Department of Chemistry

Abigail Smith

Mentor: Mary Sever

Small Molecules as MicroRNA Regulators

MicroRNAs (miRNAs) are a class of short, non-coding RNAs, which scientists have recently identified as important regulators of gene expression. MiRNAs inhibit protein production by binding to complementary sequences on messenger RNA (mRNA) leading to mRNA cleavage or translational repression. In order to become functional, miRNAs undergo processing by enzymatic complexes. It has been shown that miRNA function can be fully silenced by inhibiting the enzyme processing pathway.[1,2] The ability to control miRNA processing is gaining significance as increasing numbers of miRNA are being linked to a variety of diseases including neurodegenerative disorders and cancer.[3] However, the biological effects of miRNA are complex and widespread, thus indiscriminate inhibition of miRNA processing would be detrimental. To this end, we examine unprocessed, immature pre-miRNAs, which exist as hairpin loop structures before undergoing cleavage by the Dicer compound. Some variable and unique properties of these hairpins include stem length, base sequence, and hairpin loop size. These unique structural traits may allow small intercalating molecules to distinguish between and selectively bind to different pre-miRNAs.[4] Bound molecules may change the stability of the miRNAs, and thereby inhibit miRNA processing by preventing the dicer complex from cleaving the hairpin loop.[5] Selective control of miRNA processing could lead to therapeutic advances in the treatment of diseases associated with miRNA over-expression.

Our goal is to use small molecules to regulate the expression of miRNA. Using four miRNAs with known hairpin structures, mir-21, mir-124, mir-15a, and mir-155, our research consists of three parts. One is to identify small molecules that can selectively bind to pre-miRNA. We do this using UV-VIS spectrometry to examine changes in the characteristic melting curves of duplex nucleotide sequences due to the binding of small molecules. We then perform cell-based experiments in which we compare the levels of pre-miRNA and mature miRNA in transfected cells that have been treated with the identified small molecules using RT-PCR technology. We also treat isolated miRNA hairpins with small molecules and look for effects using UV-VIS spectroscopy or Circular Dichroism spectroscopy in order to determine the effects of the molecules on the miRNA separate from possible interactions with the cells other genetic material.

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