Platonin induces autophagy-associated cell death in human

陳淑華

Chen YJ;HuangWP;Yang YC;Lin CP;Chen SH;Hsu ML;Tseng YJ;Shieh HR;Chen YY;Lee JJ

摘要

Abstract

Platonin is a photosensitizer used for photodynamic therapy. In this study, we tested the effect of platonin on human leukemic cells. Treatment with platonin in the dark markedly reduced cell membrane integrity, and induced significant G0/G1 arrest of a panel of human leukemic cell lines, including U937, HL-60, K562, NB4 and THP-1. Development of hypodiploid cells was not evident in these cell lines within 24 h, but was noted in U937, HL-60 and NB4 cells after 24 h. No myeloid differentiation of these cells was noted after 5-day treatment. Intriguingly, exposure of monoblastic U937 cells to platonin caused changes characteristic of autophagy, including appearance of cytoplasmic membranous vacuoles and formation of acidic vesicular organelles (AVO) in more than 95% of cells. The platonin-induced autophagy was accompanied by localization of microtubule-associated protein 1 light chain 3 to autophagosomes. Pretreatment with pancaspase inhibitor Z-VAD-fmk abrogated the platonin-induced hypodiploidity, but had no effect on growth inhibition and formation of AVO, indicating a caspase-independent autophagy-associated cell death. Pretreatment of cells with 3-methyladenine attenuated platonin-mediated growth inhibition and formation of AVO. Platonin augmented the expression of BNIP3 in both U937 and K562 cells, whereas had an opposite effect on phosphorylation of mTOR downstream molecule p70S6K. Platonin, at the condition inducing autophagy, induced the mitochondrial membrane permeation. These results suggest that the platonin is capable of inhibiting growth as well as inducing cell death, mainly autophagy-associated, in leukemic cells via a mitochondria-mediated and caspase-independent pathway. A markedly less viability inhibition was noted to human monocytes, the normal counterpart of these myeloid leukemic cells. Platonin, other than a photodynamic agent, may offer significant promise as a therapeutic agent against leukemia.