Inhibition of autophagy enhances Dihydroartemisinin (DHA)-induced cytotoxicity

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Artemisinin (ART) and its derivatives are effective for malaria treatment and also have shown potential anti-cancer activities in various cancer types. Dihydroartemisinin (DHA), an analogue of ART, is more potent than ART in inhibiting tumor cell proliferation. In our study, DHA exhibits antiproliferative activity in several solid tumors, especially against colorectal cancer (CRC) HCT116 cells. DHA suppresses cell proliferation and induces caspase-dependent apoptosis without inducing necrosis-like cell death in HCT116 cells. In addition, DHA interferes autophagy pathway by upregulating of LC3 II formation in HCT116 cells. Inhibition of autophagy with either autophagy inhibitor 3-methyladenine (3MA) or KD of ATG5 potentiated DHA-induced cell death. We found DHA increased expression level of DR5 while had no effect on DR4 expression level on surface of tumor cells. Further, cell-surface DR5 expression was significantly elevated in DHA-treated ATG5-KD cells. These findings suggest that inhibition of the autophagy enhances DHA-induced cytotoxicity through DR5 upregulation.