

SÉMINAIRES ET CONFÉRENCES



Michael Witcher

Department of Oncology and experimental Medicine,
McGill University

« Targeting chromatin related processes in breast cancer »

Breast Cancer is the most frequent and one of the deadliest cancers afflicting women. In our we aim to understand the mechanisms whereby transcriptional and DNA damage repair processes become aberrant in cancer and to utilize this information to develop new therapeutic approaches.

Deletion of chromosome 16q22.1 is one of the most frequent genomic alterations across a spectrum of cancers, including ~50% of breast cancers. The smallest recurrently deleted region of 16q22.1 encompasses the haploinsufficient tumor suppressor gene CTCF. Beyond copy number loss, CTCF is also found mutated in a spectrum of cancers including breast and endometrial cancer. CTCF plays an important role in maintaining a proper balance between oncogene and tumor suppressor gene expression and we recently identified a novel role for CTCF in the repair of DNA double strand breaks. Here, we found that post-translational modification of CTCF by poly (ADP-ribosylation) facilitates recruitment of BRCA2 to sites of damage. We now aim to understand how CTCF deletion or mutation impacts oncogenic progression.

Using CRISPR/Cas9 we engineered the mammary epithelial cell line MCF10A to carry either a single copy number loss of CTCF, or insertion of a breast cancer-specific H284N mutation. Through ChIP-seq profiling we uncovered that CTCF aberrations lead to not only a loss of binding, but surprisingly, a concomitant gain of binding sites as well. RNA-seq analysis revealed oncogenic pathways involved in cell migration and adhesion are altered in CTCF heterozygous cells. Consistent with this, these cells acquired the capacity to invade through matrigel and grow large mammospheres. We are not using this new information to explore avenues to target critical pathways in CTCF defective cells.

There is evidence that CTCF, and perhaps other proteins, lose poly (ADP-ribosylation) in tumors. However, the mechanism underlying this condition is unknown. We have now published that enzyme responsible for removing protein poly (ADP-ribosylation), PARG, is overexpressed in breast tumors and acts as an oncogene, promoting tumor growth and metastasis in animal models of breast cancer. In collaboration with the Quebec-based drug discovery company NEOMED, we have develop novel inhibitors of PARG that show anti-proliferative activity in the nanomolar range.

Overall, our lab is utilizing insights from studying basic mechanisms of transcriptional and DNA repair deregulation to predict novel means to treat poor prognosis breast cancers.



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Faculté de médecine
Département de biochimie
et médecine moléculaire

Université 
de Montréal

Pavillon Roger-Gaudry

Salle : G-415

John Pascal

Tél : (514) 343-4890 courriel : john.pascal@umontreal.ca