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Ubiquitination and Regulation of Akt Activity

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The serine/threonine protein kinase Akt (protein kinase B, PKB) is a member of the AGC family of protein kinases. Akt is involved in regulation of many different cellular processes, such as cell growth, survival, proliferation, apoptosis, metabolism and angiogenesis. There are three known Akt isoforms, Akt1, Akt2 and Akt3, which are closely related and widely expressed in mammals.

Activation of Akt includes several major steps. First, PI3K (phosphoinositide 3-kinase) phosphorylates PI (4,5)P2 (PIP2) to form PI(3,4,5)P3 (PIP3), which is required for the recruitment of Akt from the cytosol to the plasma membrane [1]. The dual specificity protein phosphatase PTEN negatively regulates this process by dephosphorylating PIP3 to PIP2 [2]. At the membrane, Akt is phosphorylated at Thr^{308} within its catalytic domain by phosphoinositol-dependent kinase 1 (PDK1) and at Ser^{473} within its C-terminal regulatory domain by mammalian target of rapamycin complex 2 (mTORC2), resulting in its full activation [3,4].

While regulation of Akt activity via Thr^{308} and Ser^{473} phosphorylation has been a subject of extensive research, much less is known about the effect of other posttranslational modifications (PTMs) on Akt activity. More recently, additional Akt regulatory PTMs were identified, including phosphorylation, acetylation, oxidation, glycosylation, SUMOylation and ubiquitination sites [5,6].

In ubiquitination, ubiquitin (Ub), a 76-amino acid protein, is covalently conjugated to lysine residues of substrate proteins through a concerted action of three enzymes: ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes. There are seven lysine (K) residues within the ubiquitin that can participate in formation of ubiquitination chains; the most extensively studied are K48 and K63 [7]. Protein modified by K48-linked ubiquitination is recognized by the 26S proteasome and is, therefore, targeted for protein degradation, whereas K63-linked ubiquitination plays non-proteolytic functions [8,9].

Degradative Ubiquitination of Akt

Several Ub E3 ligases have been described as responsible for incorporating K48-linked polyUb chains into Akt protein: E3 ligases BRCA1 (breast cancer early-onset 1); CHIP [C-terminus of the Hsc (heat-shock cognate) 70-interacting protein]; TTC3 (tetratricopeptide repeat domain 3); and MULAN [mitochondrial ubiquitin ligase activator of NF-κB (nuclear factor κB) 1] [6]. Recent study suggested that Lys^{284} in Akt is a specific residue for MULAN-mediated Akt ubiquitination [10]. Generally, these E3 ligases facilitate K48-linked ubiquitination of Akt and its subsequent degradation that results in attenuation of endogenous Akt signaling or termination of its activity.

Non-degradative Ubiquitination of Akt

Recent ground-breaking study demonstrated that an increase in Akt ubiquitination occurred in response to various Akt-activating stimuli, such as growth factors or cytokines [11]. This polyubiquitination was non-degradative, affecting Akt activation but not stability. Furthermore, TRAF6 (tumor-necrosis-factor-receptor-associated factor 6) was identified as a direct Akt E3 Ub ligase, which promoted Akt recruitment to the plasma membrane and its subsequent activation. Interestingly, different E3 Ub ligases can mediate ubiquitination-dependent activation of Akt in response to different extracellular stimuli. TRAF6 was shown to mediate K63-linked ubiquitination of Akt in response to IGF-1 (insulin growth factor 1) and serum treatment [11,12]. We have recently demonstrated that TRAF6 promotes K63-linked polyubiquitination of Akt upon laminin-integrin interaction in the renal collecting duct epithelial cells (Yazlovitskaya, 2015). The E3 ligase complex Skp2/SCF (S-phase kinase-associated protein 2/Skp1-Cullin-F-box) mediates Akt ubiquitination in response to EGF (epidermal growth factor) through ErbB receptors [13]. Akt ubiquitination by the E3 ligase NEDD4-1 occurs in fibroblasts in response to IGF-1 or insulin but not to EGF or serum stimulation [14]. The same study demonstrated that Akt ubiquitination by NEDD4-1 secures membrane recruitment of Akt and membrane anchoring which are necessary for its consequent phosphorylation/activation. Moreover, NEDD4-1-mediated Akt ubiquitination regulates its trafficking to nuclear/perinuclear compartments along its activation [14].

Deubiquitinating Enzymes (DUBs)

DUBs can affect Akt ubiquitination in two ways, either via direct deubiquitination of Akt directly or through the action on Akt-specific Ub E3 ligases whose activity is regulated by autoubiquitination. CYLD (cylindromatosis) was identified as a DUB that interacts directly with and deubiquitinates Akt. This protease specifically cleaves K63-linked polyUb chains on Akt, thus reducing Akt activation upon extracellular stimulation [15]. Interestingly, CYLD also removes K63-linked ubiquitin chains from TRAF6, an Akt E3 ubiquitin ligase for Akt, thus causing its inactivation [16]. Similar function was shown for the ubiquitin editing enzyme A20 (also known as TNFAIP3) [17]. Interestingly, A20 binds ubiquitin and displays either E3 ubiquitin ligase or deubiquitinating activities depending on the cell type and stimulus [17]. The carboxy-terminal domain of A20 binds ubiquitin and supports E3 ubiquitin ligase activity, while its DUB activity is mediated by an amino-terminal motif [18].

In summary, recent studies identified the processes of ubiquitination/deubiquitination of Akt as a fine-tuning regulation of this kinase that modulates cellular functions.

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