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Controllo dei processi di proliferazione e morte cellulare

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Mesenchymal stem cells: growth factors and cytokines

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Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche (BioNeC)
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Parthenolide induces caspase-independent cell death mediated by AIF in osteosarcoma and melanoma cells

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Parthenolide, the major bioactive sesquiterpene lactone present in Feverfew (*Tanacetum parthenium)*, has recently attracted considerable attention because of its complex pharmacological action involving anti-microbial, anti-inflammatory and anti-cancer effects.
However, the mechanism of its cytotoxic effect on tumor cells still remains scarcely defined today.
The aim of this study was to analyse the mechanism of parthenolide action on two lines of cancer cells, the human osteosarcoma MG63 and the melanoma SK-MEL-28 cells, on which parthenolide exerted its action inducing similar effects.
Staining with Hoechst 33342 showed that parthenolide induced in the first phase of treatment (0-5 h) in most of cells of both the lines condensation of chromatin while only few cells were PI-positive. Moreover, cells assumed a rounded shape, detached from substrate and showed a reduction of their volume. In the second phase of treatment (5-15 h) a progressive increase in the percentages of PI-positive cells was observed, suggesting that extensive damage of cellular plasma membranes occurred only after long periods of treatment. All these events were not counteracted by z-VAD-fmk and other caspase inhibitors, but were dependent on oxidative stress. In fact the study of mechanism of action of partenolide revealed that all cytotoxic effects were prevented by NAC and after a short period of time (1-2 h) ROS production occurred by inducing activation of extracellular signal-regulated kinase1/2 (ERK1/2) and NADPH oxidase. This event caused depletion of thiol groups and glutathione, NF-kB inhibition, JNK activation, cell detachment from the matrix and cellular shrinkage. The increase of ROS generation together with the mitochondrial accumulation of Ca^{2+} also favoured dissipation of $\Delta\psi m$, which seemed primarily determined by PTP opening, since ψm loss was partially prevented by the inhibitor cyclosporin A. In addition, immunofluorescence analysis revealed that at this stage AIF translocated from mitochondria to the nucleus and co-localized with areas of condensed chromatin. Prolonging the treatment (5-15h) ATP content declined while PI-positive cells strongly augmented, denouncing the increase of necrotic effects. All these effects were prevented by NAC, while caspase inhibitors were ineffective. We suggest that AIF exerts a crucial role in parthenolide action. In accordance, down-regulation of AIF markedly inhibited parthenolide effect on the production of cells with apoptotic or necrotic signs.
Taken together our results demonstrate that parthenolide causes in the two cell lines a caspase-independent cell death, which is mediated by AIF.