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Michael is a postdoctoral fellow in the laboratory of Dr. Postovit in the Department of Oncology. His research focuses on exploring often overlooked mechanisms of gene expression in breast cancer and translating that research into clinically relevant preclinical models. Michael finished his Ph.D. in 2019 and started as a postdoctoral fellow immediately after graduating. His work looks at the role of stress pathways, mTOR, and integrated stress response (ISR) in facilitating the acquisition of plasticity in response to both naturally occurring microenvironmental stresses and stress responses due to the administration of chemotherapy.

In our recent paper published in Nature Communication, we demonstrate that an embryonic protein, NODAL, is re-expressed in breast cancer. NODAL expression causes an increase in a subset of highly tumourigenic and plastic cells called breast cancer stem cells (BCSCs). We then show that hypoxia, low oxygen, a common feature of solid tumours, increases the expression of NODAL along with plasticity in our breast cancer cell lines. Using RNA-seq we show that NODAL is part of a much broader change in gene expression that supports these changes. However, we also observed that NODAL's upregulation happens at the protein level independent of changes in transcript abundance.

Assessing the alterations in translation, we confirmed the long-known phenomenon, that cancer cells decrease translation to conserve energy under hypoxic conditions. Transcripts that are driving the observed phenotypes escape the ~90% decrease in translation. The pathways known to regulate translation like this are mTOR/4E-BP1 and eIF2α. Major regulatory motifs can be found in the 5`UTR of transcripts that alter the rate of translation in response to the abundance of translation regulating proteins that result from mTOR and eIF2α. We discovered that most plasticity supporting mRNAs like NODAL, NANOG and SNAIL have multiple mRNA isoforms that code for the same protein but have unique 5`UTRs. Each isoform displayed different expression dynamics in response to hypoxia or pharmacologic manipulation of the mTOR and eIF2α pathways. These isoforms allowed expression of plasticity-related genes in normal growth conditions and maintained or enhanced expression during stress.

Having established the mechanism for stress-induced plasticity, we tested ISRIB. This small molecule prevents translation inhibition through the eIF2α pathway. ISRIB reverses the induction of translation of plasticity factors. To establish the role these pathways play in tumour progression we demonstrate that the induction of translation inhibition through; the mTOR pathway with INK128; the eIF2α pathway with Salubrinal; or both through chemotherapeutic stress from paclitaxel enhances cancer progression primarily through plasticity and chemoresistance. We do this using in vitro and in vivo assays, showing these pathways increase the number of BCSCs, enhance metastatic potential, and increase chemoresistance. Using ISRIB as a co-treatment, the adaptation that is conferred by translational alterations is prevented while increasing the chemotherapeutic efficacy of INK128 and paclitaxel. Broadly, this paper shows a convergent mechanism between naturally occurring stresses and those elicited by treatment that accelerates tumour progression through increased plasticity and chemoresistance.