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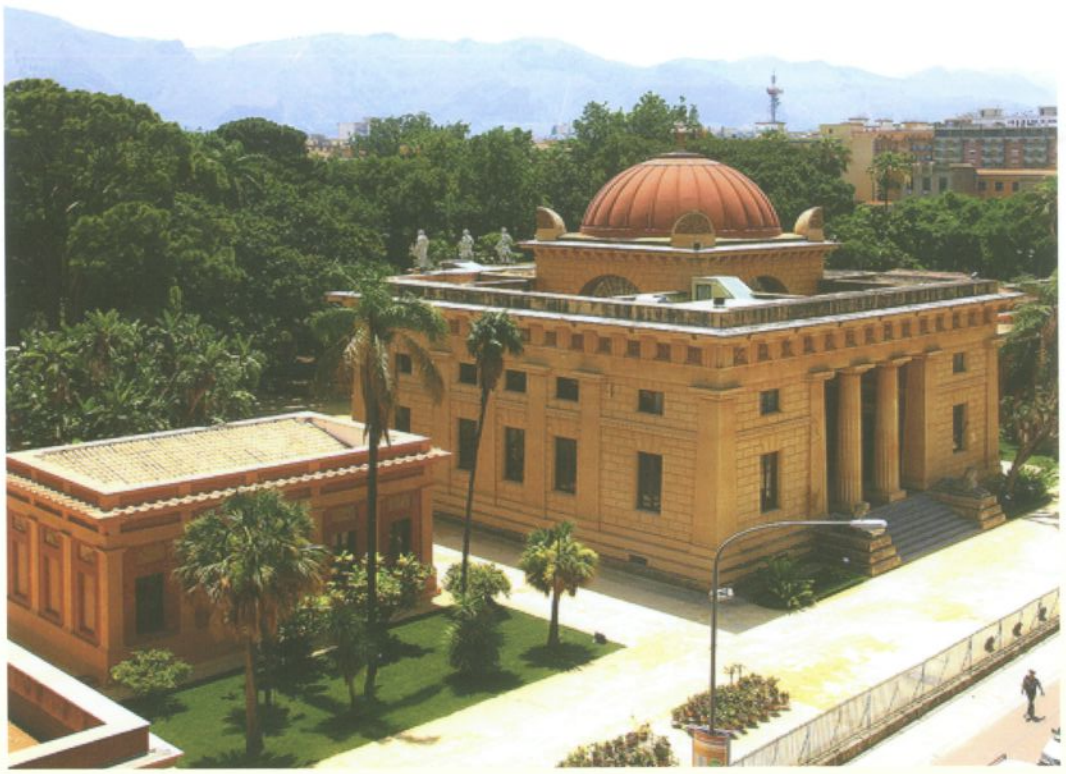

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Different expression of PPARs in WIN-treated cells: the game of roles

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Peroxisome Proliferator-Activated Receptors (PPARs) are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily. PPARs have been implicated in many normal and disease-related processes including lipid and energy metabolism, inflammation, diabetes and cancer. There are three main isotypes of PPARs: PPARα, PPARβ/δ, and PPARγ, which are distinguished by tissue- and developmental-specific patterns of expression and by the distinct nature of ligands. Although many reports demonstrate that PPARs are involved in the inhibition of malignant cell growth, they are also indicated as tumor promoters. The ability of PPARs to promote or suppress tumorigenesis seems to be related to cell type, tumor grading or differentiative stage. Moreover, mounting evidence addresses PPARs as additional targets of cannabinoids, a class of chemical compounds with a wide range of central and peripheral effects. Cannabinoids also exert anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-invasive effects in different in vitro and animal models of cancer.

The aim of the present study was to investigate the involvement of PPARs in the cytotoxic effects induced by WIN55,212-2 (WIN), a potent synthetic ligand of cannabinoid receptors, in different cancer cells in culture.

In HepG2 hepatocellular carcinoma cells WIN induces apoptosis with a marked increase in PPARγ level which anticipated and contributed to the cytotoxic effect of the drug. In fact, the addition of GW9662 and T007, two specific inhibitors of PPARγ, markedly counteracts WIN cytotoxicity.

On the contrary, in HT29 colon carcinoma cells WIN induces a marked reduction in PPARγ levels and up-regulation of the main markers of ER stress, CHOP, TRB3 and GRP78. These events stimulate the activation of an autophagic and apoptotic interplay which is responsible for the strong cytotoxic effects induced by the cannabinoid. In fact, in the first phase of WIN treatment (8-16 h) we observe the appearance of the typical autophagic markers (formation of acidic vacuoles, increase in the levels of beclin-1 and LC3-II) which are reverted in the presence of the autophagy inhibitor 3-methyladenine. After prolonged exposure to the cannabinoid (36 h), the apoptotic signals overtake the autophagic ones.

The pharmacological inhibition of PPARγ or its down-regulation by gene-silencing mimics WIN effects in HT29 cells thus indicating that the induction of ER stress and the activation of the autophagic pathway are strongly dependent on PPARγ-decrease.

In another colon carcinoma cell line, HCT116, WIN induces cytotoxic effects similar to those described in HT29 cells but, differently from the last ones, they are not related to changes in PPARγ level. Instead, we observe a marked and time-dependent increase in the levels of the isotype α of PPAR receptor after WIN treatment. A role for PPARα in WIN signalling seems to be confirmed by our preliminary data which indicate that the pharmacological inhibition of PPARα counteracts WIN effects.

Studies are currently underway to find answers regarding the different behaviour of PPAR isoforms following cannabinoid treatment. We believe that this study represents an interesting source of speculation on the action mechanism of cannabinoids and on the different role of PPARs in the control of the switch between cell survival and cell death.