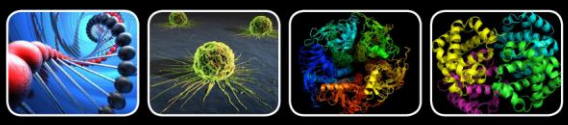

SPECIFIC CATEGORY
SVILUPPO E DIFFERENZIAMENTO E APOPTOSI, AMMINE BIOGENE

Okadaic acid-Parthenolide combination at subtoxic doses induces potent synergistic apoptotic effects in human retinoblastoma Y79 cells by upregulating PTEN.

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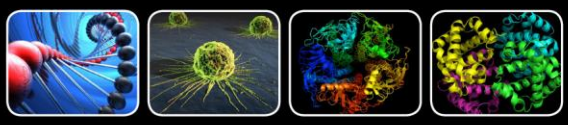
Retinoblastoma is the most common intraocular malignancy afflicting children. The incidence is higher in developing countries, where treatment is limited and long-term survival rates are low. Vincristine, etoposide, and carboplatin -the agents commonly used in the treatment of retinoblastoma- determine side effects causing significant morbidity to pediatric patients and significantly limiting dosing. Thus, identifying new drugs and molecular targets to facilitate the development of novel therapeutics, and finding natural drug combinations to kill cancer cells by synergistically acting at subtoxic doses, may be a good goal. Here, we investigated the effects of two natural compounds, okadaic acid (OKA) and parthenolide (PN), in human retinoblastoma Y79 cells. We showed that OKA/PN combination at subtoxic doses induces potent synergistic apoptotic effects accompanied by decrease in p-Akt, increase in the stabilized p53 forms and potent decrease in pS166–Mdm2. We also showed the key involvement of PTEN which, after OKA/PN treatment, potently increased before p53, suggesting that p53 activation was under PTEN action. PTEN-knockdown increased p-Akt/ pS166Mdm2 over basal levels and significantly lowered p53, while OKA/PN treatment failed both to lower p-Akt and pS166–Mdm2 and to increase p53 below/over their basal levels respectively. OKA/PN treatment potently increased ROS levels while decreased those of GSH. Reducing cellular GSH by butathionine-sulfoximine treatment significantly anticipated the cytotoxic effect exerted by OKA/PN. The effects of OKA/PN treatment on both GSH content and cell viability were less pronounced in PTEN silenced cells than in control cells.



Our study reports for the first time both a synergistic apoptotic action between OKA and PN and the involvement of PTEN as key player in the apoptotic mechanism in human retinoblastoma Y79 cells. The results provide strong suggestion for combined inhibition of the PTEN/Akt/Mdm2/p53 pathway.