ヒト膠芽腫細胞U-87におけるAs^{III}とブファジエノライドの併用による殺細胞効果の増強

Enhanced cytotoxicity of arenite combinated with bufadienolides against human glioblastoma cell line U-87

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Novel therapeutic approaches are urgently needed to fight glioblastoma in view of its resistance to conventional therapies. Cytotoxicity of trivalent arsenic derivative (arsenite, As^{III}) combined with arenobufagin or gamabufotalin, two active bufadienolide compounds, was investigated in human U-87 glioblastoma cells. Synergistic cytotoxicity with upregulated intracellular arsenic levels was observed when treated with As^{III} combined with arenobufagin instead of gamabufotalin. Apoptosis and the activation of caspase-9/-8/-3 was induced by As^{III} and was further strengthened by arenobufagin. The magnitude of increase in the activities of caspase-9/-3 was much greater than that of caspase-8, suggesting that intrinsic pathway played a much more important role in the apoptosis. An increase in the number of necrotic cells along with enhanced LDH leakage and intensified G_2/M phase arrest was observed. A remarkable increase in the expression level of γH2AX, a DNA damage marker, was induced by As^{III} plus arenobufagin. Concomitantly, the activation of autophagy was observed, suggesting that autophagic cell death associated with DNA damage was partially attributed to the cytotoxicity of As^{III} plus arenobufagin. Suppression of Notch signaling was confirmed in the combined regimen-treated cells, suggesting that inactivation of Jagged1/Notch signaling would probably contribute to the synergistic cytotoxic effect of As^{III} plus arenobufagin. Given that both As^{III} and arenobufagin are capable of penetrating into blood-brain barrier, our findings may provide fundamental insight into the clinical application of the combined regimen for glioblastoma.