattern of PI3K Enzymes

PI3K Class	Isoform	Tissue Distribution	Mouse$^{-/-}$ Major Phenotype	Function
I A	p110α	Leukocytes and ubiquitous	Embryonic lethal	Proliferation, differentiation, survival, migration, chemotaxis, phagocytosis, metabolism
	p110β	Leukocytes and ubiquitous	Embryonic lethal	
	p110δ	Leukocytes, thymus, breast	Impaired B cell development	
I B	p110γ	Leukocytes, thymus, heart, endothelium	Impaired inflammation (+ p110δ$^{-/-}$: severe T cell and NK cell defect)	Cell migration, chemotaxis, inflammation

Abbreviations: NK = natural killer; PI3K = phosphatidylinositol-3-kinase.