

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Reciprocal actions of REST and a microRNA promote neuronal identity

by

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MicroRNAs regulate diverse cellular processes by mediating the post-transcriptional repression of many mRNAs. Understanding how microRNAs integrate into the complex gene regulatory networks that control cell fate specification and lineage determination requires elucidation of the mechanisms of microRNA gene regulation and the identification of microRNA targets. Here, I show that a family of microRNAs are regulated by REST, a transcription factor best known for its role in controlling the expression of fundamental neuronal traits. One of the REST-regulated microRNAs, miR-124a, exhibits abundant brain-specific expression and has previously been shown to be capable of promoting a neuronal-like mRNA profile in HeLa cells by decreasing the levels of hundreds of non-neuronal transcripts. In this study, we show that miR-124a can also promote neuronal differentiation of cortical progenitors. Extensive experimental validation of putative targets identified a cohort of non-neuronal mRNAs that are directly downregulated by miR-124a. These target transcripts encode various proteins with functions that may be unnecessary, or even antagonistic, to proper neuronal development and activity. Analysis of the characteristics of validated targets revealed the importance of miR-124a seed sites and 3'UTR sequence context on microRNA-mediated repression. The results of this study suggest a model wherein miR-124a and REST, through their reciprocal actions, play a central role in promoting neuronal differentiation of progenitor cells and may be critical for maintaining the stability of the neuronal phenotype.

Date: May 11, 2007

Time: 10:45-11:45

Place: Life Sciences Bldg, Room 038

Program: Molecular and Cellular Biology

Dissertation Advisor: Gail Mandel