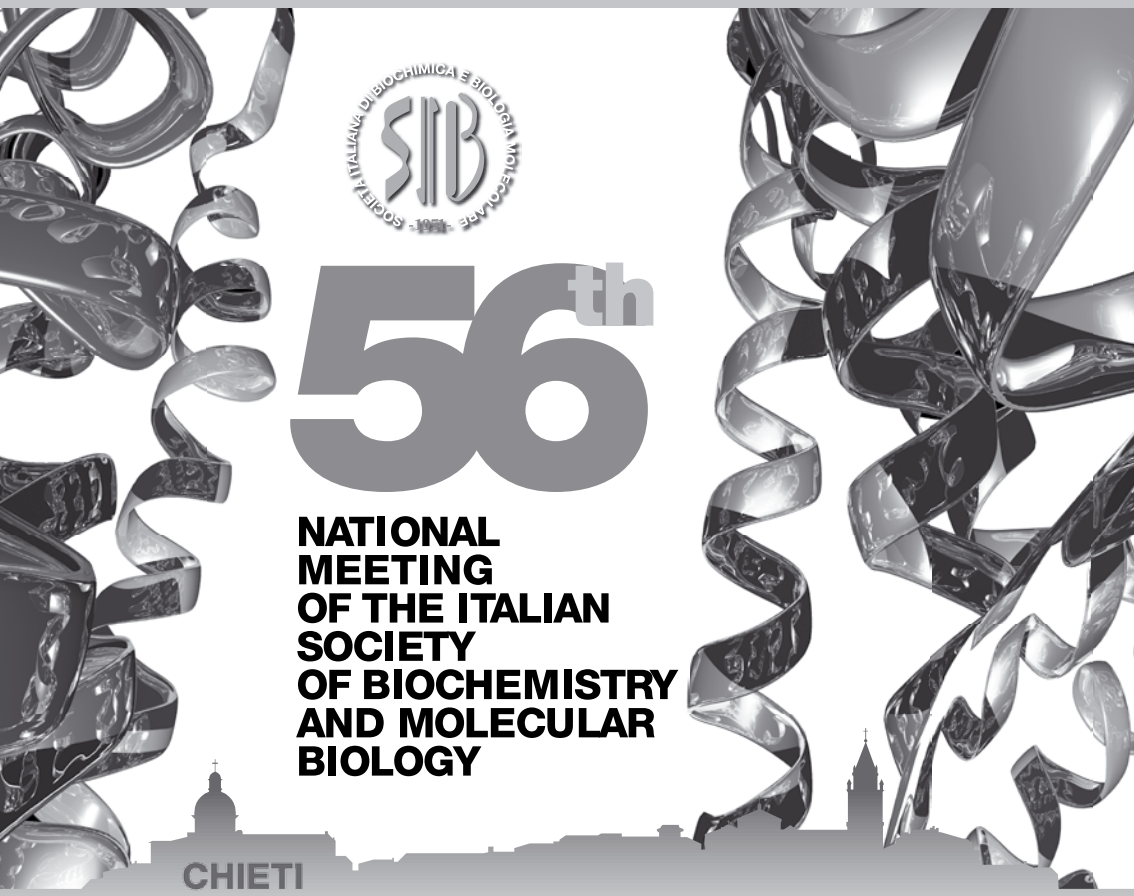

56th NATIONAL MEETING OF THE ITALIAN SOCIETY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

CHIETI
26th-29th SEPTEMBER 2012
Venue: New Rectorate Auditorium

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Parthenolide induces caspase-independent cell death in osteosarcoma, melanoma and breast cancer cells through the induction of oxidative stress

Carlisi Daniela, D'Anneo Antonella, Lauricella Marianna, Emanuele Sonia, Martinez Roberta, Vento Renza, Tesoriere Giovanni

Dipartimento di Biomedicina Sperimentale e Neuroscienze cliniche, Sezione di Scienze Biochimiche, Università degli Studi di Palermo

Parthenolide, a sesquiterpene lactone found in European feverfew, is used in traditional medicine for its anti-inflammatory activity. In addition, parthenolide has been considered as a novel and effective anti-tumor agent because it induces cytotoxic effects in several tumor cell lines.

Our studies demonstrated that parthenolide exerted strong cytotoxic effects in osteosarcoma MG63 and melanoma SK-Mel28 cells in culture. Staining with Hoechst 33342 revealed in most cells after brief periods of treatments (3-5h) chromatin condensation and fragmentation, while only few cells were PI-positive. Prolonging the treatment (5-14h) PI-positive cells strongly augmented, denouncing the increase of necrotic effects. All these effects were prevented by NAC, while caspase inhibitors were ineffective, thus suggesting a caspase-independent cell death. The study of the mechanism of action provided evidence that treatment with parthenolide rapidly stimulated (1-2 h) ROS generation, in particular by inducing activation of extracellular signal-regulated kinase1/2 and NADPH oxidase. This event caused depletion of thiol groups and glutathione, NF-$\varkappa$B inhibition, JNK activation and cell detachment from the matrix. ROS generation together with mitochondrial accumulation of Ca^{2+} favoured dissipation of $\Delta\psi m$, which appeared primarily determined by the opening of the permeability transition pore (PTP), since $\Delta\psi m$ loss was partially prevented by cyclosporin A, an inhibitor of PTP opening.

Recently, we focused our attention on MDA-MB231 cells, a very aggressive and poorly differentiated breast cancer cell line, which is negative for estrogen receptor alpha. Preliminary results suggested that parthenolide induced cell death in these cells with a mechanism similar to that demonstrated in osteosarcoma and melanoma cells. Interestingly, we demonstrated that in MDA-MB231 cells the effect of parthenolide was potentiated by the addition of z-VAD-fmk, a general inhibitor of caspases. Studies are in progress to elucidate the mechanism of this interaction which could suggest new strategies for the treatment of ER-α negative breast cancer.