Hydroxytyrosol inhibits EGFR signaling and enhances the antitumor effects of EGFR inhibitors in colorectal cancer

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We demonstrated that hydroxytyrosol (HT), a polyphenol of olive oil, downregulates epidermal growth factor (EGFR) expression and cell proliferation in colon cancer cells (Terzuoli et al., 2016). The molecular mechanisms by which it causes growth arrest and whether it might enhance the therapeutic potential of EGFR inhibitor is unknown. In this work, we studied whether the treatment of human colon cancer HT-29 and WiDr cells with HT could enhance the inhibitory effect of the monoclonal antibody against EGFR cetuximab, on cell proliferation and clonogenic potential. We observed that in the combination, HT-induced down-shift of cetuximab potency, without compromising its antitumor efficacy. We demonstrated that inhibition of HT-29 and WiDr cell proliferation was associated with cell cycle arrest at G1/S and G2/M phases, and with apoptosis, measured as sub G0/G1 peak. At molecular level, the combination of low concentrations of HT and cetuximab reduced the expression of cyclins B, D1, and E, and cyclin-dependent kinase (CDK) 2, CDK4, and CDK6 proteins, and induced expression of CDK inhibitors p21 and p27. Further, the combination of the two molecules also promoted AIF-mediated apoptosis and regulated cell autophagy. No effects were observed on human keratinocytes or colon fibroblasts exposed on HT and cetuximab, suggesting that an appropriate diet might considerably attenuate the severe side effects (e.g.. skin disturbances) often associated with cetuximab and other agents with similar mechanism, which are commonly administered at maximal effective doses. We concluded that HT may be a competent therapeutic agent in colorectal cancer where it can enhance the effects of EGFR inhibitors.

References

Terzuoli E, Giachetti A, Ziche M, Donnini S. Hydroxytyrosol, a product from olive oil, reduces colon cancer growth by enhancing epidermal growth factor receptor degradation. Mol Nutr Food Res. 2016 Mar;60(3):519-29.

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