DaJhnae Gambrell-Sanders

Enhancing the therapeutic efficacy of FTI tipifarnib in HRAS-mutant head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a significant public health problem. RAS is a membrane-associated GTPase protein that is a well established driver for cancer progression. HRAS is the only oncoprotein whose signaling can be inhibited through delocalization by farnesyl transferase inhibitors (FTIs). One therapeutic inhibition of this RAS isoform is inhibiting the enzymes that target the RAS CAAX tetrapeptide motif in order to prevent membrane association. This inhibition is encouraging because HRAS requires membrane localization in order to perform critical biological processes. Recent clinical trials treating HRAS-mutant HNSCC with FTI tipifarnib have shown encouraging results, but there is room for improvement. A CRISPR screening was performed to identify targets that would sensitize HRAS mutant HNSCC to tipifarnib; the genetic screening identified regulators of the MAPK pathway as a sensitizer. We hypothesized that low doses of tipifarnib in combination with previously studied doses of ERK inhibitors would cause significant cell death and inhibit HRAS. I first evaluated the effect of a range of doses of tipifarnib by immunoblotting for the loss of HRAS through phase separation. I then evaluated apoptosis in HNSCC with the combination of tipifarnib and ERK inhibitors using flow cytometry. The results showed that some cell lines were more synergistic than others, but the combination treatment does enhance apoptosis and inhibit growth of HNSCC. Further studies are needed to evaluate why some cell lines are more synergistic than others.