

Regulation of gene expression and promotion of genome integrity by RNAi related pathways in *C. elegans*.

In RNAi-related pathways, small RNAs engage a protein cofactor of the Argonaute family and utilize base-pairing interactions to identify and regulate complementary genetic information. During my graduate work in the laboratory of Dr. Craig Mello, I have investigated how RNAi-related pathways regulate gene expression and promote genome integrity in the model organism *C. elegans*.

My research has revealed how functionally and structurally distinct argonaute proteins act sequentially to silence target mRNAs in response to double stranded RNAs. I demonstrated how an almost undetectable silencing signal leads to the generation of an abundant pool of small RNAs that mediate target silencing. In addition, I demonstrated that the amplified small RNAs interact with a group of argonaute proteins that are shared with competing endogenous small RNA pathways.

I have also investigated the role of small RNAs in maintaining germline integrity in *C. elegans*. I demonstrated that 21U-RNAs directly bind a piwi argonaute, and that both are restricted in their expression to the germline, establishing 21U-RNAs as the *C. elegans* piRNAs, a small RNA super-family important for germline integrity in all metazoans, including humans.

The most abundant small RNAs in the germline, the 22G-RNAs, play a central role in several germline-specific small RNA pathways. One of these pathways functions in the cytoplasm, where it promotes the degradation of aberrant transcripts such as pseudogenes, cryptic loci and transposons. A second 22G-RNA pathway functions in the nucleus where 22G-RNAs guide complexes that promote the proper organization of chromatin domains in the *C. elegans* holocentric chromosome.

We now appreciate how - through the interaction between argonaute proteins and tens of thousands of distinct small RNAs - RNAi related pathways function on a genome wide scale to regulate many aspects of cell biology and organismal homeostasis, from chromosome structure to gene expression.