Vitamin K2-induced cell growth inhibition via autophagy formation in cholangiocellular carcinoma cell lines.


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Abstract

Vitamin K2 (MK4) has antitumor effects on various types of cancer cell lines in vitro, and its efficacy has also been reported in clinical applications for patients with leukemia, myelodysplastic syndrome, and hepatocellular carcinoma (HCC). However, details of the mechanism of the antitumor effects of MK4 remain unclear. In the present study, we examined the antitumor effects of MK4 on cholangiocellular carcinoma (CCC) cell lines and its mechanism of action using the HL-60 leukemia cell line that exerts MK4-induced cell growth inhibition via apoptosis induction and cell cycle arrest as a control. MK4 exerted dose-dependent antitumor effects on all three types of CCC cell lines. However, apoptosis occurred in a smaller percentage of cells and there was less cell cycle arrest compared with other cancer cell lines studied previously, which suggested slight MK4-induced cell growth inhibition via apoptosis induction and cell cycle arrest. On the contrary, histopathological findings showed a large number of cells containing vacuoles in their cytoplasm, and electron microscopic findings showed a large number of cytoplasmic autophagosomes and autolysosomes. These findings suggested evidence of autophagy-related cell death. Fluorescence microscopy following acridine orange staining revealed an increase in the number of cytoplasmic acidic vesicular organelles characteristic of autophagy. Moreover, there were few cells forming autophagic vesicles in the control group, while the percentage of cells containing vacuoles in the MK4-treated group increased with the duration of culture. These results suggested that, unlike in leukemia, gastric cancer, HCC, and other cancer cells, the antitumor effects of MK4 on CCC cells are induced via autophagy formation.

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