TOWARDS A NOVEL MODEL TO STUDY NUCLEAR AGING: BIOPHYSICAL CHARACTERIZATION OF AGE-TUNED MEMBRANES

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Aging is a major risk factor for various diseases, yet understanding of cellular aging is incomplete. Many aging-related changes emerge in the nucleus [1]. Recently, altered cell mechanical properties have become a hallmark of aging [2], with the nuclear envelope (NE) and lamins playing a pivotal role in maintaining nuclear integrity [3]. Although the interplay between NE and lamina during aging is not fully understood, we hypothesize that the lipidome of the NE influences lamin binding and organization. Our preliminary lipidomics findings indicate a decline in ether lipids with age progression. This might impact the biophysical properties of membranes and lead to differential lamin binding. Thus, we propose to create age-tuned synthetic models to investigate nuclear aging, NE-lamin interactions, and overall nuclear structural integrity.

Firstly, we designed membrane models mimicking the NE of both young and old healthy donors with distinct ether lipid content. To characterize the bulk membrane properties of our model vesicles, we performed DPH fluorescence anisotropy, Laurdan generalized polarization (GP), and time-dependent fluorescence shifts. We are using fluorescence correlation spectroscopy, confocal microscopy, and atomic force microscopy to quantify lamin-model interactions and characterize lamin polymerization. Our results indicate that a decrease in ether lipid content does not alter the hydrophobic core of the membrane but makes it more ordered closer to the surface. Such organization of the membrane can significantly impact how lamins interact with the models.

These findings serve as a foundation for upcoming experiments aimed at establishing a novel system to study nuclear aging. The incorporation of key lamina proteins into nucleus-sized models will provide new insights into protein-lipid interactions during healthy human aging. Furthermore, the highly tunable nature of these models will allow for modifications to study age-prone diseases.

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