Abstract

The incidence of colon cancer is wide-spread and rising worldwide. Despite current therapeutic achievement, colorectal cancer still possesses third leading position in cancer incidence and mortality. Akt is a serine/threonine kinase that controlled multiple cellular signaling pathways associated with tumorigenesis, chemo-resistance and radio-resistance. Previous studies suggested that BI-69A11, an Akt inhibitor, is more effective in inhibiting Akt and eliciting cell death in melanoma cells exhibiting elevated Akt activity. With this background in this piece of work, we have focused on the potential of BI-69A11 in providing new-age cancer therapeutics through varied mechanistic approaches. First our study elucidated that the apoptosis-inducing effect of BI-69A11 occurred through deregulation in the phosphorylation of Akt and its downstream targets. Further, BI-69A11 in combination with Ad.5/3-*mda-7*/IL-24 promoted the inhibition of cell proliferation, invasion and angiogenesis *in vitro* and *in vivo* model by blocking Akt-dependent pathway. We investigated whether BI-69A11 mediated apoptosis was associated with early-phase autophagy to improvise the therapeutic efficacy of BI-69A11. We found that BI-69A11 induced autophagy at earlier time point through the inhibition of Akt/mTOR/p70S6kinase pathway. We also generated a novel combination therapy by pretreatment with chloroquine that inhibited the autophagy and accelerated the apoptotic potential of BI-69A11. Next we dissected the ability of BI-69A11 to reduce metastasis progression through the inhibition of epithelial to mesenchymal transition. BI-69A11 potentially hampered cellular migration, invasion and adhesion through β-catenin dependent pathway. BI-69A11 also strengthened the adherens junction and focal adhesion junction by restoring the expression of E-cadherin and Vinculin at membrane. Further it disrupted the augmentation of TGF-β-induced EMT by inhibition of Akt/IκB/NF-κB signaling. We next employed BI-69A11 in combination with Celecoxib to enhance radiosensitization in colon carcinoma. The combinatorial effect of BI-69A11 and celecoxib diminished the phosphorylation of Akt in accordance with attenuation of IR-induced activation of ATM and its substrates. Our study showed the therapeutic efficacy exerted by BI-69A11 alone or in combination with ad.5/3-*mda-7*, chloroquine and Celecoxib in pre-clinical model that could be employed as effective inducer for chemo and radiotherapy.
Keywords: BI-69A11, Colon Cancer, chemotherapy, radiotherapy, autophagy, apoptosis