“Development of Quantitative Proteomic and Transcriptomic Approaches to Decipher Posttranscriptional Regulation in Cancer Pathogenesis “

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Abstract: Gene expression is routinely measured by microarrays, but mRNA expression levels only account for about 40% of the variation observed in protein levels. Recently, it has been shown that cancer cells compared to non-transformed cells express mRNA isoforms with shorter 3' untranslated regions (3'UTRs) that result from alternative cleavage and polyadenylation (APA), and that these shorter mRNAs typically produce ten-times more protein than their corresponding full-length mRNAs. APA can lead to oncogenic transformation without mutations in the DNA sequence. Recently, new technologies have become available to assess mRNA levels including transcript isoform variation as well as protein levels genome-wide. The aim of this proposal is to monitor the extent of post-transcriptional gene regulation across different transformed and non-transformed cell lines using Solexa sequencing-based digital gene expression (DGE) and a proteomic approach. DGE provides data on mRNA abundance and on 3' end variation of mRNA transcripts. In parallel, protein abundance measurements by SILAC and mass spectrometry (MS) will be obtained. The ratios for mRNAs and their corresponding proteins will inform us on the extent of cell-type- and transformation-dependent post-transcriptional gene regulation. We also want to investigate the consequences of APA during oncogenic transformation, tumor progression and metastasis and find regulators of APA. Finally, we want to uncover groups of transcripts subject to coordinated post-transcriptional processes and identify the regulators. This project will help us obtain a deeper understanding of events leading to cancer that do not necessarily involve mutations and might provide new strategies for diagnosis and treatment.