



ASSOCIAZIONE ITALIANA
DI COLTURE CELLULARI
Onlus



UNIVERSITÀ DEGLI STUDI DI VERONA
Dipartimento Scienze della Vita e della Riproduzione
Sezione di Chimica Biologica

PROGRAMME & ABSTRACT BOOK

27th Annual Conference of Italian Association of Cell Cultures (ONLUS-AICC)

**OXIDATIVE STRESS AND CELL DEATH:
IMPLICATIONS IN CHRONIC-DEGENERATIVE
PROCESSES AND CANCER**

November 12th-13th, 2014

5th International Satellite Symposium AICC-GISM

**ADVANCES IN MESENCHYMAL
STEM CELL RESEARCH**

November 14th, 2014

Auditorium Banco Popolare
Viale delle Nazioni, 4 - Verona

27th
Annual Conference

Synergistic effect of the HDAC inhibitor SAHA and the sesquiterpene lactone parthenolide in triple negative breast cancer cells

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Objective

The sesquiterpene lactone Parthenolide (PN) exerts cytotoxic effects on MDA-MB231 cells, a triple-negative breast cancer (TNBC) cell line. However, PN is ineffective at low doses, thus restricting its therapeutic potential. This study shows that the association of the histone deacetylase inhibitor SAHA (suberoylanilide hydroxamic acid) to PN clearly improves the cytotoxic activity of this drug.

Materials and Methods: After a pre-treatment with 2 μ M SAHA for 20h, MDA-MB231 cells were co-incubated with SAHA/PN for various times. The analyses were performed by: MTT cell viability test, monodansylcadaverine staining for autophagy, AnnexinV-PI for apoptosis, colorimetric method for GSH, JC-1 test for mitochondrial membrane potential, fluorescence microscopy for Nrf2 localization, western blotting for factors involved in PN/SAHA molecular mechanism.

Results

Our results demonstrated that SAHA synergistically interacts with PN lowering MDA-MB231 cell viability. PN alone stimulated Akt/mTOR survival pathway and promoted the nuclear translocation of Nrf2, while treatment with SAHA alone induced an autophagic process. However when the cells were exposed to SAHA/PN combination, SAHA suppressed PN effect on Akt/mTOR/Nrf2 axis, while PN reduced SAHA-induced prosurvival autophagy. In addition combined treatment triggered apoptosis with GSH depletion, dissipation of $\Delta\psi$, release of cytochrome c and activation of caspase 3. We also demonstrated that SAHA/PN treatment maintained both H3 and H4 histone hyperacetylation induced by SAHA. Moreover, two important effects induced by PN, namely the down-regulation of DNMT1 expression as well as the inhibition of the DNA binding activity of NF- κ B were observed also after combined treatment.

Conclusions

We demonstrated that a synergistic interaction occurs between SAHA and PN and ascertained the molecular nature underlying their effect showing that PN/SAHA combination inhibits the cytoprotective responses induced by the single compounds, while does not alter the mechanisms leading to the cytotoxic effects.