From DEPARTMENT OF ONCOLOGY AND PATHOLOGY

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# INTERROGATION OF GENE EXPRESSION PROGRAMS IN PERTURBED SYSTEMS

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Interrogation of gene expression programs in perturbed systems

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# Abstract

Transcriptome-wide studies of translation efficiencies increase our on understanding of translational regulation to better formulate treatment strategies in disease. In **Study 1** we developed an algorithm for analysis of translation efficiency data, called anota2seq. We show that anota2seq outperforms current methodologies and, due to its unique approach of analysis among its peers, 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 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 effecs 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 to that the transcriptional response was translationally offset. mTOR in its complex 1 formation is a major regulator of translation initiation by regulation of eIF4E availability, which facilitates formation of the eIF4F complex. Hypoxia leads to a reduction in mTOR activity. 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.

# List of publications

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†Equal contribution.

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