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Review

The links between AKT and two intracellular proteolytic cascades: Ubiquitination and autophagy

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ABSTRACT

The serine threonine kinase AKT plays a central role in the regulation of cell survival in a variety of human neoplastic diseases. A series of studies have revealed a connection between AKT signaling and two important protein degradation pathways in mammalian cells: the ubiquitin–proteasome system and autophagy. Two distinct ubiquitination systems have been reported to regulate AKT signaling: K63-linked ubiquitination, which promotes the oncogenic activation of AKT, and K48-linked ubiquitination, which triggers the proteasomal degradation of phosphorylated AKT. Autophagy is an evolutionarily conserved mechanism for the gross disposal and recycling of intracellular proteins in mammalian cells. AKT signaling may play a regulatory role in autophagy; however, the underlying mechanisms have not been fully clarified. Recently, AKT was shown to phosphorylate key molecules involved in the regulation of autophagy. Furthermore, lysosomal co-localization of the AKT–Phafin2 complex is reportedly critical for the induction of autophagy. In this review, we will discuss the connection between AKT, a core intracellular survival regulator, and two major intracellular proteolytic signaling pathways in mammalian cells.

Contents

Abbreviations: BRCA1, breast cancer susceptibility gene 1; BRCT, Brca1 C-terminal; CHIP, chaperone-associated ubiquitin ligase; CYLD, cylindromatosis; DAPK, death-associated protein kinase; DUB, deubiquitinating enzyme); EGF, epidermal growth factor; FADD, fas-associated protein with death domain; FGFR1, fibroblast growth factor receptor 1; Hsp90, heat shock protein 90; IAP1/2, inhibitors of apoptosis 1/2; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IGF-1, insulin-like growth-factor 1; JNK1, c-Jun N-terminal kinase; MULAN, mitochondrial ubiquitin ligase activator of NF-κB; mTOR, mammalian target of rapamycin; Myr, myristoylated; NEDD4, neural precursor cell expressed developmentally down-regulated protein 4; NFκB, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase; PAK1, p21 protein-activated kinase 1; PAS, pre-autosomal structures; PH, pleckstrin homology; PIAS1, protein inhibitor of activated STAT-1; PTEN, phosphatase and tensin homolog deleted from chromosome 10; RNF8, ring finger protein 8; S6K1, p70 S6 kinase 1; Skp2, SKP1 interacting partner 2; 3-MA, 3-methyladenine; TNF, tumor necrosis factor; TPR, tetratricopeptide repeat; TRAF6, tumor necrosis receptor-associated factor 6; TRAIL, TNF-related apoptosis-inducing ligand; TSC, tuberous sclerosis complex; TTC3, tetratricopeptide repeat domain 3; Ubl, ubiquitin-like; ULK1, Unc-51 like autophagy activating kinase 1; Vps34, vacuolar protein sorting 34

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1. Introduction

The serine threonine kinase AKT, also called protein kinase B (PKB), regulates a range of cellular processes, including cell survival, cell cycle progression, cytoskeletal organization, vesicle trafficking, glucose transport, and platelet function. Deregulation or malfunction of AKT contributes to a wide variety of human diseases including cancers, glucose intolerance, schizophrenia, viral infections, and autoimmune diseases [1–3]. Two major proteolytic pathways are present in mammalian cells: autophagy and the ubiquitin–proteasome system [4–6]. A series of studies has shown that the PI3K (phosphoinositide 3-kinase) –AKT–mTOR (mammalian target of rapamycin) pathway, which mediates anti-apoptotic signaling, may play an important role in the regulation of autophagy and the ubiquitin-proteasomal system in mammalian cells [7–13].

Ubiquitin was originally proposed to deliver tagged proteins to the cellular waste disposal machinery via the 26S proteasome. Ubiquitin, a 76-residue protein, is covalently associated with protein substrates. Protein ubiquitination is mediated by the concerted action of essentially three enzyme families (E1, E2, and E3). Ubiquitin is activated first by a ubiquitin-activating enzyme (E1) through an ATP-dependent reaction to form an E1-thioesterlinkage, and the activated ubiquitin is transferred to a member of the ubiquitin-conjugating enzyme E2 family. A ubiquitin–protein ligase (E3) then mediates the transfer of ubiquitin from E2 to the substrate protein by promoting the formation of an isopeptide bond between the ubiquitin (Ub) carboxyl-terminus and specific lysine side chains on the substrate [14,15]. In the human genome, there are over 500 genes that appear to be E3 ligases, and there are potentially over 1500 molecules that can be targeted by ubiquitin and/or ubiquitin like protein modifications [16]. E3 ligases can generally be classified into two families: RING (really interesting new gene) type E3 ligases, and HECT (homologous to the E6-associated protein C terminus) type E3 ligases. The activity of the ubiquitin system is dependent on the specificity of the E3 ubiquitin ligases [17].

In addition to its control of protein turnover, protein ubiquitination of protein has an additional impact on various cellular functions, including facilitation of cell-surface-receptor turnover and control of gene transcription [15].

Two distinct ubiquitination systems for AKT have been reported: K63-linked ubiquitination of lysine of ubiquitin by TRAF6 (tumor necrosis receptor-associated factor 6) [18], Skp2 (SKP1 interacting partner 2) [12], or NEDD4 (neural precursor cell expressed developmentally down-regulated protein 4) [19], induces AKT activation by promoting plasma membrane translocation and/or nuclear translocation. In contrast, K48-linked ubiquitination of lysine of ubiquitin by BRCA1 (breast cancer susceptibility gene 1) [8], MULAN (mitochondrial ubiquitin

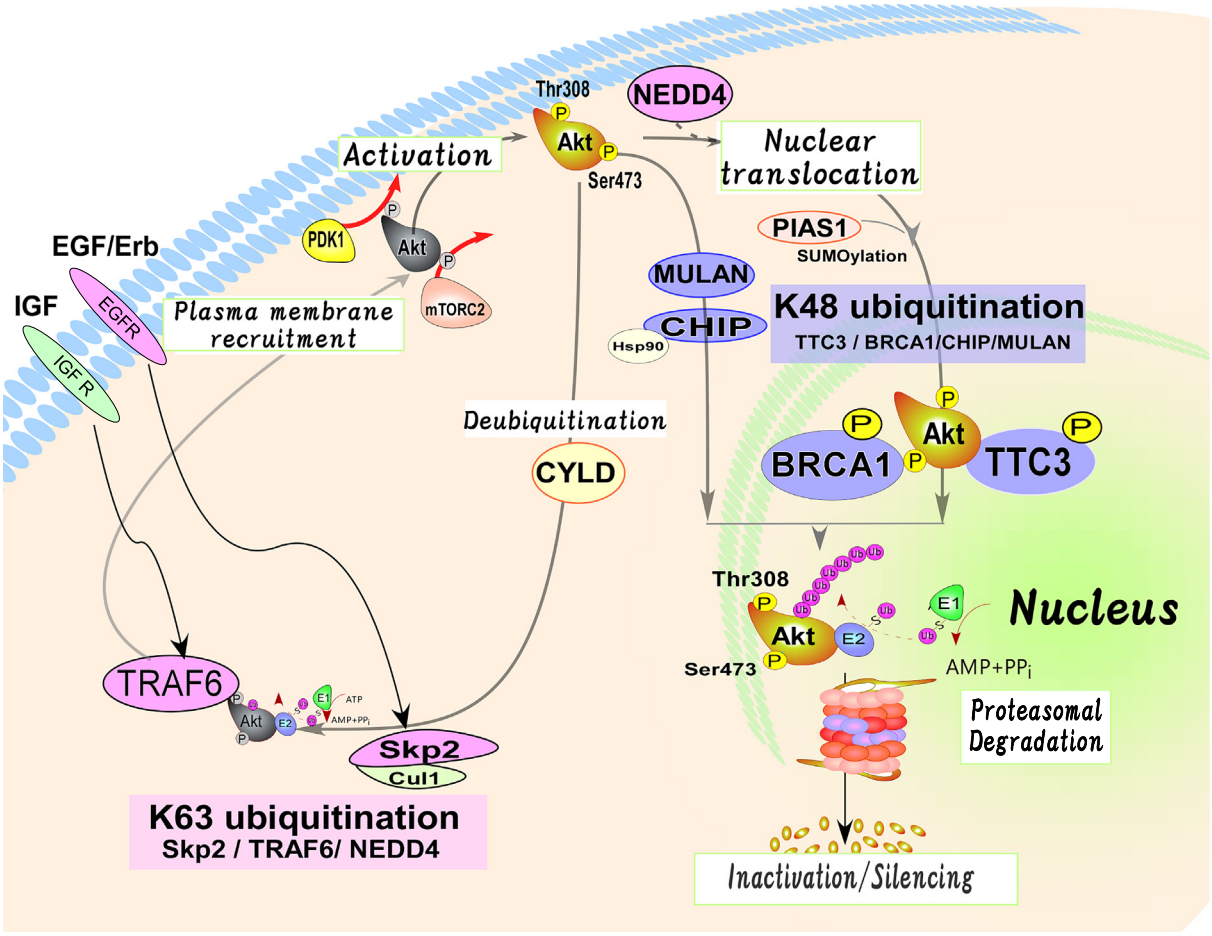

Fig. 1. Two distinct ubiquitination systems regulate AKT and downstream cellular responses. K63-linked ubiquitination by TRAF6/Skp2 induces the translocation of AKT to the plasma membrane, which is important for oncogenic AKT activation. NEDD4 catalyzes K63-linked ubiquitination of phosphorylated AKT to promote its nuclear translocation. K48-linked ubiquitination of AKT by TTC3, CHIP, or MULAN, or BRCA1 promotes proteasomal degradation. PIAS1-mediated SUMOylation of AKT, which occurs mainly in the nucleus, is also essential for the activation of AKT and downstream responses such as proliferation and tumorigenesis. In contrast, K48-linked ubiquitination mediated by BRCA1 or TTC3 occurs in the nucleus and triggers proteasomal degradation. MULAN- and CHIP-mediated ubiquitination likely to occurs in the cytosol. Moreover, the CYLD deubiquitinase controls the balance between AKT ubiquitination and deubiquitination.