

25° Convegno Annuale della Associazione Italiana di Colture Cellulari (ONLUS - AICC)

Controllo dei processi di proliferazione e morte cellulare
Nuovi sviluppi della ricerca oncologica preclinica

International Satellite Symposium AICC-GISM **Mesenchymal stem cells: growth factors and cytokines**

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Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche (BioNeC)
Sezione di Scienze Biochimiche

Evaluation of the *in vitro* and *in vivo* antineoplastic effects of Parthenolide on MDA-MB231 breast cancer cells

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Triple-negative breast cancer refers to an aggressive subtype of breast cancer in which the tumor cells lack receptors for estrogen, progesterone and the HER2 protein on their surfaces. This type of breast cancer does not respond to treatments such as hormone therapy, like tamoxifen and aromatase inhibitors, or drugs that target HER2, like Herceptin. It is important, therefore, the identification of new selective drugs for the treatment of these tumors.

Parthenolide (PN), a sesquiterpene lactone extracted from the medical plant *Tanacetum parthenium*, exerts anticancer activity on several tumor cell lines in culture, acting through diverse molecular mechanisms. Our previous studies have shown that the PN exerts strong cytotoxic effects on MG63 osteosarcoma and SK-Mel28 melanoma cells, through a caspase-independent mechanism which is associated with production of oxidative stress.

Recently, we have undertaken a study in order to investigate the antineoplastic activity of PN on MDA-MB231 cells, a triple-negative breast cancer cell line. Our results demonstrated that this compound reduced the viability of MDA-MB231 cells in a dose- and time- dependent manner. This effect was not prevented by the addition of z-VAD-fmk, a general inhibitor of caspase, thus suggesting a caspase-independent cell death. Time-course experiments provided evidence that the cytotoxic effect of PN occurs in two different phases. In the first phase of treatment (8h) cells resulted positive to monodansylcadaverine (MDC), a fluorochrome that binds to autophagic vacuoles. Prolonging the treatment (16h) MDC-positive cells lowered, and an increase of PI-positive population was found, suggesting the appearance of necrotic events. The study of the mode of PN action provided evidence that treatment with parthenolide induces ROS generation, activation of JNK and inhibition of NF- κ B activity. All these effects were prevented by the addition of NAC, thus suggesting the involvement of oxidative stress.

The antineoplastic activity of PN has been also assayed *in vivo* employing diamminoparthenolide (DMAPT), a soluble analogue of PN. Nude mice bearing breast carcinoma MDA-MB231 xenografts were treated daily with DMAPT (50 mg/Kg). It was observed that DMAPT increased survival of MDA-MB231 xenograft-bearing nude mice as well as reduced MDA-MB231 xenografts tumor growth. Moreover, immunohistochemical studies showed that DMAPT was able to decrease the expression of MMP-2, MMP-9 and VEGF, all factors involved in metastatic events.

These data suggest a possible use of parthenolide for the treatment of triple negative breast cancers.