Role of Tumor Metastases Suppressor Gene Drg-1 in Breast Cancer

Principal Investigator: Ko Watabe, Ph.D.
Funding Agency: Department of the Army

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among women in the United States. Unfortunately, the majority of patients already have a metastatic disease at the time of a clinic visit. Despite significant improvement in surgical techniques and chemotherapies, none of the current medical technologies "cures" the metastatic disease, and the patients who have acquired metastatic cancer inevitably die. There is an urgent need to develop a novel therapeutic approach that directly attacks the metastatic tumor cells.

A variety of positive and negative factors control malignant cells' ability to metastasize. Emerging evidence from recent studies indicates that a tumor metastases suppressor gene, Drg-1, plays a crucial role in the metastatic development of breast cancer cells. Dr. Watabe and his staff have shown that the expression of the Drg-1 gene is controlled by the tumor suppressor gene, PTEN, which often is deleted or mutated in breast cancer and the reduced expression of Drg-1 is significantly correlated with metastatic disease in breast cancer patients and their survival. Therefore, understanding the molecular mechanism of DRg-1 function is expected to significantly contribute to the development of new therapeutic methodologies for breast cancer treatment. This project will determine whether Drg-1 is involved in the process of tumor metastases in breast cancer.

Dr. Watabe hypothesizes that Drg-1 and PTEN gene expression and the methylation status of the Drg-1 promoter can serve as biomarkers to predict patient outcome.

He is working to clarify the role of the Drg-1 gene in the progression of breast cancer, to clarify the control mechanism of the Drg-1 gene by PTEN both *in vitro* and *in vivo* and to evaluate the diagnostic/prognostic value of Drg-1 in breast cancer. This research should help clarify if Drg-1 and other Drg-1 controlling factors can be used to accurately predict metastatic status of patients. Dr. Watabe and his team also will test if PTEN controls tumor metastases through Drg-1. This work could open new avenues in metastasis research and help develop anti-metastatic drugs.

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Mechanism of Nerve Growth Factor Regulation of Vanilloid Receptor-1 Expression

Primary Investigator: Vickram Ramkumar, Ph.D.
Funding Agency: SIU Central Research Committee

This project will investigate the mechanism underlying nerve growth factor (NGF) regulation of pain receptors (TRPV1) in cultured cells. Dr. Ramkumar hopes to determine the steps by which this growth factor signals to the cell to synthesize more TRPV1 receptors by exposing cells to NGF and determining which signaling pathways are activated.

The primary focus in this study is the NADPH oxidase system, a free-radical generating system in the cell that NGF activates. Dr. Ramkumar believes that free radicals produced by this enzyme activate different pathways leading to activation of the TRPV1 gene. He speculates that altered regulation of this process in diabetes could lead either to enhanced or reduced TRPV1 expression. This could account for either the hyperalgesic or hypoalgesic responses observed by patients experiencing diabetic peripheral neuropathy — a result of poorly-controlled diabetes that causes permanent peripheral and automatic nerve dysfunction.

A better understanding of the NGF signaling cascade could enable development of specific drugs to help patients with diabetic peripheral neuropathy.

Opioid Peptide Gene Expression during Lactation

Primary Investigator: Lydia Arbogast, Ph.D.
Funding Agency: National Institutes of Health

Many pediatricians strongly encourage breast-feeding for at least the first six months of life as the safest and most nutritionally beneficial feeding for newborn infants. The hormone prolactin acts on mammary epithelial cells to produce nutritive components of the milk and is essential for competent lactation.

When the infant suckles, nerves in the mammary gland are stimulated and send a message to the brain by a complex pathway. Research implicates dopamine and endogenous opioid peptides in this neuronal pathway. Dopamine neurons in the hypothalamus provide the major control to the anterior pituitary to inhibit prolactin secretion. The suckling stimulus turns off these dopamine neurons to allow prolactin levels to rise during lactation so that milk can be produced. Dr. Arbogast's hypothesis is that endogenous opioid peptide neurons are part of the pathways for the suckling stimulus to decrease dopamine neuronal activity.

Dr. Arbogast's team is working on identifying which opioid neuronal groups within the hypothalamus are important in regulating prolactin secretion. They are evaluating differences in neuronal activity when the suckling stimulus is present or absent and are using modern gene knockdown techniques to selectively ablate specific opioid input.

Determination of which receptors are localized on dopamine neurons, evaluation of changes in receptor expression during lactation and the use of selective pharmacological agents to block specific receptor subtype actions will help identify important interactions.

Furthermore, this research is directed to understanding intracellular changes in dopamine neurons resulting from the suckling stimulus as well as the role of opioid peptides if a direct action of opioid peptides on dopamine neurons is implicated.

These studies will contribute to understanding the complex neuronal pathways involved in maintaining lactation.

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