Pharmacology & Therapeutics 172 (2017) 101–115

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: B. Teicher

Maximising the potential of AKT inhibitors as anti-cancer treatments

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ARTICLE INFO

Available online 3 December 2016

Keywords:
AKT
PKB
PI3K/AKT signalling
AKT inhibitors
Cancer

ABSTRACT

PI3K/AKT signalling is commonly disrupted in human cancers, with AKT being a central component of the pathway, influencing multiple processes that are directly involved in tumourigenesis. Targeting AKT is therefore a highly attractive anti-cancer strategy with multiple AKT inhibitors now in various stages of clinical development. In this review, we summarise the role and regulation of AKT signalling in normal cellular physiology. We highlight the mechanisms by which AKT signalling can be hyperactivated in cancers and discuss the past, present and future clinical strategies for AKT inhibition in oncology.

Contents

1. Introduction

The AGC kinases, named after the protein A, G and C kinases, are an evolutionarily conserved group of proteins that share a hydrophobic motif at the c-terminus of their catalytic core. This motif, composed of F-X-X-F/Y-S/T-Y/F, is known as the PIF-pocket and regulates catalytic activity (Arencibia, Pastor-Flores, Bauer, Schulze, & Biondi, 2013; Manning & Cantley, 2007). The AGC kinase family comprises 14 family members, of which AKT (also known as PKB; protein kinase B) is a key member.

There are three AKT isoforms, transcribed from separate genes, which share three highly conserved domains: a central catalytic domain and two regulatory domains: a lipid-binding N-terminal PH (plektrin homology) domain, and the hydrophobic motif (Fig. 1). The PH domain contains a lipid-binding module that promotes the interaction of AKT

Abbreviations: AE, adverse event; CRPC, castrate resistant prostate cancer; DLT, dose limiting toxicity; DNA-PK, DNA-dependent protein kinase; DSB, double strand break; GSK3β, glycogen synthase kinase beta; INPP4B, polyphosphate 4-phosphatase type II; MTD, maximum tolerated dose; OS, overall survival; PD, pharmacodynamics; PDK1, 3-phosphoinositide-dependent kinase-1; PFS, progression free survival; PH domain, plektrin homology domain; PHLPP, PH domain and leucine rich repeat protein phosphatase 1; PI3K, phosphatidylinositol 3-kinases; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PK, pharmacokinetics; PP2A, protein phosphatase 2A; PR, partial response; PTEN, phosphatase and tensin homolog; RP2D, recommended phase II dose; RTKs, receptor tyrosine kinases.

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http://dx.doi.org/10.1016/j.pharmthera.2016.12.001

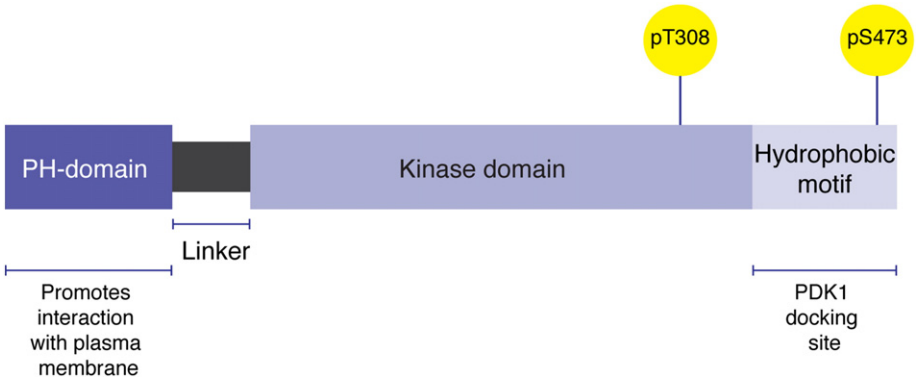

Fig. 1. Structural domains of AKT.

with the plasma membrane, an important step in AKT activation. The hydrophobic motif contains an important docking site for the activating kinase PDK1 (3-phosphoinositide-dependent kinase-1) and also provides allosteric regulation of catalytic activity (Scheid & Woodgett, 2003; Fig. 1). There is approximately 80% sequence homology between the isoforms with most variability occurring in the linker region between the PH and catalytic domains (Brodbeck, Cron, & Hemmings, 1999; Cheng et al., 1992; Hanada, Feng, & Hemmings, 2004; Jones, Jakubowicz, Pitossi, Maurer, & Hemmings, 1991).

2. AKT activation

Mechanisms of AKT activation have been reviewed previously (Liao & Hung, 2010; Scheid & Woodgett, 2003), but essentially, AKT activity is regulated downstream of receptor tyrosine kinases (RTKs), such as those within the EGF (epidermal growth factor), insulin, PDGF (platelet derived growth factor), FGF (fibroblast growth factor) and VEGF (vascular endothelial growth factor) families. RTKs activate class I phosphatidylinositol 3-kinases (PI3K), either directly, or in conjunction with adaptor proteins such as IRS-1/2 (insulin receptor substrate-1/2; Fig. 2). The PI3Ks phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). AKT binding to PIP3 at the plasma membrane induces a conformational change that results in phosphorylation of AKT, predominantly on two highly conserved residues, Thr^{308} and Ser^{473} leading to AKT activation (Fig. 1). Phosphorylation of Thr^{308} in the activation T-loop of the catalytic domain by PDK1, results in a conformational change that enhances substrate affinity and promotes AKT kinase activity (Alessi et al., 1997). Phosphorylation of Ser^{473} within the PIF pocket of AKT by mTORC2 (mammalian target of rapamycin complex 2) is thought to promote AKT activity by increasing the affinity of AKT to PDK1 (Sarbassov, Guertin, Ali, & Sabatini, 2005). In fact, multiple different kinases for Ser^{473} have been described in the literature and it's likely that mechanisms determining full activation of AKT are context dependent. It has been accepted, for example, that following DNA damage, the PI3K-like kinase (PIKK) DNA-PK (DNA-dependent protein kinase) is responsible for AKT Ser^{473} phosphorylation and that AKT activation prevents apoptosis following ionizing radiation (Bozulic, Surucu, Hynx, & Hemmings, 2008). Multiple other phosphorylation sites on AKT have been described, although the physiological importance of these is not yet fully understood (Risso, Blaustein, Pozzi, Mammi, & Srebrow, 2015) and mechanisms of constitutative activation of AKT signalling in cancer are discussed further below.

Important negative regulators of the PI3K/AKT signalling pathway include the tumour suppressor genes and phosphatases PTEN (phosphatase and tensin homolog), PP2A (protein phosphatase 2A) and PHLPP (PH domain and leucine rich repeat protein phosphatase 1; Gao, Furnari, & Newton, 2005), which dephosphorylate PIP3, AKT $pThr^{308}$ and AKT $pSer^{473}$ respectively (Toker & Marmiroli, 2014; Fig. 2). PTEN hydrolyses the 3′-phosphate on PIP3 to terminate PI3K signalling. The SH2 domain-containing inositol phosphatases (SHIP-1/2) are able to hydrolyse the 5′-phosphate on PIP3 to generate PI(3,4)P2, the function of which is not clear, although some studies suggest that like PIP3, PI(3,4)P2 is able to facilitate PDK1 activation of AKT (Gewinner et al., 2009). Recently, a fourth putative tumour suppressor of the PI3K/AKT pathway has been described namely, polyphosphate

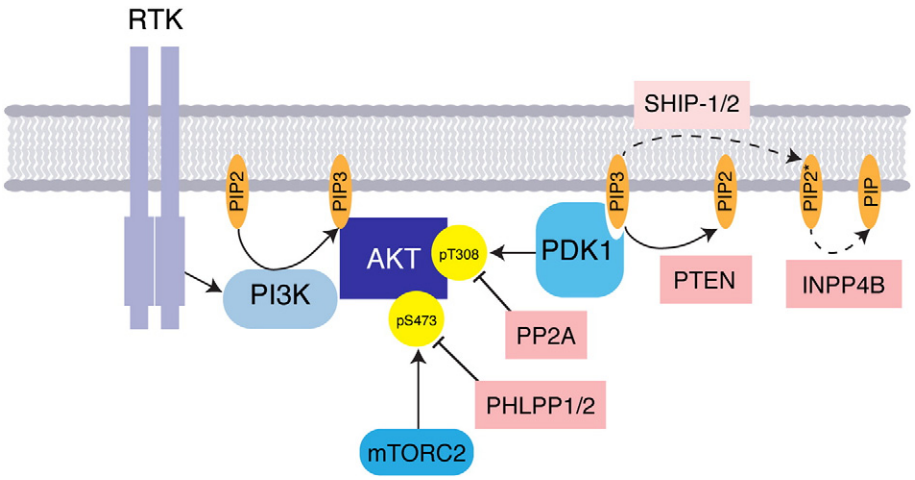

Fig. 2. Activation and negative regulation of AKT. See text for details.