Resveratrol provoca mais apoptose em meio peri-tumoral ácido no câncer

Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer.


Source

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Abstract

Many critical factors such as hypoxia, nutrient deficiency, activation of glycolytic pathway/Warburg effect contribute to the observed low pH in tumors compared to normal tissue. Studies suggest that such tumor specific acidic environment can be exploited for the development of therapeutic strategies against cancer. Independent observations show reduction in pH of mammalian cells undergoing internucleosomal DNA fragmentation and apoptosis. As such, our group has extensively demonstrated that anticancer mechanisms of different plant polyphenols involve mobilization of endogenous copper and consequent internucleosomal DNA breakage. Copper is redox active metal, an essential component of chromatin and is sensitive to subtle pH changes in its microenvironment. Here we explored whether, acidic pH promotes growth inhibition, apoptosis and DNA damaging capacity of chemopreventive agent resveratrol. Our results reveal that growth inhibition and internucleosomal DNA fragmentation induced apoptosis in Capan-2 and Panc-28 pancreatic cancer cell lines (and not in normal HPDE cells) by resveratrol is enhanced at lower pH. Using comet assay, we further demonstrate that DNA breakage by resveratrol is enhanced with acidification. Membrane permeable copper specific chelator neocuproine (and not iron chelator orthophenanthroline) abrogated growth inhibition and apoptosis by resveratrol. Western blot results show enhanced activation of DNA laddering marker H2.aX by resveratrol at acidic pH that was reversed by neocuproine and not by orthophenanthroline. Our findings provide irrevocable proof that low pH

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PMID:
21678400