Seeds4Hope

A program of the Windsor Essex County Cancer Centre Foundation

2014 Seeds4Hope Grant Recipient

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"*Systemic Profiling of SCF E3 Ligase Regulatory Attributes at Play in Cell Cycle Control and Cancer*"

SUMMARY OF RESEARCH PROJECT

Proteins play an extremely important role in all cells, facilitating processes ranging from cell division to metabolism. Regulating the quantity and function of proteins in different parts of the cell and over time is vital in ensuring a properly functioning cell. This regulation is governed, in part, by the controlled destruction of proteins controlled by the ubiquitin-proteasome system. This system involves the attachment of a small protein called ubiquitin to a target protein through a process known as ubiquitination. Protein ubiquitination is widely known to facilitate the targeted destruction of proteins that are no longer needed or improperly folded in the cell. The fate of ubiquitinated protein is dependent upon what kind of ubiquitination occurs. A protein can be modified by one or many ubiquitin molecules, and different types of chains can be formed. Ubiquitination is performed by three enzyme complexes the third of which, the E3 ubiquitin-ligase, is thought to determine which specific target proteins are to be ubiquitinated and destroyed.

Defects in genes encoding proteins involved in the ubiquitin-proteasome pathway are implicated in the development of several cancers including breast, cervical, colon, renal, and prostate, as well as other diseases. The current state of knowledge in ubiquitin biology indicates there is much to be learned about the regulation of the machinery governing protein ubiquitination, with implications for cancer biology and treatment.

A well-known subclass of E3 ubiquitin-ligases is the SCF complex, named for its components: the Skp1 adaptor protein, a cullin backbone, and an F-box protein that varies for each different SCF complex and is responsible for recruiting specific targets as substrates for ubiquitination. To date, our understanding of SCF complex regulation is incomplete and confined to the level of cullin protein modification. Our lab, in collaboration with others from Harvard University, University of Washington and University of Toronto have recently discovered that the Skp1 'adapter' subunit is modified by the attachment of a phosphate group, which controls its association with the other SCF components and regulates the activity of the SCF complex.

Determining the significance of Skp1 modification for SCF function will shed new light on how SCF complexes are regulated, and potentially offer new therapeutic approaches for the regulation of cell division and DNA repair, both key processes in the development of human malignancies.

HOW THIS RESEARCH HELPS ADVANCE QUALITY CANCER CARE IN OUR COMMUNITY

The presence or absence of specific proteins at different times in the life of a cell can contribute to development of cancer, which in many cases is caused by the improper regulation of components of the ubiquitin-proteasome pathway. Defects in some of these components have been implicated in susceptibility to developing cancer, including breast and prostate cancers. Understanding how the SCF subclass of ubiquitin-ligase complexes can be turned on and off will provide valuable insight into the regulatory mechanisms involved, and potentially lead to the development of novel therapies that specifically target improperly functioning complexes in human cancers with minimal toxicity on healthy tissues.