Curriculum Vitae

- Zhiyuan Luo, Ph.D.
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Profile

- Highly self-motivated Ph.D. with demonstrated research experience in cortical development and RNA biology
- Eager to absorb as knowledge and insight as possible in the pursuance of goals
- Strong interpersonal skills
- Computer skills: Unix/Linux/Windows, R

Research Interests

- Cortical development
- Regulation of Notch Signaling
- Long non-coding RNA
- Bioinformatic analysis

Research Experiences

- **Regulation of Notch signaling**

  Notch signaling is an evolutionarily conserved signaling pathway that regulates a plethora of developmental and oncogenic processes. The release and nuclear translocation of the intracellular domain of Notch receptor (NICD) is essential for Notch signaling mediated transcriptional activation and repression. However, little is known about how the levels of NICD is controlled via post-translational regulation. Although NUMB, a cell-fate determinant and an adaptor protein, is largely believed to antagonize Notch by facilitating Notch receptor's endocytosis and subsequent degradation, some studies suggest NUMB could play roles like Notch.

  Using a NOTCH1 intracellular domain (N1ICD) stably expressed cell line, we unveiled that NUMB stabilizes N1ICD via regulating the ubiquitin-proteasome machinery, which is independent of NUMB's function in modulating endocytosis. By screening E3 ubiquitin ligases and deubiquitinases (DUBs), BAP1 (BRCA1-associating protein) was identified as a key N1ICD regulator downstream of NUMB, and NUMB facilitates the association between N1ICD and BAP1 to stabilize N1ICD. Intriguingly, BAP1 stabilizes N1ICD independent of its DUB activity but relying on the BRCA1-inhibiting function. Consistently, BAP1 maintains the stem-like properties of cortical neural progenitor cells.

- **Long non-coding RNA**

  Long non-coding RNAs (lncRNAs) are a heterogeneous class of RNAs that generally defined as non-

protein-coding transcripts longer than 200 nucleotides. In general, they have lower primary sequence conservation, less abundancy and display more tissue-specific expression patterns than protein-coding genes. An increasing number of studies have shown that lncRNAs can be involved in various critical biological processes, such as chromatin remodeling, gene transcription, protein trafficking.

We identified lncRNA-*Dubr* is both expressed in the nucleus of cortical intermediate progenitor cells and neurons in the dorsal forebrain, and its expression level significantly increases as neurogenesis process. *Dubr*-/- mice were born at normal Mendelian ratios and are indistinguishable from their wide-type littermates. However, by postnatal day 3 (P3), *Dubr*-/- mice presented prominent growth retardation with significant lighter body and organ weights.

TAR DNA binding protein 43 (TDP-43) was identified as a *Dubr* associated protein via biotinylated RNA pull-down assay. Domain mapping experiments showed this interaction was dependent on the RRM1 domain of TDP-43. CLIP-qPCR and CLIP-Seq further verified the specificity of this interaction. The expression level of *Dubr* is not affected by TDP-43 knockdown and *Dubr* loss do not influence the expression of TDP-43.

To investigate the mechanism of *Dubr* loss leading to growth retardation, primary MEF (mouse embryonic fibroblast) cell was isolated and immortalized. We found *Dubr* loss affects p53 protein. Further studies are ongoing to determine how the interaction between *Dubr* and TDP-43 regulates p53.

Future Research Directions

Over the past decades, the research emphasis of cortical development is focused on transcriptional regulation, such as transcriptional factors, histone modification. The discovery of reversible mRNA methylation opens a new realm of post-transcriptional gene regulation in eukaryotes. N^6-methyladenosine (m6A) is the most abundant internal modification of mRNA. Recently, the m6A modification is shown to influence varieties of developmental processes including cortical neurogenesis, spermatogenesis.

How the epitranscriptome helps orchestrate brain development, it is an intriguing question. I envision my future research to investigate the roles of m6A modification in neurogenesis. How dysregulation of epitranscriptome contributes to brain disorders? Which m6A targets are critical to modulating the tempo of cortical neurogenesis? How does the cellular machinery target m6A to the correct transcripts? Answering these questions will advance the understanding of brain development and cell fate decision.

Technical Skills

- Histochemistry: Frozen section, Golgi staining, Immunochemistry, Immunofluorescence, *In situ* Hybridization (ISH), X-gal staining
- Bioinformatics: RNA-Seq, ChIP-Seq, ATAC-Seq, CLIP-Seq
- Cell Culture: Neurosphere culture, Isolation and culture of primary MEF, Stable cell line construction
- Animal testing: Mice breeding, *In Utero* Electroporation (IUE)

- Protein Biochemistry: Immunoprecipitation, Immunoblot, CLIP, ChIP, RNA Pull-Down
- Molecular Biology: General molecular biology procedures including PCR, cloning, mutagenesis etc.

Publications

Zhiyuan Luo, Lili Mu, Yue Zheng, Wenchen Shen, Jiali Li, Lichao Xu, Bo Zhong, Ying Liu, and Yan Zhou (2019). NUMB enhances Notch Signaling by repressing ubiquitination of NOTCH intracellular domain. Journal of Molecular Cell Biology.

Wei Li, Wenchen Shen, Bo Zhang, Kuan Tian, Yamu Li, Lili Mu, **Zhiyuan Luo**, Xiaoling Zhong, Xudong Wu, Ying Liu, and Yan Zhou (2019). Long non-coding RNA *LncKdm2b* regulates cortical neuronal differentiation by *cis*-activating *Kdm2b*. Protein & Cell.

Education

- Wuhan University, Wuhan, China — Ph.D. Cell Biology, Dec 2019
- Northeast Forestry University, Harbin, China — B.S. Biological Science, 2012

Contacts for References

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