

RESEARCH INTERESTS – CASTORA LAB

A major interest of my laboratory involves the role mitochondrial function plays in aging and in the development of Alzheimer's Disease (AD). Several reports link reduced cytochrome oxidase activity to AD. Since three of the subunits of cytochrome oxidase are encoded on mtDNA, an AD-associated decrease in cytochrome oxidase activity could result from a mutation in these mtDNA-encoded genes. I have obtained autopsy-confirmed AD brain samples as well as age-matched controls and screened these samples for mutations in mtDNA. My laboratory group has identified a mutation that occurs in a higher frequency in AD brains than in age-matched controls. One way we hope to establish the effect of this mutation is by using the rho zero human cell system (the rho zero cell lacks mtDNA) to determine whether this mutation is associated with the inability of the neuronal cells of AD patients to meet the energy demands of the cell. I plan to introduce mitochondria from AD and control cells into these rho zero cells in a collaboration with Dr. Russell Swerdlow at the University of Kansas School of Medicine. Defects in mtDNA will be evident from a reduced function of the mitochondria in the resulting cytoplasmic hybrids (cybrids).

I am also using these rho zero cells for two other projects for which funding is being sought (NIH R-21 and AREA grant proposals in preparation). Briefly, one project is designed to establish the role of mitochondria in the onset of migraine headaches. This project will involve preparing and characterizing cybrids generated by fusing platelets from migraineurs with rho zero cells. The assessment of mitochondrial function in the resulting cybrids will identify any population or subset of migraineurs whose condition is related to mtDNA mutations. This project was initiated in collaboration with Dr. Donald Lewis, M.D., former pediatric neurologist and Chairman of the Pediatrics Department but, due to his untimely passing, it is being continued with Dr. John Harrington, also a member of the Pediatrics Department.

The same approach will be applied to the study of childhood autism. Cybrids developed by the fusion of enucleated lymphocytes from autistic patients with rho zero cells will be used to identify any subset of autistic patients with mtDNA mutations influencing the development of this perplexing neurologic disorder. This project involves a joint collaboration with Dr. Steven Deutsch, Chairman of the Department of Psychology and Dr. Harrington of Pediatrics.

A final area of interest in my laboratory is the role that mitochondrial function may play in the process of fertilization and also of endometriosis. I am currently collaborating with Dr. James Swanson of Old Dominion University and Drs. Howard Jones and Sergio Oehninger of EVMS to investigate the role of mitochondria in oocyte health. We are currently using a hamster model for our studies on fertilization. Oocytes removed from female hamsters are analyzed for mtDNA number and mutations and ATP levels are determined. We want to introduce fresh, purified, stained mitochondria from hamsters back into oocytes recovered from aged hamsters to follow their migration in the oocyte cytoplasm and to determine if pregnancy potential is enhanced by the added mitochondria. We also have access to human oocyte material for similar studies in humans. This project has recently been funded for four years with funds available from the Jones Institute Foundation. Similar analysis of oocytes and granulosa cells from patients with and without endometriosis are being performed with Dr. Albert Hsu, a fellow at the Jones Institute. These latter experiments are designed to elucidate whether compromised mitochondrial function plays a role in endometriosis-associated infertility.