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Non-Canonical Beclin-1-Independent Autophagy and Apoptosis in Cell Death Induced by Rhus coriaria in Human Colon HT-29 Cancer Cells

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Abstract : Background: Cancer therapies have witnessed great advances in the recent past, however, cancer continues to be a leading cause of death, with colorectal cancer being the fourth cause of cancer-related deaths. Colorectal cancer affects both sexes equally with poor survival rate once it metastasizes. Phytochemicals, which are plant derived compounds, have been on a steady rise as anti-cancer drugs due to the accumulation of evidences that support their potential. Here, we investigated the anticancer effect of Rhus coriaria on colon cancer cells. Material and Method: Human colon cancer HT-29 cell line was used. Protein expression and protein phosphorylation were examined using Western blotting. Transcription activity was measure using Quantitative RT-PCR. Human tumoral clonogenic assay was used to assess cell survival. Senescence was assessed by the senescence-associated beta-galactosidase assay. Results: Rhus coriaria extract (RCE) was found to significantly inhibit the viability and colony growth of human HT-29 colon cancer cells. RCE induced senescence and cell cycle arrest at G1 phase. These changes were concomitant with upregulation of p21, p16, downregulation of cyclin D1, p27, c-myc and expression of Senescence-associated-β-Galactosidase activity. Moreover, RCE induced non-canonical beclin-1independent autophagy and subsequent apoptotic cell death through activation of activation caspase 8 and caspase 7. The blocking of autophagy by 3-methyladenine (3-MA) or chloroquine (CQ) reduced RCE-induced cell death. Further, RCE induced DNA damage, reduced mutant p53 protein level and downregulated phospho-AKT and phospho-mTOR, events that preceded autophagy. Mechanistically, we found that RCE inhibited the AKT and mTOR pathway, a regulator of autophagy, by promoting the proteasome-dependent degradation of both AKT and mTOR proteins. Conclusion: Our findings provide strong evidence that Rhus coriaria possesses strong anti-colon cancer activity through induction of senescence and autophagic cell death, making it a promising alternative or adjunct therapeutic candidate against colon cancer.

Keywords : autophagy, proteasome degradation, senescence, mTOR, apoptosis, Beclin-1
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