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Apatone® induces autoschizic cell death in human bladder cancer cells

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Abstract

Human bladder cancer cell lines RT4 and T24 were treated with Apatone®, a combination of Vitamin C (VC) and Vitamin K_3 in a 100:1 ratio, or VC or VK_3 alone. An MTT assay compared a 1hr pulsed versus a 5day continuous exposure. VC:VK_3 was synergistic, increasing the antitumor activity 12- to 24 fold for RT-4 cells and 6- to 41-fold for the T24 cells. Further study using flow cytometry revealed a growth arrested population and a population undergoing cell death. Growth arrested cells were blocked near the G_0/G_1- S-phase interface, while cell death was due to autoschizis. VC:VK_3 pulsed versus continuous exposure produced comparable CD_{50} values, indicating a triggered response involving a catalase reversible redox mechanism generating hydrogen peroxide and other reactive oxygen species (ROS). ROS production caused lipid peroxidation and depletion of cellular thiols. When ATP levels were measured over 5hrs to determine metabolic effects, a transient increase in ATP production was seen for VC and decreased ATP levels were seen following VK_3 treatment. VC:VK_3, caused a unique spike in ATP levels after which ATP levels fell slowly. Further microscopic evaluation using live cell imaging with JC-1 revealed VC:VK_3 induced a loss in mitochondrial membrane potential. Though the exact cause of the ATP spike is unknown a possible mechanism is a shunt formed around a defective region of complex III of the electron transport chain from coenzyme Q to cytochrome c, producing a shift from glycolytic to oxidative metabolism and a dimunition of lactic acidosis.

Biography

Karen McGuire is a biomedical engineer with a doctoral degree in cellular and molecular biology. She has worked in the area of drug development and cancer biology for the past 8 years testing a range of anti-cancer drugs to evaluate their synergistic activity and toxicity profiles both *in vitro* and *in vivo*. She has multiple peer reviewed publications and patent applications. She is the current president elect of the microscopy society of northeast ohio, with experience in a range of imaging techniques including high content imaging for drug screening. She is also a member of the AACR and NAPW.