Cardiac glycosides induce autophagy in human non-small cell lung cancer cells through regulation of dual signaling pathways.

Wang Y, Qiu Q, Shen JJ, Li DD, Jiang XJ, Si SY, Shao RG, Wang Z.


Source

The Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, PR China.

Abstract

Na(+)/K(+)−ATPase targeted cancer therapy has attracted increasing interests of oncologists in lung cancer field. Although multiple anti-cancer mechanisms of cardiac glycosides as Na(+)/K(+)−ATPase inhibitors are revealed, the role of autophagy and related molecular signaling pathway for the class of compounds in human non-small cell lung cancer (NSCLC) cells has not been systematically examined. We herein investigated the anti-cancer effects of two representative cardiac glycosides, digoxin and ouabain, in A549 and H460 cell lines. Both agents caused significant growth inhibition at nanomolar level. The cardiac glycosides were found to induce moderate G(2)/M arrest but not apoptosis at IC(50) level in the NSCLC cell lines. Moreover, autophagy was markedly induced by both agents, as evidenced by the time- and dose-dependent increase of LC3-II, up-regulation of Atg5 and Beclin1, as well as by the observations through acridine orange staining, transmission electron microscopy and quantification of GFP-LC3 fluorescence. Importantly, AMP-activated protein kinase (AMPK) pathway was activated, resulting in mammalian target of rapamycin (mTOR) deactivation during autophagy induction. Moreover, extracellular-signal-regulated kinase 1/2 (ERK1/2) activation was simultaneously found to be involved in the autophagy regulation. Co-treatment with respective inhibitors or siRNAs could either block the autophagic phenotypes and signals, or significantly increase the cellular viability, indicating the drugs-induced autophagy plays tumor-suppressing role. This work provides first evidence showing that the cardiac glycosides induce autophagy in human NSCLC cells through regulation of both mTOR and ERK1/2 signaling pathways. The autophagy may at least partially account for the growth inhibitory effects of the compounds in human NSCLC cells.

Copyright © 2012 Elsevier Ltd. All rights reserved.

PMID: 22750415