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My research program is centered on the study of microRNA regulation of cell viability and drug response in cancer, and is aimed at developing sensitive, non-invasive methods for early cancer detection and novel therapeutic agents targeting specific cancer subtypes. We have four ongoing projects: microRNA regulation of (1) drug response in non-small cell lung carcinoma (NSCLC), (2) cell viability in neuroendocrine tumors, (3) cell viability of KRAS-dependent lung cancers, and (4) PI3K and drug response in PI3K-driven oncogenesis. All of the projects integrate *in silico*, *in vitro* and *in vivo* approaches.

In an unbiased and comprehensive approach, we have combined a high-throughput screening platform with a library of chemically synthesized microRNA mimics and inhibitors. We have used this platform to identify mimics and inhibitors that reduce cell viability in general, and those that specifically sensitize cells to taxanes.

We have identified several miRNAs for which over-expression or inhibition has a dramatic and selective effect on cell viability or drug response. We have demonstrated that miR-337-3p mimic sensitizes NSCLC cells to taxanes. By combining *in vitro* and *in silico* approaches, we identified STAT3 and RAP1A as direct targets that mediate the effect of miR-337-3p by enhancing taxane-induced arrest in the G2 phase of the cell cycle. We have also identified an inhibitor of miR-139-5p as a potent and selective regulator of SCLC cell viability. Inhibiting miR-139-5p decreases SCLC cell viability by over 80%, but has a minimal cytotoxic effect on that of NSCLCs or immortalized human bronchial epithelial cells. We are currently investigating the targets of miR-139-5p that mediate its effect on SCLC cell viability.

An inhibitor of miR-10a has the opposite effect and increases cell viability in NSCLC cells. Manipulation of miR-10a levels alters cellular response to paclitaxel and results in significant changes in both mRNA and protein levels of its predicted target, the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which has been shown to play a major role in proliferation and survival in a number of human cancers and is a significant therapeutic target. In NSCLC patients, high miR-10a levels correlate with longer overall survival, suggesting that miR-10a levels may be correlated with patient response to chemotherapy, especially PI3K inhibitors.

These investigations have contributed to our understanding of microRNA roles in and beyond lung cancer pathogenesis and have established a foundation on which we can build in several orthogonal directions. We are extending the work to drugs with different mechanisms of action, to different histological subtypes of lung cancer, and finally to different cancer types, including breast cancer, neuroblastoma and pheochromocytoma. There are few cancers for which detection is so efficient and drug response so thorough that a better understanding of the mechanisms by which microRNAs control tumor cell survival and how they can serve as the basis for improved diagnostic strategies or increased therapeutic efficacy cannot be achieved.