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Deconstructing the Nucleus to Elucidate Cellular Pliancy in the Retina

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We define cellular pliancy as the ability of a cell to adapt and respond to stress, injury or disease. Cells with low pliancy have a lower ability to respond to stress, and as a result are more prone to death. Cells with high pliancy are much more adaptable, able to survive stressful conditions, and even be prone to re-enter the cell cycle, potentially creating a permissive state for cancer initiation. We have proposed that the purposeful organization of the genome in the nucleus contributes to cell type specific pliancy. The neural retina proves to be an ideal model to study this trait, as it contains several different cell types from one common progenitor, that span the spectrum of pliancy behavior[1]. Since the model of cellular pliancy hypothesizes that the adaptability of a cell depends on its ability to access responsive genes in times of stress, the way that specific gene organization affects cellular function needs to be fully understood.

Beyond the general posit that "form supports function", there is evidence that the structure of the nucleus plays a role in cellular behavior. Nuclear landscapes change dynamically through neuronal development[2], and examples of mutations in proteins that help organization at the nuclear periphery often result in diseases classified as nuclear envelopathies[3]. These examples point to a role for global architecture in cellular function. However, our laboratory has shown that the inversion of nuclear architecture for cell types in the retina did not result in changes to gene expression[4]. This suggests that the global organization of chromatin can be decoupled from how chromatin is packaged for gene regulation. We therefore we still need to better understand how the genomic landscape affects gene expression, and specifically its association with cell type specific responses to stress.

We have utilized the dCas9-SunTag system[5] using CARGO sgRNAs[6] to visualize individual genomic locations in live cells, and generated a Lattice Light Sheet to 3D-electron microscopy CLEM pipeline to understand specific differential gene organization between cells. While our efforts to address this question are still a work in progress, using these methods in conjunction with other sequencing readouts, we are developing a 1D, 2D and 3D map of the retina in order to understand the molecular and cell type specific underpinnings of cellular pliancy.

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