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OVEREXPRESSION OF THE RNA-BINDING PROTEIN HUR IMPAIRS TUMOR GROWTH IN TRIPLE NEGATIVE BREAST CANCER ASSOCIATED WITH DEFICIENT ANGIOGENESIS

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Breast cancer is the second most common cancer in women and causes the death of 519,000 people worldwide. Many cancer genes are posttranscriptionally regulated by RNA-binding proteins (RBPs) and microRNAs. The RBP HuR binds to the AU-rich (ARE) regions of labile mRNAs, such as proto-oncogenes, stabilizing their mRNA and facilitating their translation into protein. HuR has been described to control genes in multiple areas of the acquired capabilities model of cancer and has been hypothesized to be a tumor-maintenance gene, allowing for cancers to proliferate once they are established. We investigated the role of HuR in aggressive and difficult to treat triple-negative breast cancer. MDA-MB-231 cells with higher levels of HuR had alterations in cell cycle kinetics and faster growth. Unexpectedly, HuR overexpression significantly interfered with tumor growth in orthotopic mouse models. Tumors overexpressing HuR had fewer blood vessels and less apoptosis than the control tumors. Microarray analysis revealed several genes overexpressed in the tumors with higher levels of HuR, including anti-angiogenic TSP1 and TSP2. Further analysis revealed TSP1 mRNA stability to be significantly increased in the cells overexpressing HuR. Additionally, VEGFα was found to be downregulated at the mRNA and protein levels in the tumors overexpressing HuR. Therefore, the putative mechanism seems to be an anti-angiogenetic effect by increasing expression of TSP1 but also surprisingly, down-regulating VEGFα, a target which HuR normally increases. An approach of modulating HuR levels may overcome limitations associated with monotherapies targeting tumor vessel formation.