Mechanisms Involved in the Anti-carcinogenic Effects of Olive Oil Phenols

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Epidemiological studies demonstrated that olive oil consumption is associated to a reduced risk of cancer in different sites. These evidences are supported by animal and in vitro studies showing that the cancer protective activity of olive oil could be mediated by the presence of potent antioxidant phenols which are able to inhibit both initiation and promotion steps of carcinogenesis. In this study we investigated the effects of one of the main olive oil phenol, hydroxytyrosol (3,4-dihydroxyphenylethanol; 3,4-DHPEA), of some other purified compounds (3,4- DHPEA-EDA and *p*HPEA-EDA) and of complex mixture of olive oil phenols extract on proliferation, cell cycle progression, apoptosis and differentiation of HL60 human promyelocytic leukemia cells. We confirm our previous results showing that 3,4-DHPEA and other related compounds inhibit proliferation and induce apoptosis in these cells. In addition, we show a potent inhibitory activity of the above reported compounds and olive oilextract on DNA synthesis and on the progression of cell cycle in synchronized HL60 cells resulting in a accumulation in the G_0/G_1 phase. It was furthermore found that 3,4-DHPEA and olive oil extracts are able to induce differentiation in a conspicuous number of HL60 cells. Among the different proteins involved in the regulation of the cell cycle 3,4-DHPEA reduced the level of cyclin-dependent kinase 6 (CDK6) and increased that of cyclin D3, whereas the expression of cyclins B1, E, and A were not significantly modified. Regarding the CDK inhibitors, p15 was not altered by 3,4-DHPEA treatment while the expression of $p21^{WAF1/Cip1}$ and $p27^{Kip1}$ was increased at both protein and mRNA levels. Since the main substrate target for the phosphorylation activity of CDK is the pRB (Retinoblastoma Protein) further experiments are in progress to investigate the phosphorilation state of this protein after treatment of HL60 cells with 3,4-DHPEA. In addition, we are clarifying whether the different effects above reported are dependent on the anti-oxidant/pro-oxidant properties of 3,4-DHPEA.