The PI3K/Akt pathway is a major signaling network for control of the growth and survival of normal and neoplastic cells and is oncogenic for multiple cancer types, including OVCa. PI3K synthesizes phosphatidylinositol 3,4,5-trisphosphate, which recruits Akt and phosphoinositide-dependent kinase 1 (PDK1) to the plasma membrane via their pleckstrin homology (PH) domains, resulting in PDK1 phosphorylation of Akt at its activation loop site Thr-308. Once phosphorylated at Thr-308, Akt phosphorylates SIN1 of the mechanistic target of rapamycin

(mTOR) complex 2 (mTORC2), which activatesmTORC2, resulting in phosphorylation of Akt at Ser-473 (9). Phosphorylation of Akt at both Thr-308 and Ser-473 is required for maximal

activation. Dephosphorylation of phosphatidylinositol 3,4,5-trisphosphate by PTEN exerts a suppressive effect on the activity of the PI3K/PDK1/Akt pathway. Akt activation results in promotion of protein translation, cell growth, and cell survival. Protein translation is mediated by Akt phosphorylation of PRAS40 (proline-rich Akt substrate 40) leading to the release of mTORC1 from an inhibited state allowing for its phosphorylation of the p70 ribosomal protein

S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) (10). Akt promotes cell growth and survival.

The pathway leading to Akt activation is typically conceptualized with PDK1 as the sole upstream kinase activating Akt by Thr-308 phosphorylation. Thus, PDK1\_/\_ embryonic stem

(ES) cells fail to show growth factor (GF)-responsive Akt phosphorylation at Thr-308 (13). Although it is well established that PDK1 is a major upstream Akt-activating kinase, it is possible

that additional kinase(s), which are not expressed developmentally at the ES cell stage, are not GF-responsive, or are overexpressed in cancer, might catalyze Akt phosphorylation. It was previously reported that in neuroblastoma–glioma NG108 cells, Akt is phosphorylated at Thr-308 by Ca2\_/calmodulin (CaM)-dependent kinase kinase (CaMKK) in response to Ca2\_ influx (14). CaMKK exists as two paralogues, 1 (\_) and 2 (\_), with closely related structures and similar enzymatic properties (15–18). CaMKK1 and CaMKK2 activate both CaMKI and CaMKIV by phosphorylating their activation loop sites (Thr-177 and Thr-200, respectively) (16). CaMKK2 is

also an upstream-activating kinase for 5\_-AMP-activated kinase (AMPK) (19–21). These latter studies established the precedents that CaMKK2-catalyzed phosphorylation may be directed to a target, which is not itself Ca2\_/CaM-dependent, and can occur in cells that express another upstream-activating kinase (STK11/LKB1) (22). Akt hyperactivation is thought to be the main contributor to platinum chemotherapeutic resistance in HGSOC (23). Underscoring the importance of this pathway for OVCa progression are the multiple clinical trials of PI3K/PDK1/Akt pathway inhibitors for OVCa therapy.