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EXAMINING MACROMOLECULAR TRANSPORT AND BINDING KINETICS IN THE ABSENCE OF GRAVITATIONAL FORCES USING A SPECIALIZED MICROGRAVITY TOOLBOX

Abstract

Living organisms of all sizes, from the human to the insect to the bacterial scale, are mechanical beings, constantly receiving and responding to mechanical cues. While this is readily evident at the human level, it is also true at the cellular level, where mechanical signals play crucial roles in regulating and influencing many biological processes, such as cell motility, cell signaling, and tissue morphogenesis. In space, where the mechanical environment is fundamentally different due to the absence of gravitational forces, many of these biological processes are altered, including structural integrity and function of the skeletal muscles, embryonic development, stem cell differentiation, immune responses, and cardiac contractility. These altered behaviors stem from variations in gene expression and post-translational modification of proteins. Though there has been a steady growth in studies characterizing altered gene expression in simulated or real microgravity, the molecular mechanism by which microgravity affects gene expression remains unclear.

In this study, I hypothesize that differential gene expression in microgravity is a result of alterations in both the diffusivity of transcription factors (TFs) and TF-chromatin binding kinetics.

To test this hypothesis, I have built a toolbox to probe TF diffusivity as well as binding kinetics to chromatin at microgravity conditions. The key component of this toolbox is a custom-built clinostat configured to simulate microgravity. The clinostat, equipped with glass bottom chambers and perfusion ports, allows high-resolution imaging in order to document morphological changes of cells and measure diffusion in a longitudinal manner. I have also built clinostat-compatible and compact magnetic tweezers to perform micro-rheology measurements of the nuclei of cells subjected to microgravity, as nuclear rheology plays a core role in determining TF diffusivity. I am currently using this toolbox to examine the diffusivity of p53, a TF known to contribute to muscular atrophy. Finally, gene expression will be profiled using mass spectrometry, and all of the results will be integrated to build a model to describe the underlying mechanism governing altered gene expression in the absence of gravitation forces.

To the best of my knowledge, this work will provide the first systematic workflow characterizing macromolecular transport and binding kinetics in the nucleus at microgravity. Deeper understanding of the underlying mechanism by which microgravity affects gene expression holds significant implications for life in space, and could provide insights into mitigating the biological impacts associated with space travel.