How to explain the AKT phosphorylation of downstream targets in the wake of recent findings

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AKT (v-Akt oncogene), a Ser/Thr protein kinase, was also identified as protein kinase B (PKB) (reviewed in ref. 1). There are three known isoforms of AKT1-3. All these AKT isoforms are highly conserved and are recruited to the plasma membrane where they bind to $PIP_{3,4,5}$ via the PH-domain and are phosphorylated. While Lučić et al. (2) studied AKT1, the study is applicable to all of the AKT isoforms. Among the three AKT isoforms, AKT2 is extensively studied due to its critical role in insulin signaling (3). AKT is a central hub for cellular signal transduction, relaying information generated at the cell surface to the cell nucleus. This process relies mainly on a series of phosphorylation events: cell surface receptor activation, activation of PI3K, and phosphorylation of AKT (of both T308 by PDK1 and S473 by mTORC2), which then phosphorylates several downstream signaling molecules, including FOXO1, which is among the many (~150) AKT substrates identified (1).

While this paradigm for AKT signaling has been the dogma for many years, this new study by Lučić et al. (2), and those previous studies from the same institute (4, 5), now show that the activation of AKT is restricted to a plasma membrane event and the activated AKT, when released from the plasma membrane, is rapidly dephosphorylated by cytoplasmic leucine-rich repeat-containing protein phosphatase (PHLPP) and protein phosphatase 2 (PP2A).

Thus, the question from these studies that emerges is, how are the downstream cytoplasmic AKT targets phosphorylated? For example, AKT-mediated phosphorylation of FOXO1 in the nucleus is well documented (6, 7) during insulin signaling such that, upon its phosphorylation in the nucleus, FOXO1 is subsequently sequestrated to the cytoplasm, resulting in termination of the transcriptional activation of gluconeogenesis. This process requires activated (phosphorylated) AKT to reach the cell nucleus from the cell surface intact (6, 7). The distance from cell surface to the nucleus has not been measured for all of the cell types, but Calleja et al. (8) and Kunkel et al. (9) suggest that this distance on average is ~20 μm in HeLa cells. Furthermore, some downstream targets are phosphorylated within seconds (<15 s). Others, like FOXO1, require anywhere from 30 to 60 s (10). Does some fraction of activated AKT avoid dephosphorylation during its passage through the cellular cytoplasm and, if so, how? Is it possible that the phosphorylated AKT is shielded by being sequestered in the endomembranes? Or are there additional but as-yet-unidentified protein kinases that rephosphorylate AKT? Could the well-documented effects of AKT on nuclear proteins be indirect and mediated by as-yet-unidentified kinases? The current study (2) and those before (4, 5) demand a reconsideration of AKT signaling mechanisms and a fresh look at an old paradigm, although the authors have not provided any guidance on these critical questions.

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