

From DEPARTMENT OF ONCOLOGY AND PATHOLOGY
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**DEVELOPING ANALYTICAL TOOLS TO
INVESTIGATE THE ROLE OF
TRANSLATION IN HOMEOSTASIS AND
DISEASE**

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Developing analytical tools to investigate the role of translation in homeostasis and disease

THESIS FOR DOCTORAL DEGREE (Ph.D.)

In light of the global pandemic the dissertation will be held online.

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Abstract

Transcriptome-wide studies of translation efficiencies increase our understanding of translational regulation to better understand homeostatic mechanisms and formulate treatment strategies in disease. In **Study 1**, we developed an algorithm for analysis of translation efficiency, called anota2seq. We show that anota2seq outperforms current methodologies and, due to its unique approach of analysis, it is the only method to statistically distinguish important modes for regulation of gene expression, i.e translation and translational buffering.

Pancreatic cancer is a lethal malignancy with very limited treatment options. In **Study 2**, we evaluate the impact of using an eIF4A inhibitor, CR-31, on mRNA translation in pancreatic cancer. eIF4A is a component of the eIF4F translation initiation complex. We show that inhibiting eIF4A in murine and human pancreatic ductal adenocarcinoma (PDA) models induces an energy crisis by impacting translation of mRNAs related to oxidative phosphorylation and glycolysis. PDAs, as a means to compensate, shifted their metabolic dependency towards reductive glutamine metabolism. Exploiting this dependence using a combined treatment of eIF4A and glutaminase inhibitors revealed an exciting therapeutic treatment strategy for PDA that did not affect healthy cells.

In **Study 3**, we investigated the effects of insulin on gene expression in malignant and non-malignant cells. This revealed that malignant cells differ in their transcriptional response to insulin from non-malignant cells, whereas in both translation was dependent on mammalian/mechanistic target of rapamycin (mTOR). However, mTOR inhibition during insulin stimulation in malignant cells lead translational offsetting of alterations in mRNA levels. mTOR is a major regulator of translation, e.g. mTOR regulates eIF4E availability, which facilitates formation of the translation initiation eIF4F complex. Comparing the effects of mTOR inhibition in malignant cells to that of hypoxia in stem cells revealed that these vastly different cell types share the ability to translationally offset mRNAs.

Collectively, these studies improved analysis of translational efficiencies and contributed to improved understanding of the role of translational dysregulation in cancer.

List of publications

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[†]Equal contribution.

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