About OMICS Group

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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
A critical role of an exon junction complex (EJC) factor in regulation of embryonic neurodevelopment and implications in neurodevelopmental disorders

Yingwei Mao
Department of Biology
Penn State University
2015 International Conferences on Transcriptomics
July 27, 2015, Orlando, Florida
Neurodevelopment and neurological diseases
Nonsense-mediated mRNA decay (NMD)

- Nonsense mediated decay (NMD) functions to detect premature termination mutations and prevent the expression of truncated or erroneous proteins.
- NMD is triggered by exon junction complexes (EJCs) and their associated RNPs that are deposited during pre-mRNA processing.
- The core complex includes Upf factors, RBM8A, eIF4AIII, MNL51/BTZ, and Magoh.
RBM8A is in 1q21.1 associated with schizophrenia and TAR syndrome

- Mutation in RBM8a is the cause of Thrombocytopenia and Absent Radius syndrome (TAR) syndrome (Nature Genetics. 2012, 44:435),
Neocortical neurogenesis and neuronal migration

(Greig, Woodworth et al. 2013)
RBM8a expression during neurodevelopment

Zou et al. *Neural Development*, 2015
Knockdown of RBM8a increases neuronal migration
Knockdown of RBM8a decreases progenitor proliferation

Cell cycle exit index = \[\frac{\text{GFP}^+ \text{ BrdU}^+ \text{ Ki67}^-}{\text{GFP}^+ \text{ BrdU}^-}\]
Overexpression of RBM8a stimulates progenitor proliferation

Zou et al. Neural Development, 2015
RBM8a conditional knockout

A

fl/fl  fl/+  +/+  fl/+  

B

RBM8a

cre  -  +  

RBM8a

Actin

weight (g)  length (cm)

6.1 ± 1.1  5.8 ± 1.2

4.03  4.8

***  ***

Colleen McSweeney
The brain deficits of RBM8a cKO mice

RBM8a<sup>f/+</sup> Nes-cre; RBM8a<sup>f/+</sup>

RBM8a<sup>f/+</sup> Nes-cre; RBM8a<sup>f/+</sup>

E16

BrdU/ DNA

NeuN/GFAP/ToPro

Dentate gyrus

Colleen McSweeney
Neuronal layer defects in RBM8a cKO brain
RBM8a downstream genes are enriched for risks of neurological diseases

A

Type of RNA
- antisense
- lincRNA
- processed transcript
- protein coding
- sense intronic
- sense overlapping
- snoRNA
- pseudogene
- polymorphic pseudogene

B

<table>
<thead>
<tr>
<th>Disease</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ASD</td>
<td>2.53 x 10^{-11}</td>
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<tr>
<td>SCZ</td>
<td>1.35 x 10^{-5}</td>
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<tr>
<td>AD</td>
<td>4.35 x 10^{-4}</td>
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<tr>
<td>ID</td>
<td>8.17 x 10^{-3}</td>
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<tr>
<td>Crohn’s Disease</td>
<td>0.736</td>
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Zou et al. Neural Development, 2015
Confirmation of RNAseq data at protein level
Pathways of RBM8a downstream genes

A. Functional clusters of differentially expressed RNAs

B. MAPK Signaling

C. Growth factor signaling

D. Rho Signaling

Zou et al. Neural Development, 2015
Functions of RBM8a in behaviors
RBM8A expression in adult brain

Allen Brain atlas
RBM8a is localized in axons and dendrites

(Alachkar et al. *Current Molecular Medicine*, 2013)
Lentiviral stereotaxic injection

(A) Lentiviral RBM8a expressing construct

(Alachkar et. al. *Current Molecular Medicine*, 2013)
Mice expressing RBM8a show increased anxious behaviors

- Open field test
- Elevated plus maze

(Alachkar et al. *Current Molecular Medicine*, 2013)
Summary

• Embryonic brain

- CP
- IZ
- VZ/SVZ

RBM8a

Neuronal maturation

NSC proliferation

behavior
Acknowledgements

Mao lab

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Dr. Benhard Luscher, PSU
Dr. Yongshen Shi, UC Irvine
Dr. Jizhong Zou, NIH

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Genome editing on RBM8a

Fengping Dong
RNA-immunoprecipitation analysis

A RNAAs

RNA-IP-RNASeq

IP

RBM8a

RNASeq

B snoRNA

sense intronic

snRNA

processed transcript

sense overlapping

antisense

lincRNA

antisense

lincRNA

miRNA

misRNA

protein coding

antisense

lincRNA

miRNA

misRNA

protein coding

rRNA

pseudogene

processed transcript

sense intronic

snoRNA

snRNA
Possibility for novel therapy/early intervention

- **Risk** (<12)
- **Prodrome** (12-16)
- **Psychosis** (16-24)
- **Chronic disability** (>24)

Early intervention /prevention

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