Masters thesis project

Title: Investigation of nucleotide and structural preferences in miRNAs that specify their binding to different Argonautes in Dictyostelium

Duration: (~20 weeks, 30hp)

Project overview

The social amoeba, *Dictyostelium discoideum* is an eukaryotic model organism with the property of *aggregative multicellularity.* This unicellular organisms upon starvation, initiates a developmental program that enables transition from free-living cells to multicellular structures. Micro(mi)RNAs are key regulators of gene regulation. Following the transcription of the miRNA gene, the primary and precursor forms are processed by the Dicer protein complex into double stranded RNAs. One of the strands of the miRNA duplex then selectively guides different Argonaute (Ago) protein complexes to silence their target genes, and hence contributing towards the regulation of several processes in multicellular transitions. *Caenorhabditis elegans*, yet another foundational model organism, is widely studied to understand fundamental biological mechanisms. The core RNA interference (RNAi) machinery—specifically the Argonaute (Ago) protein family—is deeply conserved between *C. elegans* and *D. discoideum*, despite the two lineages diverging roughly one billion years ago. However, why the Argonaute select specific miRNAs to repress their target genes, has not been well studied. *The current project investigates the preferential selection of microRNAs by Ago protein subfamilies from both model organisms.*

Scientific aim

The project aims to build a deep learning-based (DL) classifier model to learn the sequence and structural preferences in microRNAs, that dictate their binding to specific Argonautes in *Dictyostelium*. With expressed RNAs, stratified into different Ago/Dicer KO conditions, and utilizing relative expression of the miRNA, cellular localization and conserved protein domains, we will build the DL classifier model. Furthermore, publicly available small RNA-seq data (and iPAR-CLIP datasets - to screen for functional miRNAs) from C. *elegans*, will be used for model inference. The project will aim to identify the nucleotide patterns necessary for *D. discoideum* miRNAs and their variants (or isomiRs) to bind to specific Ago in the cell. The resulting model will serve as a baseline that can be extended to Argonautes/dicers from other organisms to discover additional rules that may specify miRNA selection.

Research question

1. Which are the sequence determinants in miRNAs important for association with the different Argonautes in *D. discoideum*?
2. Can isomiR variants of miRNA alter their preferential selection to their Argonaute partners? If so, how does it vary over *D. discoideum* development?

Expected outcomes

The analysis will reveal necessary RNA sequence (and structure) preferences in the double stranded miRNA to be selected by their respective Ago protein subfamilies.

Requirements

- python programming and bash scripting
- basics of machine learning and deep learning, building models and inference

- basic bioinformatics knowledge will be helpful
- interest in learning about small RNA biology

References

1. Liao, Zhen, et al. "Global characterization of the Dicer-like protein DrnB roles in miRNA biogenesis in the social amoeba Dictyostelium discoideum." *RNA biology* 15.7 (2018): 937-954.
2. Brosnan, Christopher A., Alexander J. Palmer, and Steven Zuryn. "Cell-type-specific profiling of loaded miRNAs from Caenorhabditis elegans reveals spatial and temporal flexibility in Argonaute loading." *Nature communications* 12.1 (2021): 2194.
3. Seroussi, Uri, et al. "A comprehensive survey of C. elegans argonaute proteins reveals organism-wide gene regulatory networks and functions." *Elife* 12 (2023): e83853.
4. Panzade, Ganesh, et al. "Global profiling and annotation of templated isomiRs dynamics across Caenorhabditis elegans development." *RNA biology* 19.1 (2022): 928-942.

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