

Role of Rab25 in Breast Cancer Progression

Primary Investigator: Krishna Rao, Ph.D.
Funding Agency: IDPH/Penny Severns Breast & Cervical Cancer Fund

Although breast cancer can be treated successfully in its early stages, patients with later stages of the disease and hormonally-insensitive tumors suffer higher mortality rates. Prognosis is poor among these patients because of limited therapeutic options and poor response to standard chemotherapeutic agents. This study aims to understand the role of a specific protein, rab25, in the development of breast cancer to improve treatment options. Initial results suggest that rab25 can suppress tumors.

Dr. Rao hypothesizes that rab25 suppresses the tumorigenic effect of ras, a cancer-causing gene (an oncogene) that can lead to cell growth, invasion, and metastasizes.

This study will utilize the spindle cell carcinoma cell line (SCC), a rare but aggressive variant of breast cancer. It is one example of a hormonally insensitive tumor with poor response to standard chemotherapy. Dr. Rao developed the SCC cell line — the world's first cancer cell line made exclusively with two human oncogenes and no viral genes. That work was published in *Cancer Letters*.

That analysis of the SCC cell line produced clinical data to suggest the loss of rab25 occurs in many common types of breast cancer, particularly hormonally insensitive tumors. Publication of these results is pending in the *International Journal of Cancer*. The current translational research will confirm a pathway to breast cancer that was initially discovered in the lab and now has additional evidence from clinical samples. Understanding hormonally insensitive breast cancers may provide insights for better treatment options.

Role of Estrogen on Lipid Internalization in Neuron

Primary Investigator: Xiangying Cheng
Funding Agency: IDPH Alzheimer Disease Research Fund

The effectiveness of hormone therapy to protect against Alzheimer Disease is controversial. Underlying this controversy is a poor understanding of how estrogen protects neurons. Estrogen increases the release of apolipoprotein E (apoE) and the growth of neurites. Cheng has shown *in vivo* that estradiol increases a receptor for apoE, the low-density lipoprotein receptor related protein (LRP). ApoE has been reported to increase LRP *in vitro*. Without apoE or if the LRP is blocked, estrogen has no effect on neurite growth *in vivo*. Cheng is testing the idea that estrogen's effect on neuron cell growth is related to lipid transport.

Cheng and his staff will determine if the increase of LRP, following estrogen treatment, is a direct effect of estrogen or an indirect effect of estrogen increasing apoE. Real-time PCR and Western blot analysis will be used to evaluate LRP expression *in vitro* following treatment with estrogen and/or various isoforms of apoE.

Finding that lipid transport may underlie estrogen stimulated neuronal process growth and repair would lead to pharmacologic interventions that could improve the protective effects of hormone therapy, thereby reducing the incidence of AD.

To achieve this goal, fluorescently labeled dodecanoic acid accumulation and neurite growth will be measured in adult primary cortical neurons from C57BL/6 and apoE knock-out mice following treatment with estrogen and apoE3 and/or apoE4.

The negative effects Cheng has observed on neurite growth of apoE4 compared to apoE3 may represent poor modulation of LRP expression by apoE4.

Growth Hormones, Longevity and Synaptic Integrity

Primary Investigator: Robert Helfert, Ph.D.
Funding Agency: SIU Central Research Committee

Dr. Helfert will explore the relationship between the excessive production of growth hormone (GH) and accelerated aging with the belief that elevated GH level or activity may lead to a variety of problems, including a process leading to early aging and reduced longevity.

The ability of GH to increase metabolism and the production of toxic metabolites may be the mechanism underlying its presumed role as an accelerant for aging. This project will examine if the overproduction of GH could lead to increases in brain toxicity at an earlier age. The researchers are measuring the ability of the brain to withstand toxic challenges. At the same time, they will determine if an abnormal increase in GH could adversely affect the structural integrity of brain circuits.

Ultimately, these studies also will address issues related to the consequences of GH overproduction in gigantism, acromegaly (a condition characterized by enlarged facial features and enlargement of the bones of the extremities), the risks of GH abuse by body builders and athletes, and the risks and benefits of GH therapy in the elderly.

For more information about these projects, contact the Office of Research and Faculty Affairs at 217-545-7936.