Seeds4Hope

A program of the Windsor Essex County Cancer Centre Foundation

2012 Seeds4Hope Grant Recipient

Dr. Dora Cavallo-Medved

"Caveolin-1 Mediates Proteolysis and Invasion in the Tumour Microenvironment of Prostate Cancer"

SUMMARY OF RESEARCH PROJECT

Prostate cancer is the most common and the third deadliest cancer amongst Canadian men. Historically, prostate cancer research has focused on the prostate cancer cells themselves, however there is now growing evidence to support a role for the normal cells that reside in prostate tumour microenvironment. The interactions between prostate cancer and normal cells are believed to activate numerous molecular and chemical pathways that mediate prostate cancer progression and invasion.

Caveolin-1 is a protein that is over-produced and secreted by highly aggressive prostate cancer cells and has been shown to promote invasion of prostate cancer. Indeed caveolin-1 has been described as a potential prognostic marker for aggressive forms of the disease. Previously, we identified an association between caveolin-1 and proteases, a class of protein-degrading enzymes that are used by cancer cells to invade and spread to other tissues. Our hypothesis is that the over expression and secretion of caveolin-1 by prostate cancer cells promotes tumour invasion by increasing the production and secretion of these proteases. Given that proteases are also produced by normal cells, we propose that the effects of caveolin-1 are not solely on the prostate cancer cells themselves but also on the normal cells within the prostate tumour microenvironment. Our objective is to understand the mechanism by which caveolin-1 promotes prostate cancer invasion via its interaction with proteases.

In this proposed study, we will examine the molecular relationship between the caveolin-1 and proteases using a 3-dimensional cell model that incorporates both living prostate cancer and normal cells. There has been an increased interest in the use of these types of cellular models in cancer biology as they are designed to mimic the conditions of the tumour microenvironment outside of a living organism. This proposed study is innovative because it is the first to link caveolin-1 to invasive enzymes in the tumour microenvironment of prostate cancer. Understanding the role of secreted caveolin-1 and the relationship between prostate cancer and normal cells can lead to significant contributions towards further development of novel biomarkers and therapeutics strategies against this disease.

HOW THIS RESEARCH HELPS ADVANCE QUALITY CANCER CARE IN OUR COMMUNITY

Prostate cancer is the most common and third deadliest cancer amongst men with an incidence rate of 1 in 7 men. Within Windsor-Essex County, there is little focus on prostate cancer research and as such this proposed project would bring both awareness and resources to this area of cancer biology within our community. Funding of this project will also be a complement to the new Regional Comprehensive Men's Health Program within our community, which is aimed at advancing local men's health services in the areas of detection, diagnosis and treatment of prostate cancer. In addition, this proposed research is relevant to regional priorities of Cancer Care Ontario, including the Prostate Cancer Disease Pathway Management Project, which aims to identify high-priority goals to improve the quality of care, processes and patient experience for prostate cancer at the regional level.

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PROGRESS REPORT - YEAR ONE

Prostate cancer is the most common cancer amongst men in Canada, and although the survival rate for prostate cancer is high relative to that of other cancers, there are very few biomarkers to detect early stages of the disease and its clinical significance. In this study, we proposed to examine the molecular relationship between the caveolin-1 and proteases using a 3-dimensional (3D) cell model that incorporates both living prostate cancer and normal prostate fibroblast cells. These types of cellular models are significant to cancer biology as they are designed to mimic the conditions of the tumour microenvironment outside of a living organism. Using this cellular model to understand the role of secreted caveolin-1 and proteases in the relationship between prostate cancer and normal cells can lead to significant contributions towards further development of novel biomarkers and therapeutic strategies against this disease.

With funding from Seeds4Hope, we were able in our first year to obtain and study four human prostate cancer cell lines that express different levels of caveolin-1. Our current studies are examining the correlation between caveolin-1 expression and protease secretion in these cells and their invasive behaviour. Investigation into these cell lines revealed that those cells that had high levels of caveolin-1 expression had increased secretion and activation of proteases (cathepsin B and uPA) that are involved in degradation of extracellular matrix proteins. These degradation events are known to be involved in tumour migration and invasion leading to metastasis. These are also characteristics observed in aggressive forms of prostate cancer. In addition, we obtained normal prostate fibroblast cells and analyzed the expression of proteases from these cells since it has been shown that normal cells can be recruited to participate in cancer invasion. We have identified one of these proteases, cathepsin B, being secreted by the normal prostate fibroblast cells. We propose that this protease contributes to prostate cancer invasion.

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PROGRESS REPORT - YEAR TWO

Prostate cancer is the most common and the third deadliest cancer amongst Canadian men. There is now growing evidence that suggests a role for the normal cells that reside in prostate tumour microenvironment, the immediate tissue surrounding the tumour, in support of prostate tumour progression and invasion. Elucidating the molecular interactions between prostate cancer and normal cells will provide a more clear understanding of the disease and it mechanism for progression and invasion.

Caveolin-1 has been described as a potential prognostic marker for the aggressive forms of prostate cancer. Caveolin-1 is a protein that is over-produced and secreted by highly aggressive prostate cancer cells. Many studies have suggested that the over production and secretion of caveolin-1 promotes prostate cancer invasion. Previously, we identified an association between caveolin-1 and proteases, a class of protein-degrading enzymes that are used by cancer cells to invade and spread to other tissues. We believe that the overexpression and secretion of caveolin-1 by prostate cancer cells promotes prostate cancer invasion by increasing the production and secretion of these proteases. Given that proteases are also produced by normal cells within the tumour micro-environment, we propose that the effects of caveolin-1 are not solely on the prostate cancer cells themselves but also on the normal cells. Our objective is to understand the mechanism by which caveolin-1 promotes prostate cancer invasion via its interaction with proteases and the role of normal cells within the tumour microenvironment.

In our study, we have been able to use a variety of prostate cancer cells that express varying levels of caveolin-1 and have found a positive correlation between caveolin-1 expression and protease production and secretion. We have also found that when normal human prostate fibroblasts cells interact with human prostate cancer cells, the production and secretion of proteases from the normal cells also changed in relation to the levels of caveolin-1. Indeed, even in the normal cells of the prostate tumor microenvironment we also found a correlation between caveolin-1 and protease expression by these cells. A reduction in caveolin-1 expression in these normal cells decreased protease expression and also inhibited cell migration, an important process that facilitates tumour invasion within the microenvironment. We are currently focused on elucidating the molecular mechanisms involved in linking caveolin-1 expression to protease production and prostate tumour progression and invasion.