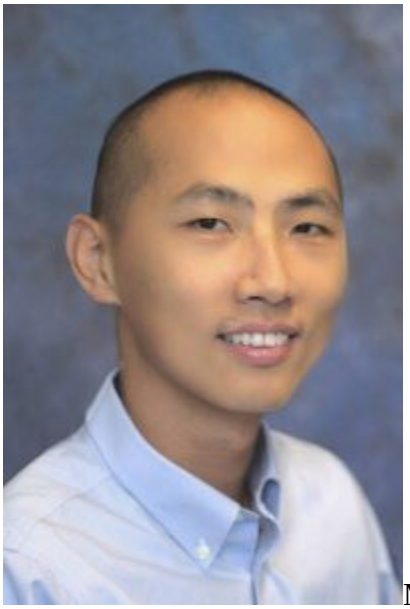
UFHealth Cancer Center

When microRNAs Clash With Their Targets

Mingyi Xie's, Ph.D., lab in the department of biochemistry and molecular biology, College of Medicine at the University of Florida studies RNA processing mechanisms that drive cancer development. They focus on a class of small RNA, called "microRNA", in gene regulation. MicroRNAs can bind to messenger RNAs (mRNAs) and reduce their stability or block their translation into proteins. Dysregulation of microRNAs has been implicated in the development of different kinds of cancer.

In a recent study entitled "Sequencing of Argonaute-bound microRNA/mRNA hybrids reveals regulation of the unfolded protein response by microRNA-320a," published in PLOS Genetics on December 16, 2021, PhD student Christopher Fields used an innovative biochemical method called "CLASH" to identify microRNA function in cultured colorectal cancer cells. From the study, the researchers found that a specific microRNA, microRNA-320a, regulates the integrated stress response.


Mingyi Xie, Ph.D.

The use of CLASH also identified RNAs involved in Target RNA-Directed miRNA Degradation (TDMD). TDMD is an exciting new area of research in microRNA biology. Degradation of a specific microRNA can affect a wide gene regulatory network controlled by this microRNA, providing rapid response to environmental cues. To date, only three human RNAs were known to

trigger microRNA degradation. In the study entitled "Widespread microRNA degradation elements in target mRNAs can assist the encoded proteins," which was published in *Genes & Development on December 1st, 2021* , post-doctoral researchers Lu Li, Ph.D., and Peike Sheng, Ph.D., significantly expanded the repertoire of TDMD trigger RNAs to more than a dozen by creatively analyzing the CLASH data, focusing on microRNA modifications specific to TDMD events. They found a TDMD trigger in an mRNA that encodes a protein critical for inducing programed cell death. Interestingly, this trigger sequence clears out two microRNAs that counteract cell death. Therefore, a novel gene regulation mechanism emerged: the protein coding sequence and the TDMD trigger of the mRNA act as partners in crime to efficiently kill the cells.

In the future, the Xie Lab will be collaborating with Rolf Renne, Ph.D, and Thomas George, M.D. groups at the UF College of Medicine to perform CLASH in patient samples to further expand our understanding of the microRNA targeting and microRNA degradation mechanisms that drive colorectal cancer.