BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Li, Jiali

eRA COMMONS USER NAME (credential, e.g., agency login): JIALILI1

POSITION TITLE: professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
West Anhui Health Vocational College	MB	06/1991	Medicine
Kunming Medical University	MS	06/2000	Pathophysiology
Fudan University, Shanghai	PHD	06/2003	Neurobiology
Mount Sinai School of Medicine	Postdoctoral Fellow	02/2007	
Rutgers, The State University of New Jersey	Postdoctoral Fellow	09/2010	

A. Personal Statement

My dedication to understanding brain aging and neurodegenerative diseases stems from witnessing their profound impact on patients and families. With extensive expertise in molecular and epigenetic regulation of Alzheimer's disease (AD) and Ataxia-Telangiectasia, I integrate findings from diverse experimental models, including rodent and nonhuman primate models, as well as patient-derived specimens. My laboratory focuses on unraveling complex regulatory networks driving neurodegeneration, particularly DNA demethylation, long noncoding RNAs, and circular RNAs. Through combined in vitro and in vivo approaches, we investigate how these elements influence astrocyte homeostasis, neuronal resilience, and disease progression. Recently, my research has expanded to examine molecular and neural circuit-based mechanisms in brain aging, studying the interplay between biobehavioral alterations and neuroimmune dysregulation to identify novel therapeutic targets. I employ multi-omics approaches with advanced imaging and functional assays to bridge the gap between molecular pathology and behavioral outcomes, working toward innovative strategies to mitigate cognitive decline and neuropsychiatric disturbances in aging populations. Beyond research, I find deep fulfillment in education and mentorship. I deliver courses on fundamental neuroscience principles and aging biology while maintaining an extensive history of mentoring undergraduate, graduate, and post-doctoral scholars. Creating an inclusive research environment where emerging scientists can develop their own voices is central to my mission. My work is driven by the potential for scientific discovery to transform lives affected by neurodegenerative diseases. With demonstrated expertise, leadership capabilities, and unwavering commitment to scientific advancement, I am prepared to tackle the complex challenges in neurodegenerative disease research and contribute meaningfully to developing effective interventions for these devastating conditions.

1. Xu K, Zhang Y, Chen Y, Zhu X, Li Y, Lv L, He X, Hu Z, Li Y, Ye M, Jiang D, He Z, Jin W, Li Y, Yu X, Zhang DF, Herrup K, Zheng P, Yao YG, Wu DD, Li J. ATM deficiency drives phenotypic diversity and Purkinje cell degeneration in a macaque model of ataxia-telangiectasia. Cell Rep Med. 2025 Sep 16;6(9):102355. PubMed PMID: 40961921.
2. Xiong W, Xu K, Sun JK, Liu S, Zhao B, Shi J, Herrup K, Chow HM, Lu L, Li J. The mitochondrial long non-coding RNA lncMtloop regulates mitochondrial transcription and suppresses Alzheimer's disease. EMBO J. 2024 Dec;43(23):6001-6031. PubMed Central PMCID: PMC11612450.
3. Zhang Z, Zhang Y, Yuwen T, Huo J, Zheng E, Zhang W, Li J. Hyper-excitability of corticothalamic PT neurons in mPFC promotes irritability in the mouse model of Alzheimer's disease. Cell Rep. 2022 Nov 1;41(5):111577. PubMed PMID: 36323265.
4. Xu K, Zhang Y, Xiong W, Zhang Z, Wang Z, Lv L, Liu C, Hu Z, Zheng YT, Lu L, Hu XT, Li J. CircGRIA1 shows an age-related increase in male macaque brain and regulates synaptic plasticity and synaptogenesis. Nat Commun. 2020 Jul 17;11(1):3594. PubMed Central PMCID: PMC7367861.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2025 -	Member, Center for Discovery and Innovation of Hackensack Meridian Health.
2022 -	professor, Hackensack Meridian School of Medicine, JFK University Medical Center
2019 - 2022	Professor, Peking University, School of Basic Medicine in Peking University Health Science Center, IDG/McGovern Institute for Brain Research at Peking University
2014 - 2018	principal investigator, Kunming Institute of Zoology, Chinese Academy of Sciences
2010 - 2013	Research assistant professor, Rutgers University

Honors

2022 - 2025	Member , The Alzheimer's Association
2009 - 2025	Member of the Society for Neuroscience , the Society for Neuroscience
2017 - 2022	Member of the academic committee , Kunming Institute of Zoology, Chinese Academy of Sciences
2016 - 2022	Member of the Nonhuman Primate Animal Care and Use Committee , Kunming Institute of Zoology, Chinese Academy of Sciences
2016 - 2022	Member of the Animal Care and Use Committee , Kunming Institute of Zoology, Chinese Academy of Sciences
2014 - 2018	Chinese Academy of Sciences "Hundred Talents Program" award, Chinese Academy Sciences
2025	NIH NOMD study section ad hoc reviewer, NIH
2025	Member of the Animal Care and Use Committee ol of Medicine, Hackensack Meridian Health, Inc.

C. Contribution to Science

1. Molecular basis and neural circuits in Alzheimer's disease Our ongoing research endeavors center around elucidating the molecular mechanisms implicated in neurodegeneration observed in Alzheimer's disease (AD). To date, our investigations have yielded significant advancements: 1) We have documented a discernible depletion of 5-hydroxymethylcytosine (5hmC) in the brains of both human AD patients and 3xTg mice. Our studies suggest that the TET family of enzymes, notably TET3, plays a pivotal role in this 5hmC loss within the AD brain in response to Aβ. 2) Through our investigations, we have uncovered the translocation of the intracellular domain (PICD) of PTPRT, a receptor-type tyrosine-protein phosphatase, to the nucleus subsequent to ADAM10- and γ-secretase-dependent cleavage. This translocation event culminates in the accumulation of phosphorylated signal transducer and activator of transcription 3 (pSTAT3Y705). Remarkably, PICD alone exhibits the capacity to diminish pSTAT3Y705 levels, mitigate Aβ deposition in AD neurons, enhance synaptic functionality, and ameliorate behavioral impairments in AD mice. 3) Our focus has also extended to investigating the neural circuits underpinning the neuropsychiatric manifestations of AD. Our findings indicate that pyramidal tract (PT) neurons projecting to the thalamus in AD mouse models display heightened excitability, correlating with increased irritability and aggression. We have identified reduced levels of Kv6.3 in corticothalamic PT neurons as a factor contributing to this hyper-excitability, which closely correlates with aggressive behaviors. Notably, the overexpression of Kv6.3 effectively counteracts abnormal excitability in corticothalamic PT neurons within the medial prefrontal cortex (mPFC) and mitigates aggressive behaviors in AD mice. 4) Maintaining mitochondrial homeostasis is crucial for cell survival and organismal health, as evidenced by the links between mitochondrial dysfunction and various diseases, including Alzheimer's disease (AD). Recently, we identified that lncMtDloop, a non-coding RNA of unknown function encoded within the D-loop region of the mitochondrial genome, maintains mitochondrial homeostasis and contributes to AD pathogenesis.
    a. Xiong W, Xu K, Sun JK, Liu S, Zhao B, Shi J, Herrup K, Chow HM, Lu L, Li J. The mitochondrial long non-coding RNA lncMtloop regulates mitochondrial transcription and suppresses Alzheimer's disease. EMBO J. 2024 Dec;43(23):6001-6031. PubMed Central PMCID: PMC11612450.

b. Liu S, Zhang Z, Li L, Yao L, Ma Z, Li J. ADAM10- and γ-secretase-dependent cleavage of the transmembrane protein PTPRT attenuates neurodegeneration in the mouse model of Alzheimer's disease. FASEB J. 2023 Feb;37(2):e22734. PubMed PMID: 36583697.

c. Zhang Z, Zhang Y, Yuwen T, Huo J, Zheng E, Zhang W, Li J. Hyper-excitability of corticothalamic PT neurons in mPFC promotes irritability in the mouse model of Alzheimer's disease. Cell Rep. 2022 Nov 1;41(5):111577. PubMed PMID: 36323265.

d. Zhang Y, Zhang Z, Li L, Xu K, Ma Z, Chow HM, Herrup K, Li J. Selective loss of 5hmC promotes neurodegeneration in the mouse model of Alzheimer's disease. FASEB J. 2020 Dec;34(12):16364-16382. PubMed PMID: 33058355.

2. Roles of Noncoding RNA-Mediated Regulation in Brain Aging In addition to the contributions described above, I worked with a team of collaborators to investigate the biological function of noncoding RNAs, including long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), in the mammalian brain during aging. Through comprehensive analyses of RNA-seq and CAGE-seq, we characterized the dynamic changes in lncRNA expression in the rhesus macaque brain across different stages of development and aging. Our findings provide insight into spatial-, age-, and sex-biased changes in lncRNA expression in the macaque brain. We observed that the distinct classification of such changes might represent a previously unappreciated regulatory system that potentially contributes to postnatal brain development and aging. Additionally, using deep RNA profiling with linear RNA digestion by RNase R, we generated a comprehensive map of changes in circRNA expression in the rhesus macaque brain during aging. Cluster analysis revealed that dynamic changes in circRNA expression exhibit spatial-, sex-, and age-biased specificities. We also identified circGRIA1, a conserved circRNA isoform derived from the genomic loci of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunit Gria1, as being involved in homeostatic synaptic plasticity via negative regulation of GluR1 expression. Our studies indicate that dynamic changes in lncRNA and circRNA expression play important roles in the biological process of brain aging. aging.

   a. Xu K, Zhang Y, Xiong W, Zhang Z, Wang Z, Lv L, Liu C, Hu Z, Zheng YT, Lu L, Hu XT, Li J. CircGRIA1 shows an age-related increase in male macaque brain and regulates synaptic plasticity and synaptogenesis. Nat Commun. 2020 Jul 17;11(1):3594. PubMed Central PMCID: PMC7367861.

   b. Xu K, Chen D, Wang Z, Ma J, Zhou J, Chen N, Lv L, Zheng Y, Hu X, Zhang Y, Li J. Annotation and functional clustering of circRNA expression in rhesus macaque brain during aging. Cell Discov. 2018;4:48. PubMed Central PMCID: PMC6141548.

   c. Liu S, Wang Z, Chen D, Zhang B, Tian RR, Wu J, Zhang Y, Xu K, Yang LM, Cheng C, Ma J, Lv L, Zheng YT, Hu X, Zhang Y, Wang X, Li J. Annotation and cluster analysis of spatiotemporal- and sex-related lncRNA expression in rhesus macaque brain. Genome Res. 2017 Sep;27(9):1608-1620. PubMed Central PMCID: PMC5580719.

3. Molecular and epigenetic basis in Ataxia-Telangiectasia (A-T) My early publications focused on the molecular and epigenetic basis of neurodegeneration in Ataxia-Telangiectasia (A-T). A-T is a hereditary neurodegenerative disease in humans, marked by early-onset progressive cerebellar atrophy. It results from mutations in the ATM gene, crucial for DNA damage repair. Our research identified several defects in the molecular and epigenetic systems of the A-T brain, including a) Nuclear accumulation and cytoplasmic depletion of HDAC4 resulting from ATM deficiency, which is a key factor leading to the degeneration of Purkinje cells in the cerebellum of A-T patients. b) Increased trimethylation of histone H3 on Lys27 (H3K27me3) mediated by the polycomb repressive complex 2 (PRC2), which is also important in the pathogenesis of A-T. c) Alteration in 5hmC-mediated epigenetic regulation, which makes a major contribution to Purkinje cell vulnerability in ATM deficiency as well as a defect in ATR-dependent DNA repair. D) Current rodent models do not accurately mimic the absence of functional ATM protein and its effects, limiting the development of new treatments for A-T. Recently, we created an ATM-deficient primate model using CRISPR-Cas9 in rhesus macaques (Macaca mulatta). Our latest study revealed that ATM-deficient macaques showed growth delays, low lymphocyte levels, increased alpha-fetoprotein, oculocutaneous telangiectasias, and increased radiation sensitivity. Notably, ATM-deficient macaques not only exhibited significant cerebellar volume reduction but also loss of Purkinje neurons, and early-stage cerebellar neurodegeneration. Purkinje and granular cells single-cell RNA sequencing (scRNA-seq) and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) revealed major changes in gene expression profile and chromatin remodeling in cerebellar neural cells of A-T macaques. I served as the primary investigator or co-investigator in all these studies.

a. Xu K, Zhang Y, Chen Y, Zhu X, Li Y, Lv L, He X, Hu Z, Li Y, Ye M, Jiang D, He Z, Jin W, Li Y, Yu X, Zhang DF, Herrup K, Zheng P, Yao YG, Wu DD, Li J. ATM deficiency drives phenotypic diversity and Purkinje cell degeneration in a macaque model of ataxia-telangiectasia. Cell Rep Med. 2025 Sep 16;6(9):102355. PubMed PMID: 40961921.
b. Jiang D, Zhang Y, Hart RP, Chen J, Herrup K, Li J. Alteration in 5-hydroxymethylcytosine-mediated epigenetic regulation leads to Purkinje cell vulnerability in ATM deficiency. Brain. 2015 Dec;138(Pt 12):3520-36. PubMed Central PMCID: PMC4668921.
c. Li J, Hart RP, Mallimo EM, Swerdel MR, Kusnecov AW, Herrup K. EZH2-mediated H3K27 trimethylation mediates neurodegeneration in ataxia-telangiectasia. Nat Neurosci. 2013 Dec;16(12):1745-53. PubMed Central PMCID: PMC3965909.
d. Li J, Chen J, Ricupero CL, Hart RP, Schwartz MS, Kusnecov A, Herrup K. Nuclear accumulation of HDAC4 in ATM deficiency promotes neurodegeneration in ataxia telangiectasia. Nat Med. 2012 May;18(5):783-90. PubMed Central PMCID: PMC3378917.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/jiali.li.5/bibliography/public/