Nuclear Morphology Changes in Response to Variations in Fluid Shear Stress

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INTRODUCTION: Recent studies in mechanogenomics have identified the nucleus as a mechanosensitive organelle that may be responsible for the regulation of cellular phenotype. The emerging field of mechanogenomics seeks to understand how mechanical forces and interactions affect the genetic regulation within the cell. As a mechanosensitive organelle, the nucleus may be affected by direct mechanical force from the cytoskeleton as well as signaling cascades that are impacted by force on the perimeter of the cell. Within the cardiovascular system, mechanotransduction in the nucleus of endothelial cells may affect the development of plaques during the onset of cardiovascular disease.

PURPOSE: The purpose of this study is to develop an understanding of how mechanical forces acting upon the nucleus affect the morphological characteristics of the organelle.

METHODS: Human Microvascular Endothelial (HEMC-1) cells were cultured in Ibidi flow chambers and exposed to laminar, unidirectional fluid shear stress at 5 dyne/cm^2 (a physiologically relevant parameter) for a period of 24 hours. A control study was done by culturing the cells in this environment under static conditions. Using Hoechst 33258 and fluorescence microscopy, the nuclei were imaged every 8-hours in five defined locations along the flow direction. ImageJ was used to analyze the cell shape index (CSI) of the nucleus and quantify the area, perimeter, circularity, angle, and aspect ratio of the defined regions of interest.

RESULTS: Analysis with ImageJ isolated nuclear regions of interest using standard thresholding techniques. A significant difference in the area and perimeter occurred in the sample sheared at 5 dyne/cm^2 during the 24-hour time point, the static sample revealed no significant change in either parameter over this time scale. The aspect ratio followed the same trend, with the sheared sample becoming elongated and no noticeable change in the static sample. Neither sample showed a preference in nuclear alignment to the axis of flow, with each having a range from 0-180° at each time point. Analysis was done using an ANOVA and two-sample T-tests with $p = 0.05$.

CONCLUSION: Exposure to fluid shear stress during cell culture has an effect on the nuclear morphology, which may lead to a change in genetic organization. It is hypothesized that a higher shear rate will lead to more dramatic changes in aspect ratio and a visible change in nuclear angle. Further study in quantifying and parameterizing this change is being done comparing variations in fluid shear stress. These variations include increases in shear stress to 10 and 15 dyne/cm^2 as well as oscillatory flow patterns. Overall results from this area of research will aid in understanding the propagation of cardiovascular disease using *in vitro* models and assist in the development of *in silico* models of disease