In vitroおよびin vivoにおけるAs^{III}とブファジエノライド化合物のヒト膠芽腫細胞U-87に対する抗腫瘍活性

Antitumor activity of arsenite combined with bufadienolide compounds against human glioblastoma cell line U-87 in vitro and in vivo

○李 ショウ美[1]、袁 博[1]、玄 美燕[1]、菊地 秀与[1]、須永 克佳[1]、岩田 直洋[1]、神内 伸也[1]、日比野 康英[1]、松﨑 広和[1]、岡﨑 真理[1]
○Jingmei Li[1], Bo Yuan[1], Meiyan Xuan[1], Hidetomo Kikuchi[1], Katsuyoshi Sunaga[1], Naohiro Iwata[1], Shinya Kamiuchi[1], Yasuhide Hibino[1], Hirokazu Matsuzaki[1], Mari Okazaki[1]

1. 城西大院薬
1. Grad. Sch. Pharm. Sci., Josai Univ.

Due to concerns over the invasiveness and drug resistance of glioblastoma, there is an urgent need to explore novel therapeutic approaches for the treatment of the fatal disease. Trivalent arsenic derivative (arsenite, As^{III}), and bufadienolide compounds, arenobufagin (Areno) and gamabufotalin (Gama) have been shown to trigger cytotoxic effects in glioblastoma cells. In the current study, the cytotoxicity of As^{III} in combination with Areno or Gama was first evaluated in the human glioblastoma cell line U-87. Treatment with As^{III}, Areno and Gama induced a dose-dependent cytotoxicity in the cells, respectively. The combination of As^{III} and Areno or Gama resulted in an enhancement of the cytotoxicity. Furthermore, synergistic cytotoxic effects of clinically achieved concentrations of As^{III} combined with Areno were observed. Apoptosis induction associated with a downregulation of proform of caspase-9 and caspase-3 was confirmed following the treatment with the combined regimen of As^{III} and Areno. The combined regimen also caused the enhancement in necrosis as evidenced by a clear increase in LDH release and propidium iodide-positive cell populations. Compared to each single drug treatment, the combined regimen clearly downregulated the expression level of p-Akt, p-mTOR; and upregulated the expression level of LC3. Collectively, the combined regimen of As^{III} and Areno exhibited a unique multivalent cytocidal effects against U-87 cells by inducing apoptotic, necrotic and autophagic cell death, suggesting that developing a new combination regimen of As^{III} and Areno may offer benefits to patients with glioblastoma. Further investigation into antitumor activity of the combined regimen in the U-87 xenograft model is ongoing in our laboratory.