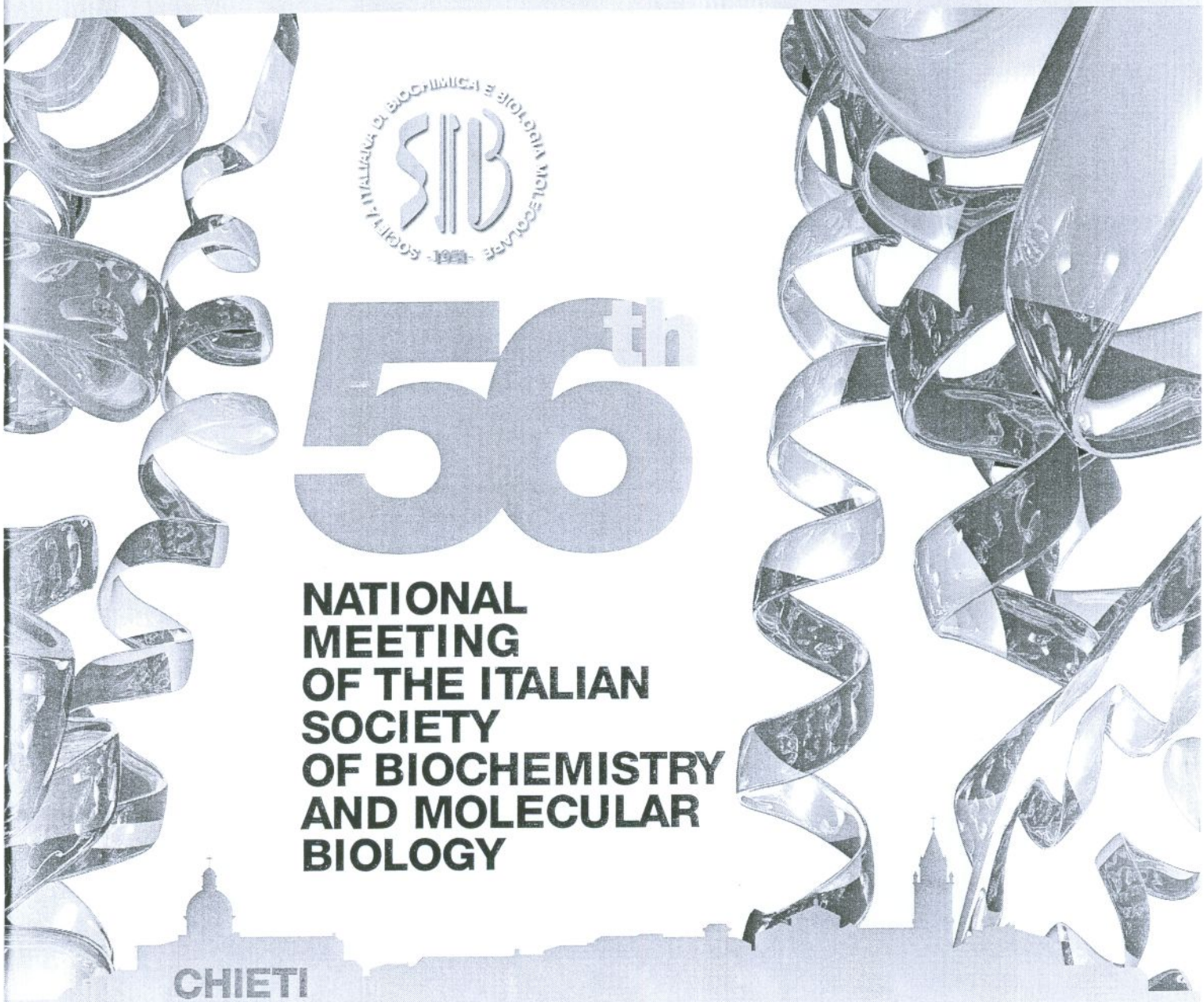

56th NATIONAL MEETING OF THE ITALIAN SOCIETY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

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

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Autophagy and ER-stress participate to cannabinoid-induced apoptosis in colon carcinoma cells

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Autophagy is a highly conserved cellular process wherein cytoplasmic materials, including organelles, are sequestered into double-membrane vesicles called autophagosomes and delivered to lysosomes for degradation or recycling. Besides its role in cellular homeostasis, autophagy represents a form of programmed cell death, designated "type II programmed cell death". Accordingly, autophagy has been proposed to play an important role in both tumor progression and cancer cell death. It is known that autophagy is also involved in the action mechanism induced by cannabinoids, a class of compounds which exert a wide variety of biological effects. In this study, we investigated the effects of the synthetic cannabinoid WIN55,212-2 on the growth of HT29 colon carcinoma cell line. WIN was capable to curb cell growth by inducing an apoptotic pathway which was preceded by ER-stress, as confirmed by the increase in ER-stress sensors such as GRP78, CHOP and TRB3. Moreover, WIN treatment triggered an autophagic pathway with the increase in the level of beclin-1 in the early phase of treatment and a progressive time-dependent conversion of LC3-I to LC3-II. We confirmed the induction of autophagic process using monodansylcadaverine, a fluorescent molecule, which is employed as a selective marker for autophagic vacuoles and especially acidic autophagolysosomes.

To understand the role of autophagy in WIN-induced apoptosis in HT29 cells, we employed 3-MA, a specific inhibitor of autophagic process. We observed that in the first phase of treatment autophagy inhibition counteract WIN-induced cell death as if autophagy was an important step of cell death induction. Differently, after prolonged treatment, 3-MA was no longer able to counteract WIN effects; this probably was a consequence of the activation of apoptotic cell death mediated by the high levels of CHOP. In fact, CHOP down-regulation by gene silencing induced a decrease in the levels of autophagy markers and delayed WIN-mediated apoptotic events.