AU-rich elements (AREs) are highly conserved mRNA 3’-untranslated region (UTR) regulatory elements while microRNAs are small noncoding RNAs that target distinct 3’UTR sites and control post-transcriptional gene expression of clinically relevant messages, including those of cytokines and potent growth factors. MicroRNAs, like AREs, are known post-transcriptional regulators in cell proliferation, development and death. Their deregulation leads to rapid and dramatic changes in expression levels promoting a broad range of critical effects, including tumor growth, chemoresistance, metastasis, recurrences, several types of leukemias, lymphomas and developmental disorders.

The primary goal of our research program is to investigate the underlying mechanisms of gene expression control of critical, cancer-associated cytokine and growth factor genes by noncoding RNAs, microRNAs and AREs, as well as their interactions and synergisms with RNA binding protein complexes (RNPs) in response to quiescent and hypoxic conditions in tumors that lead to tumor progression and recurrence. A complementary direction is to investigate the regulation of expression and function of microRNAs and RNPs by distinct cellular conditions, in particular, in response to quiescent and hypoxic conditions in tumors and germ cells. An important focus of our research is to functionally characterize the selective interactions between regulatory noncoding RNAs, RNPs, and their mRNA targets that encode for critical growth and cell state regulators, and to develop specific therapeutic approaches against tumor resistance and recurrence.

Several studies indicate that cells that survive clinical therapy include dormant, quiescent GO-like cells, observed as a small—but clinically relevant—population in leukemias.
Regulation of gene expression in cancer by noncoding RNAs and RNPs.

and in several solid tumors associated with poor survival rates. Quiescence or G0 is a unique, adaptive, nonproliferating state that provides an advantageous escape from harsh situations and chemotherapy, allowing cells to evade permanent outcomes of tumor-negative environments such as senescence, differentiation or apoptosis. Instead, the cell is suspended reversibly in an assortment of transition phases that retain the ability to return to proliferation and contribute to tumor heterogeneity, resistance and recurrence. Quiescence involves gene expression reprogramming, upregulating those mRNAs and regulatory RNAs—including specific microRNAs—required for survival and persistence in the G0 state. The key finding of our studies on cytokine and growth factor gene expression, which forms the basis of our research program, is that AREs, microRNAs and RNPs are transformed by such cellular conditions to alter expression patterns of specific, clinically important genes. We further identified post-transcriptional effectors associated with these RNAs under distinct conditions by developing an in vivo crosslinking-coupled affinity purification method to purify endogenous RNP complexes. These findings opened a novel, unexplored area of research into gene expression control in response to tumor-associated conditions by highly potent RNA regulators, and have major implications for understanding gene expression that contributes to tumor progression, resistance and recurrence.

The lab has four core directions:

1. To functionally characterize microRNAs and specific noncoding regulatory RNAs and identify their associated cofactors and target mRNAs that control expression of clinically important cytokines, cancer and cell state regulators, using previously developed in vivo crosslinking coupled affinity purification methods and confirmatory assays.

2. To investigate the mechanism of gene expression control and interconnections of the identified RNA regulators, AREs, microRNA target sites and RNPs.

3. To elucidate the regulation of expression and function of microRNAs, AREs and RNPs by specific cellular conditions.

4. To characterize the selective interactions between small regulatory RNAs and their mRNA targets in order to develop antisense manipulations of these interactions as specific therapeutic approaches. These studies should lead to a greater understanding of the versatile role of regulatory small noncoding RNAs in the pathogenesis of cancers and to novel approaches in RNA-based therapeutic applications.

Selected Publications:


