

## **OLEUROPEIN-INDUCED APOPTOSIS IS MEDIATED BY MITOCHONDRIAL GLYOXALASE 2 IN NSCLC A549 CELLS: A MECHANISTIC INSIGHT**

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Oleuropein (OP) is a bioactive compound derived from plants of the genus Oleaceae exhibiting anti-tumor properties in several human cancers, including non-small-cell lung cancer (NSCLC). Recent evidence suggests that OP has pro-apoptotic effects on NSCLC cells via the mitochondrial apoptotic pathway. However, the exact molecular mechanisms behind the apoptogenic action of OP in NSCLC are still largely unknown. Glyoxalase 2 (Glo2) is an ancient enzyme belonging to the glyoxalase system involved in the detoxification of glycolysis-derived methylglyoxal. However, emerging evidence suggests that Glo2 may have also non-enzymatic roles in some malignant cells. In the present study we evaluated whether and how Glo2 participated in the pro-apoptotic effects of OP in NSCLC A549 cells. Our results indicate that OP is able to induce apoptosis in A549 cells through the up-regulation of mitochondrial Glo2 (mGlo2), mediated by the superoxide anion and Akt signalling pathway. Moreover, our data shows that the pro-apoptotic role of mGlo2, observed following OP exposure occurs via the interaction of mGlo2 with the pro-apoptotic Bax protein. Conversely, OP does not alter the behavior of non-malignant human BEAS-2B cells or mGlo2 expression, thus suggesting a specific anti-cancer role for this bioactive compound in NSCLC. Our data identify a novel pathway through which OP exerts a pro-apoptotic effect in NSCLC and suggest, for the first time, a novel, non-enzymatic anti-apoptotic role for this ancient enzyme in NSCLC.

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