Exploring the Effects of GRN on Chemotherapy Response in Small Cell Lung Cancer

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Lung cancer is the second most prominent type of cancer and accounts for the most cancer-related deaths each year. Small cell lung cancer, a major subtype of lung cancer, has a 5-year survival rate of merely 6%. Patients respond well to initial rounds of chemotherapy, but most patients relapse and become resistant to treatment. Using a previously defined gene signature associated with chemotherapy response and a novel SCLC Bayesian Network, granulin (GRN) was identified as a key driver for both poor prognostic signatures and etoposide-cisplatin negative responsive genes. This study aims to elucidate the role of GRN in mediating resistance to chemotherapy response in small cell lung cancer. First, cell lines were identified with varying levels of GRN expression and correlated to cisplatin-etoposide response. GRN expression was either ablated in GRN high cell lines via CRISPR/Cas9 or was overexpressed in GRN low cell lines utilizing viral vectors and followed with investigating chemotherapy response. I found that GRN expression confers resistance to cisplatin-etoposide treatment. Transcriptomic profiling revealed neuronal development genes were upregulated with the expression of GRN. Additionally, genes upregulated with exogenous GRN expression included genes from cisplatin-resistant signatures derived from patient derived xenografts providing mechanistic insight for altered chemotherapy response. Utilizing CMap datasets, I identified CCK B inhibitors as GRN-antagonizing compounds. I performed combination therapy with this compound and cisplatin-etoposide, which significantly sensitized resistant SCLC cell lines to treatment. The findings of this study imply GRN as a novel biomarker associated with resistance to chemotherapy in SCLC.