CRISPR/Cas9-Mediated Knockout of AEG-1 Promotes Sensitivity to Sorafenib in Human Hepatocellular Carcinoma (HCC)

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Hepatocellular carcinoma (HCC) is the most common form of liver cancer and is the third leading cause of cancer-related death worldwide. Over 90 percent of these cancer-related deaths are due to drug resistance or metastasis. Sorafenib, the only FDA-approved drug for advanced stage liver cancer, has shown increasing chemoresistance especially at higher doses. AEG-1 is an oncogene and a key regulator of HCC. Therefore, the purpose of this experiment is to determine the effect of CRISPR/Cas9-mediated AEG-1 knockout on human HCC cells, including the effect of the gene in HCC's resistance to Sorafenib. Three cell lines (AEG-1 knockout, partial knockout, no knockout) were established and characterized for their cancerous properties along with their susceptibility to Sorafenib (2.5, 5.0, 10.0 μM). MTT, colony formation, and migration assays were used to measure the proliferative and metastasizing properties of the cells. The AEG-1 KO cell line (A3) displayed significantly decreased proliferation and migration relative to the control (A26) over 72 hours ($p<0.01$). A two-way ANOVA of colony formation assays with Sorafenib treatments indicated that the main effect of cell line and treatment were significant and that Sorafenib was effective in a dose-dependent manner ($p<0.01$). Thus, AEG-1 knockout significantly reduces chemoresistance to Sorafenib and is a potential combinatorial therapy to treat HCC. This was the first experiment to knockout AEG-1 using CRISPR/Cas9 and to investigate its role in Sorafenib resistance. Future studies include investigating the apoptotic and DNA repair pathways associated with Sorafenib resistance in HCC.