

American Cancer Society – Institutional Research Grants 2015

“The Role of Differential mRNA Localization in the Stress Adaption of Cancer Cells”

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Inherent to oncogenic transformation is increased exposure to adverse conditions in the tumor microenvironment, through oxidative, metabolic, replicative, ER stress and DNA damage. Adaption to stressful conditions is required for cancer cell survival and future cell growth. Translational control has been found to be a key node of gene regulation during the response to stress.

Translational control has also been found to be important to the etiology of cancer as a broad spectrum of cancers upregulate various translation factors and mutations in several components of the translational apparatus underlie spontaneous cancers. Previously I found that mRNA localization to stress induced membrane-less compartments is a key means of translational regulation during stressful conditions in yeast.

Our hypothesis is that differential mRNA localization plays a key role to the stress-induced translational changes that take place in cancerous cells, which contributes to their ability to survive and adapt to the stressful tumor microenvironment. Two mRNAs we will focus on are the HSP70 and HSP90 mRNAs, which have previously been found to be excluded from stress granules in stressful conditions in mammalian cells. Understanding the regulation of gene expression for these heat shock proteins is important as both of these proteins are implicated in cancer progression and the ability of cancer cells to combat the stressful tumor microenvironment.

In this proposal we will use a combination of next-generation sequencing, quantitative single-cell microscopy and computational analysis to investigate the conservation of translational control by differential mRNA localization in cancer cells. To accomplish this, my lab will: a. use ribosome-profiling to quantify stress induced translational changes in various cancer cell lines, b. investigate the cytoplasmic localization of mRNAs that are differentially translated upon stress as well as determine the control mechanisms for their localization.

This study will give new insight into the mechanism by which cancer cells are able to survive a stressful tumor microenvironment through translational control. In the long term these basic mechanisms of translational control may provide chemotherapeutic targets that are selective against cancer cells because of their inherently stressful tumor microenvironment.