Seeds4Hope

A program of the Windsor Essex County Cancer Centre Foundation

2009 Seeds4Hope Grant Recipient

Dr. Dora Cavallo-Medved

"Three-Dimensional Live-Cell Imaging to Profile Proteolytic Pathways Associated with Lymphatic Invasion in Inflammatory Breast Cancer"

SUMMARY OF RESEARCH PROJECT

Inflammatory breast cancer is the most aggressive and lethal form of breast cancer. Although it accounts for approximately 5% of all diagnosed breast cancers, the 5-year survival rate is less than 45%. Clinically, inflammatory breast cancer is very distinct from other breast cancers as it is characterized by the rapid onset of breast swelling and redness often without a well-defined lump, therefore, challenging traditional diagnostic methods such as mammography and ultrasound. Furthermore, the propensity of inflammatory breast cancer to invade the lymphatic system of the skin and infiltrate lymph nodes defines it as a highly aggressive disease. Invasion of tumor cells into the lymphatic vessels is an area of tumor biology that is poorly understood. In our studies, we propose to explore the interactions between inflammatory breast cancer and lymphatic endothelial cells, the cells that constitute lymphatic vessels. We will establish a multi-cellular system using both inflammatory breast cancer cells and endothelial cells to study these interactions. Specifically, we will examine how endothelial cells affect the expression and secretion of proteases, enzymes that participate in tumor invasion, by the tumor cells and factors (cytokines) that regulate this process. In addition, we will use imaging technologies to view the interactions of live cancer cells with endothelial cells over periods of time in an effort to mimic the events that occurs within tumors of breast cancer patients. This proposed study is innovative because it examines, for the first time, the pathway in which inflammatory breast cancer cells invade into the lymphatic system. It examines this cancer beyond the cancer cells and also investigates the role of non-cancer cells in the progression of the disease. As well, it utilizes a live-cell system as a tool to investigate the interactions between inflammatory breast cancer and endothelial cells, which can also be applied to other cells associated with cancer. Finally, establishing a molecular link between inflammatory breast cancer cells and endothelial cells will identify novel biomarkers for earlier diagnosis and aid in the development of new target therapies that will advance the treatment of this disease.

HOW THIS RESEARCH HELPS ADVANCE QUALITY CANCER CARE IN OUR COMMUNITY

With a 5-year survival rate of less than 45%, inflammatory breast cancer is considered the deadliest form of breast cancer. In addition, inflammatory breast cancer appears to target younger women as compared to other types of breast cancer. Unfortunately, the biology involving the development and progression of the disease is severely understudied. Our proposed project will begin to provide insight into the molecular and cellular mechanisms underlying inflammatory breast cancer and in particular its invasive nature. Insights into these mechanisms will aid in the identification of biomarkers that will improve diagnosis of the disease. Furthermore, elucidating the mechanisms in which the disease progresses will provide information for the development of new therapeutic strategies in which to improve treatment of inflammatory breast cancer for patients within the community. These strategies are ultimately aimed at advancing cancer care in these patients.

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PROGRESS REPORT

Inflammatory breast cancer is the most aggressive and lethal form of breast cancer with a dismal 5-year survival rate of less than 45%. In addition, the average age for onset of disease for IBC is 5-10 years younger than that of other types of breast cancer. Although there have been studies examining the clinical presentation of IBC, there remains very little known about the basic biological mechanisms that dictate the onset, progression and invasion of this disease. Since cancer cells are known to invade into the blood vasculature and lymphatic systems, the aim of our study is to investigate the role of endothelial cells, which are normal cells of bloods vessels, on the aggressive nature of IBC cells. Specifically, we are examining the effects of endothelial cells on a class of enzymes produced by cancer cells that propagates their invasion. With funding from the Seeds 4Hope program, we have been successful in establishing a 3D cellular model that allows us to examine the interactions between these normal endothelial and IBC cells in real-time. The different cell types within these 3D cellular models are fluorescently tagged and examined over time using optical imaging techniques. Images are compiled into 3D reconstructions illustrating cellular structure and biological activity. From our findings, we have found that in the presence of endothelial cells, the IBC cells grow larger and produce more irregular 3D cellular structures, indicative of the aggressive character of the disease. In addition, these IBC cells produce high levels of enzymes involved in tumor invasion as observed by the presence of green fluorescent products in the 3D images. We have also identified several factors that are secreted by endothelial cells that may stimulate the invasion of IBC cells. Our current objective is to further investigate which of these factors are involved in mediating IBC invasion and then determine their mechanisms of action. We anticipate that our study will provide significant clues towards understanding how normal cells contribute to progression and invasion in IBC. Our ultimate goal is for our results to contribute to the discovery of novel biomarkers for earlier diagnosis of IBC and the development of new target therapies to eradicate this disease.

"The Seeds4Hope grant has given us an opportunity to begin to accumulate preliminary data that we can build upon to continue examining the biology of inflammatory breast cancer. This in turn will aid in the development of novel therapeutic strategies to combat this aggressive disease."

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FINAL REPORT

Inflammatory breast cancer (IBC) is the most aggressive and lethal form of breast cancer yet very little is known about the basic biological mechanisms that dictate the onset, progression and invasion of this disease. Often IBC does not form a palpable mass but instead forms small nests of cancer cells that are undetected by self-examination and/or mammography. One of the clinical hallmarks of IBC is the formation of tumor aggregates in the lymphatic vasculature of skin that leads to lymph node invasion. This results in the swelling, redness and warmth of the breast tissue.

Our study is aimed at investigating the role of normal endothelial cells, which line the vessels of the lymphatic system, on the aggressive nature of IBC cells. Specifically, we are interested in determining the effects of endothelial cells on a class of enzymes called proteases that are produced by cancer cells and propagate their invasion. With our Seeds4Hope funding, we have successfully established a 3D cellular model system of normal endothelial grown with IBC cells that allows us to examine the interactions between these two cell types in real-time. In the presence of endothelial cells, the IBC cells grow larger and produce more irregular 3D cellular structures, indicative of the aggressive character of the disease. This is accompanied by an over production proteases by the cancer cells that involved in tumor invasion. We have also identified two inflammatory factors, IL-8 and MCP-1, which are secreted by endothelial cells that augment the invasive properties of IBC cells. These factors in part function by increasing the production and release of proteases by the cancer cells. These proteases digest the protein material surrounding the cancer cells thereby increasing their ability to invade nearby tissue. Our ongoing objective is to further investigate the mechanisms of action of these inflammatory factors in mediating IBC invasion. We anticipate that our study will provide significant clues towards understanding how normal cells contribute to the progression and invasion of IBC. Our long term goal is to use our data to develop novel therapeutic strategies to eradicate this disease.

We are now planning to expand our current research on IBC and lymphatic endothelial cells to also include monocytes/macrophages. The inflammatory factors, IL-8 and MCP-1, have been shown to recruit monocytes to the tumor micro-environment where they are activated to macrophages. Macrophages have been known to produce and secrete a number of proteases into the tumor micro-environment that augment invasion of tumor cells into the vasculature. Analyzing all three cell types and the paracrine signaling between them will provide more clues in understanding the
progression and invasion of IBC.