

Post-transcriptional Gene Silencing in Neuronal Differentiation, Development and Schizophrenia

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DECLARATION

This thesis contains no material which has been accepted for the award of any other Degree or Diploma in any University or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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NATALIE J. BEVERIDGE

March, 2011

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ABSTRACT

Efforts to understand the underlying mechanisms driving changes in gene expression have focused predominantly on genetic and epigenetic influences on transcription mediated by alterations in signal transduction pathways, their transcription factors, or gene promoter elements and associated chromatin structure. However, recent studies have emerged that also highlight the impact of post-transcriptional regulation of gene expression. Post-transcriptional influences mediated by microRNA (miRNA) play a major role in coordinating the regulation of gene expression during the differentiation and development of the brain. This study has established the specific patterns miRNA expression throughout neuronal differentiation, normal human brain development and schizophrenia.

Using a custom microarray, miRNA expression was examined in differentiating neuroblasts *in vitro*. This revealed that the entire miR-17 family of miRNA displayed reduced expression in response to the differentiation process and was shown to target several known neuronal markers. This result suggested that the miR-17 family might be working co-operatively to fine tune the gene expression changes taking place in the neuronal differentiation process. miRNA expression was also examined in human neurodevelopment. These results demonstrated that a large proportion of miRNA displayed distinct expression changes with age and are likely to be responsible for many of the gene expression changes observed during brain maturation and throughout aging. Perhaps even more significantly, miRNA expression profiling of postmortem brain in the superior temporal gyrus and dorsolateral prefrontal cortex revealed an increase in miRNA expression and biogenesis that suggested a role for miRNA expression in the neuropathology of schizophrenia.

The findings presented in this thesis support mounting evidence that miRNA play a crucial role in the regulation of gene expression in normal neurodevelopment and alterations to miRNA expression contributes to the pathogenesis of schizophrenia.

LIST OF ABBREVIATIONS

3'-UTR	3' untranslated region
Ago	Argonaute
BDNF	brain-derived neurotrophic factor
<i>C. elegans</i>	<i>Caenorhabditis elegans</i>
CAMK2γ	Calcium/calmodulin-dependent protein kinase type II gamma
CLOCK	Circadian Locomotor Output Cycles Kaput
CNV	copy number variant
CREB	cAMP response element-binding
DGCR8	DiGeorge critical region 8
DISC1	Disrupted in schizophrenia 1
DLPFC	dorsolateral prefrontal cortex
DNA	deoxyribonucleic acid
ERBB4	Receptor tyrosine-protein kinase erbB-4
FEZ1	Fasciculation and elongation protein zeta-1
FMR1	fragile X mental retardation 1
FMRP	fragile X mental retardation protein
GABA	γ -Aminobutyric acid
GWAS	genome-wide association study
IRES	internal ribosome entry site
LIMK1	Lim-domain-containing protein kinase 1
MECP2	methyl CpG binding protein 2 (Rett syndrome)
miRNA	microRNA
mRNA	messenger RNA
NDEL1	Nuclear distribution protein nudE-like 1
NMDA	N-Methyl-D-aspartic acid
NRG1	neuregulin-1
P bodies	processing bodies
PABP	polyA binding protein
PDE4B	cAMP-specific 3',5'-cyclic phosphodiesterase 4B
pre-miRNA	precursor miRNA
pri-miRNA	primary miRNA
PTBP1	Polypyrimidine tract-binding protein 1
REST	RE1-Silencing Transcription factor
RISC	RNA induced silencing complex
RNA	ribonucleic acid
RNAi	RNA interference
rRNA	ribosomal RNA
siRNA	short-interfering RNA
SLITRK1	SLIT and NTRK-like family, member 1
SNP	single nucleotide polymorphism
STG	superior temporal gyrus
tRNA	transfer RNA