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The low-molecular-weight compound MS-444 selectively targets cancer cells via inhibition of the mRNA stability factor HuR

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Colorectal cancer (CRC) is the third most common cancer among American adults and a leading cause of cancer-related mortality. The initiation and progression of colorectal tumorigenesis is characterized by genetic alterations that promote aberrant expression of oncogenic and tumor-promoting factors. In normal cells, the mRNAs of these inflammation- and cancer-associated genes are targeted for rapid decay through AU-rich elements (ARE) present in the mRNA 3'UTR. However, loss of ARE-mediated mRNA decay is a characteristic feature contributing to pathogenic gene overexpression in colorectal cancer. Our prior work identified enhanced expression of the RNA-binding protein HuR to occur during colon tumorigenesis and HuR overexpression is correlated with poor clinical prognosis. In this capacity, HuR acts as a mRNA stability factor by promoting ARE-containing mRNA stabilization. Therefore, HuR has emerged as a novel pharmacological target with potential selectivity for cancer cells. This was examined by treating HuR-overexpressing CRC cell lines HCT116, SW480, RKO, and HT-29 with the small molecule inhibitor of HuR MS-444. Growth inhibition was observed in all CRC lines with IC50 values of 7-12 μM and cancer cell selectivity was observed with 4- to 5-fold increased MS-444 IC_{50} in non-transformed intestinal and colonic epithelial cells. HuR is predominantly nuclear in non-transformed cells, whereas in CRC cells aberrant cytoplasmic HuR trafficking is observed indicating that cytoplasmic localization is a necessary component for HuR-mediated ARE-mRNA stabilization and cancer cell survival. In HCT116 cells treated with MS-444, complete inhibition of cytoplasmic HuR was observed along with induction of apoptosis. Similarly, long-term siRNA-mediated knockdown of HuR in HCT116 cells resulted in cellular apoptosis, and cells with attenuated levels of HuR exhibited a 5-fold higher sensitivity to MS-444 treatment. Taken together, these findings indicate that small molecule-based inhibition of HuR results in selective cancer cell death while also indicating that overexpression of HuR is a necessary component for colorectal tumor cell survival.