Short Communication

Akt Inhibitors and COL11A1 in Epithelial Ovarian Carcinoma: A Short Note

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Short Commentary

Epithelial ovarian carcinoma (EOC) is the most lethal gynecologic malignancy. Currently, the treatment of patients with EOC usually includes surgery and chemotherapy [1]. The survival rate of patients with EOC remains low despite advances in surgical techniques and chemotherapy. One of the obstacles to the use of chemotherapy is drug resistance. To improve the survival rate, efforts must be made to overcome chemoresistance.

Akt, a key protein in the Akt/PI3K signaling pathway, is a serine/threonine protein kinase that, once activated by phosphorylation, plays an important role in the process of malignant transformation [2]. The phosphorylated form of Akt (p-Akt) has been implicated in the induction of signals that affect cell apoptosis and the promotion of cell proliferation and invasiveness through mammalian target of rapamycin (mTOR) activation [3]. Investigations have shown that overexpressed p-Akt is associated with a poor prognosis of human cancer [4–6] that includes ovarian cancers [7–9]. Our recent report showed that patients with tumors overexpressing p-Akt had a poorer survival rate, and the p-Akt overexpression was associated with high-grade tumors and cancer death [10]. In addition, more patients with high p-Akt levels were allocated to the group of clinically defined chemoresistance, although this difference did not achieve statistical significance [10]. Therefore, p-Akt overexpression may be a common prognostic factor shared by multiple types of human cancers, and thus has the potential to be a therapeutic target of clinical significance.

Collagen type XI alpha 1 (COL11A1) belongs to the collagen family, which is the major component of the interstitial extracellular matrix. We previously found that COL11A1 plays an important role in EOC. Our results indicated that COL11A1 promotes tumor progression by up regulating the transforming growth factor-β1 (TGF-β1)/matrix metalloproteinase-3 (MMP3) axis, through the involvement of the nuclear transcription factor Y subunit alpha (NF-YA) binding site in the COL11A1 promoter, and predicts a poor clinical outcome in ovarian cancer patients [11]. We also found that COL11A1 promotes cancer cell sensitivity to anticancer drugs via activation of the Akt/c/EBPβ (CCAAT/enhancer-binding protein beta) pathway and attenuates phosphoinositide-dependent kinase 1 (PDK1) ubiquitination and degradation [12]. In addition, COL11A1 reduced

chemotherapy-induced apoptosis through up regulating Twist-related protein 1 (TWIST1)-mediated induced myeloid leukemia cell differentiation protein (Mcl-1) and growth arrest-specific 6 (GAS6) expression [13]. Our recent report indicated that SC66, an inhibitor of Akt and mTOR, inhibited COL11A1 expression and enhanced the sensitivity of cells to anticancer drugs through the dual suppression of c/EBPβ and NF-YA binding to the COL11A1 promoter [10].

A previous study [14] described that the Akt inhibitor MK-2206 enhances the efficacy of anticancer drugs in ovarian cancer cells. However, our results showed that COL11A1 mRNA expression and COL11A1 promoter activity were regulated by SC66, but not by MK-2206 [10]. We also found out that the expression of PDK1 was inhibited by SC66, but not by MK-2206 [10]. These results suggest that Akt inhibitors might exert their effect on Akt signaling through different mechanisms. Further investigation is required to explore the precise molecular mechanisms underlying Akt inhibitor-regulated Akt-related signaling.

Conclusion

The PI3K/Akt signaling pathway has become the focus of interest as a critical regulator of cancer cell survival, and a number of Akt pathway inhibitors with different efficacy and specificity have been identified. In our opinion, Akt inhibitors might exert their effect on Akt signaling through different mechanisms, and evaluation of PI3K/Akt/mTOR pathway inhibitors is required to confirm the patterns of sensitivity observed in preclinical studies before they can be applied in the clinic.

References

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