Project 1.9 The role of intrinsically disordered domains of transcription factors in cellular differentiation

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Background:

The transcriptional landscape is completely reorganized during animal development as individual cells begin to differentiate into specific cell types. In that process, specialized transcription factors (TFs) cooperate with basic transcriptional machinery to establish the expression of multiple target genes leading to the establishment of cell fate. How this process is spatially organized within the nucleus is not well understood. Most TFs are composed of structurally defined DNA binding domains that recognize specific sequences in the genome and intrinsically disordered regions (IDRs) responsible for gene activation. IDRs promote activation of gene expression by recruitment of transcriptional co-factors, such as the Mediator and Polymerase II complexes, through interactions with their disordered domains. These interactions enable the clustering of TFs and cofactors at specific sites, thus elevating the local concentration of proteins required for transcription. Experiments in mammalian cells suggest that transcriptional assemblies might form through phase separation of pioneer TFs and co-factors directly on the DNA driven by multivalent interactions between the IDRs. However, it is still unclear if the transcriptional condensate model is accurate, universal, evolutionary conserved, and relevant in a physiological context. Experiments in a whole organism could help answer these questions and provide important insight into how the individual IDRs of TFs organize transcription during embryonic development.

Aim:

The functions of biological molecules emerge from their structural and biophysical properties. Understanding the mechanisms that mediate this relation is at the heart of modern biological studies. The project aims to investigate the role of disordered protein regions (IDRs) in transcriptional activation using Caenorhabditis elegans as a model organism. It entails designing and generating transgenic C. elegans lines and using them in various genetic, biochemical, and physiological assays, including loss of function assays, cellular reprogramming assays, gene expression analysis, and chromatin immunoprecipitation. Using these tools, we will study how the sequence of the IDRs relates to their function within a living organism. We will also determine their role in regulating the spatial organization of transcription using high-resolution microscopy on live C. elegans embryos. Experiments in nematodes will be complemented by biochemical and biophysical assays on recombinant purified proteins.

Requirements:

- A master's degree (or an equivalent) in molecular biology, molecular biomedicine, biochemistry, medicine, genetics, bioinformatics, or biotechnology
- excellent written and spoken English
- excellent scientific track record in relation to career stage
- good organizational skills
- strong motivation and ability to drive the project independently
- well-developed collaborative skills
- knowledge of the standard molecular biology and biochemistry techniques
- curiosity for the discovery of biological processes
- experience with working with C. elegans, protein purification, or programming skills will be an advantage.