2ND ANNUAL SYMPOSIUM CENTER FOR RNA BIOLOGY AND MEDICINE

November 3, 2023

Center for RNA
Biology and Medicine

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Cover Image:
David Nikom, Graduate Student
Sika Zheng Lab, Biomedical Sciences-UC Riverside
“Viral Mutant Tau Propagation from Entorhinal Cortex to Hippocampus”

Special thanks to our symposium poster judges:
Changcheng Zhou, Jernej Murn, Ted Karginov

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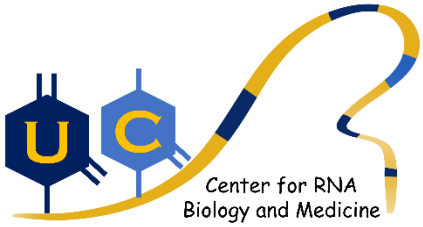

Welcome to the Second Symposium
Center for RNA Biology and Medicine

In the ever-evolving realm of modern biology and medicine, RNA research remains a guiding light, illuminating new avenues for discovery and innovation. This was epitomized in the 2023 Nobel Prize in Physiology or Medicine, awarded to Katalin Karikó and Drew Weissman for their discoveries in nucleoside base modifications which paved the way for the development of effective mRNA vaccines.

While we celebrate the triumph of mRNA vaccines, we also pay homage to the enduring values of persistence, dedication, and unwavering belief in basic research, exemplified by Dr. Karikó's journey. Her story reminds us that the pursuit of scientific knowledge often demands resilience in the face of adversity, serving as an inspiration for our commitment to advancing basic research.

As we convene for our 2nd Symposium of the Center for RNA Biology and Medicine, we embrace the relentless spirit of scientific exploration that unites us. Our voyage continues, driven by curiosity, passion, and the quest for knowledge. In these challenging times, I often find research one of the best daily activities to see the light of values and a better future we all strive for. We come together not only to share our discoveries but to bind our community.

Lastly, as some have inquired over the past year, a unique connection resides within our Center's logo, offering a subtle blend of "UCR" and the elements found in RNA. The 'U' and 'C' symbolize the two RNA bases, while 'R' represents a segment of pre-mRNA interconnected by exons in blue and introns in gold. The light blue segment hints at a mysterious alternative exon. 'U' and 'C' also denote a part of the intronic polypyrimidine tract near a 3' splice site. The design credit for this innovative logo goes to Sabrina Z. Zheng.

Thank you for being part of this symposium. We extend our gratitude to our sponsor, Zymogen, whose generous support ensures that this intellectual exchange remains accessible to all, as well as Pica Preston and the entire team of staff and student volunteers who bring this symposium to life. Each participant enriches this gathering, and we eagerly anticipate the insights, discussions, and collaborations that will emerge.

Sika Zheng, Ph.D.

Director, Center for RNA Biology and Medicine

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Sincere appreciation to our RNA center volunteers and faculty:

Trainee volunteers:

Allen Seylani, Medical student, UCR School of Medicine
David Nikom, Graduate student, Neuroscience Program
HeaJin Hong, Graduate student, Department of Biochemistry
Lin Lin, Postdoctoral Fellow, Biomedical Sciences
Naoto Kubota, Postdoctoral Fellow, Biomedical Sciences
Shiyuan Chen, Graduate Student, Genetics, Genomics & Bioinformatics Program
Yannan Hu, Graduate student, Genetics, Genomics & Bioinformatics Program
Yi-Li Lam, Graduate student, Biomedical Sciences

RNA Faculty:

Julia N. Bailey-Serres, PhD: Botany and Plant Sciences
Gregor Blaha, **PhD**: Biochemistry
Sihem Cheloufi, PhD: Biochemistry
Meng Chen, PhD: Botany and Plant Sciences
Qi Chen, PhD: Division of Biomedical Sciences
Weitao Chen, PhD: Mathematics
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Heyrim Cho, PhD: Mathematics
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UC Center for RNA Biology and Medicine

UC RIVERSIDE | Center for RNA Biology and Medicine

2nd Annual Symposium
Center for RNA Biology and Medicine

Friday November 3, 2023

Genomics Auditorium and Lobby

Agenda

8:30 – 9:10 am	**Registration, Badge pick-up, and Poster set-up**
9:10 am	**Symposium Opens – Welcome and Introduction to Center for RNA in Biology and Medicine** Sika Zheng, Ph.D., Center Director | University of California, Riverside
9:10 – 9:15 am	**Welcome address** Rodolfo H. Torres, Vice Chancellor for Research and Economic Development
9:20 – 10:20 am	**"Designer DNA Drug Therapy for Neurodegenerative Disease"** Don Cleveland, Ph.D., Keynote Speaker | University of California, San Diego
10:20 – 10:25 am	**Group Photo**
10:25 – 10:45 am	**Coffee Break**

SESSION I, RNA PROCESSING AND QUALITY CONTROL – CHAIR: MARIA NINOVA, PHD.

10:45 – 11:20 am	**"mRNA 3' processing and deflation"** Yongsheng Shi , Ph.D. | University of California, Irvine
11:20 – 11:55 am	**"Small non-coding RNA quality control in gene expression and disease"** Jens Lykke-Andersen, Ph.D. | University of California, San Diego
11:55 am – 1:15 pm	**Lunch and Poster Presentations**

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SESSION II, TRANSLATION – CHAIR: SEAN O'LEARY, PHD.

1:15 – 1:50 pm	**"The exquisite choreography of translation initiation"** Jody Puglisi, Ph.D. | Stanford University
1:50 – 2:25 pm	**"The cellular impact and regulation of long undecoded transcript isoform production and destruction"** Gloria Brar, Ph.D. | University of California, Berkeley
2:25 – 3:05 pm	**Afternoon Break and Poster Presentations**

SESSION III, RNA IN DISEASES – CHAIR: DJURDJICA COSS, PHD.

3:05 – 3:40 pm	**"RNA Modifications in Nucleotide Repeat Expansion Diseases"** Yinsheng Wang, Ph.D. | University of California, Riverside
3:40 – 4:15 pm	**"Posttranscriptional regulation of RNA splicing in leukemia"** Lili Wang, Ph.D. | City of Hope
4:15 – 4:50 pm	**"Buffering of transcription rate by mRNA half-life in Rett syndrome neurons and in neurodevelopment"** James Ellis, Ph.D. | SickKids Research Institute
4:50 – 5:00 pm	**Award Announcements and Closing Remarks**

2023 RNA Symposium Keynote Lecture: Don W. Cleveland, PhD.

Distinguished Professor and Chair, Department of Cellular and Molecular Medicine, University of California, San Diego

2018 Breakthrough Prize in Life Sciences

Don Cleveland is Professor and Chair of Cellular and Molecular Medicine at UC San Diego He has been elected to the U.S. National Academy of Sciences and National Academy of Medicine. He has identified principles of genome instability in cancer, demonstrating that single chromosome missegregation can trigger repeated chromosome shattering (chromothripsis) that initiates and drives genome evolution in cancer. For this work, in 2019 he became the 15th recipient of India's Genome Valley Excellence Award.

In neurosciences, he purified and characterized the first microtubule associated protein – tau – which misassembles in neurons in Alzheimer's disease and chronic brain injury. He uncovered mechanisms underlying the major genetic forms of Amyotrophic Lateral Sclerosis (ALS) and developed "designer DNA drugs" for silencing disease-causing genes responsible for the major diseases of the nervous system, with clinical trials now ongoing in ALS, Parkinson's, and Alzheimer's diseases. For his efforts in neurosciences, he received the 2018 Breakthrough Prize in Life Sciences, the 2019 Sean M. Healey International Prize for Innovation in ALS, the 2022 Lalji & Family ALS Endowed Award for Innovative Healing, the 2022 E.B. Wilson Medal, and the 2023 Rainwater Prize.

Gloria Brar, PhD.

Associate Professor, Molecular and Cell Biology- University of California, Berkeley

Dr. Gloria Brar attended UC Berkeley as an undergraduate, after which she started graduate school at MIT in 2002 where she worked with Angelika Amon, studying the factors that drive the stepwise loss of chromosome cohesion that occurs during meiosis. Following completion of her PhD in 2008, she joined Jonathan Weissman's lab at UCSF. Dr. Brar was one of the first to use the ribosome profiling method to measure translation globally, applying it to a timecourse of meiosis and identifying many surprises in the process, including pervasive non-AUG initiation, uORF translation, and synthesis of short proteins.

In 2014, Gloria started her independent group in the MCB department at UC Berkeley, earning tenure in 2020. At Berkeley, the Brar lab has focused on uncovering the strategies that cells use to ensure successful gamete production. As one example, in partnership with the Ünal lab, they defined a previously overlooked mode of gene regulation that is common and produces previously unrecognized noncoding RNAs.

Jens Lykke-Andersen, PhD.

Professor, Department of Molecular Biology- University of California, San Diego

Dr. Jens Lykke-Andersen received his Ph.D. from University of Copenhagen, Denmark in 1997. He was a postdoctoral fellow at Yale University Medical School before joining the faculty of MCD Biology at University of Colorado Boulder in 2001. He was named a Pew Scholar in 2003. He joined the Division of Biological Sciences at UCSD in 2009.
The Lykke-Andersen laboratory studies the mechanisms of regulation of translation and mRNA turnover in human gene expression. Research in recent years has revealed the importance of regulated mRNA translation and stability in the correct control of gene expression, and how its deregulation can lead to disease. Many of the general factors that direct mRNA translation and the enzymes that degrade mRNAs have been described in recent years. Our laboratory is interested in how these factors are differentially regulated on individual mRNAs to control their rates of translation and mRNA turnover, and how this is regulated by cell signaling.

Joseph Puglisi, PhD.

Jauch Professor, Department of Structural Biology - Stanford University

Dr. Joseph (Jody) Puglisi is Jauch Professor and CZI Biohub Investigator in the Department of Structural Biology at Stanford University School of Medicine. His work focuses on the biophysical and structural analysis of RNAs and RNA-protein interactions and his group uses broad biophysical and biochemical methods to understand the interplay of structure and dynamics in a variety of systems, in particular translation. Born and raised in scenic New Jersey, he received a B.A. degree in Chemistry in 1984 from The Johns Hopkins University and a Ph.D. in Biophysical Chemistry from UC Berkeley in 1989 working with Ignacio Tinoco, Jr. After postdoctoral research in Strasbourg and MIT, he joined the faculty at UC Santa Cruz in Chemistry and Biochemistry in 1993. Dr. Puglisi moved to Stanford University in 1997, where he was Chair of the Department of Structural Biology from 2004 to 2014. He is a member of the US National Academy of Sciences.

Yongsheng Shi, PhD.

Professor & Chancellor's Fellow, Department of Microbiology & Molecular Genetics
School of Medicine, University of California, Irvine

Dr. Yongsheng Shi received his B.S. in Molecular Biology from Nankai University, China in 1996, and his Ph.D. in Biology from Syracuse University in 2002. The Shi lab is broadly interested in post-transcriptional gene regulation and its role in stem cell biology and in virus-host interactions. Their current focus is on the mRNA 3' end processing. The 3' ends of most eukaryotic mRNAs are formed by an endonucleolytic cleavage and the subsequent addition of a string of adenosines. Interestingly, the transcripts of ~70% of genes in all eukaryotes have alternative 3' ends that are formed by cleavage/polyadenylation at different sites, a phenomenon called mRNA alternative polyadenylation (APA). APA not only expands the proteomic and functional diversity, but also plays important roles in gene regulation. Deregulation of mRNA 3' processing and APA have been implicated in a wide spectrum of human diseases. However, it remains poorly understood how poly(A) sites are recognized and how their recognition is regulated.

The goal of the Shi lab is to decipher the rules that govern poly(A) site choice, or the "polyadenylation code", by using a combination of biochemical, genomic, and genetic approaches. Their studies aim to provide novel insights into the basic mechanisms of post-transcriptional gene regulation as well as its role in many physiological and pathological processes.

Lili Wang, MD. PhD.

Associate Professor, Department of Systems Biology,
Beckman Research Institute, City of Hope National Medical Center

Dr. Lili Wang completed her medical education at China Medical University in Shenyang, China. She further pursued her PhD in Immunology from Tokai University in Japan. She received postdoctoral training in basic immunology and cancer biology at the University of Illinois at Chicago and Dana-Farber Cancer Institute at Boston. In 2012, she became her career as a junior faculty member at Harvard Medical School, later joining Beckman Research Institute at City of Hope in 2017.

During her time at Dana-Farber Cancer Institute, Dr. Wang utilized cancer genome sequencing approach to delve into the genetic landscape of chronic lymphocytic leukemia (CLL). Notably, she made a significant discovery by identifying the RNA splicing factor SF3B1 as one of the most recurrently mutated genes in this deadly disease. This breakthrough promoted her to focus on understanding how RNA splicing dysregulation contributes to oncogenesis. Through her research, she and her team have identified both splicing factor mutation-dependent and -independent RNA splicing dysregulation in CLL. Dr. Wang's work has been published in prestigious journals such as the New England Journal of Medicine, Cancer Cell, Blood, JCI among others.

Yinsheng Wang, PhD.

Distinguished Professor, Chemistry Department - University of California, Riverside

Dr. Yinsheng Wang received his PhD. degree from Washington University in St. Louis after obtaining his BS and MS degrees from Shandong University and Dalian Institute of Chemical Physics, Chinese Academy of Sciences, respectively. He is currently a distinguished professor and Donald T. Sawyer Endowed Founder's Chair in Chemistry at the University of California Riverside. Dr. Wang's research involves the use of mass spectrometry, along with synthetic organic chemistry and molecular biology, for investigation about the occurrence and biological consequences of DNA damage as well as for the identification and functional characterizations of nucleic acid- and nucleotide-binding proteins. He has trained or in the process of training of over 90 PhD. students and post-doctoral fellows, and he has co-authored over 350 research articles.

Yinsheng was named as a fellow for the American Association for the Advancement of Sciences in 2012, and he was the recipient for the inaugural Chemical Research in Toxicology Young Investigator Award from the Division of Chemical Toxicology of the American Chemical Society (2012), the 2013 Biemann Medal from the American Society for Mass Spectrometry, the 2018 EAS Award for Outstanding Achievements in Mass Spectrometry, the 2020 RIVER award from the National Institute of Environmental Health Sciences, and the 2023 Founders Award from the ACS Division of Chemical Toxicology.

James Ellis, PhD.

Senior Scientist, Developmental and Stem Cell Biology
SickKids Research Institute

Dr. Ellis completed his B.Sc. at McGill University and his PhD at the University of Toronto with Dr. Alan Bernstein developing retrovirus vectors for gene targeting. His post-doctoral fellowship studying the beta-globin Locus Control Region was mentored by Dr. Frank Grosveld in London, UK. Dr. Ellis established his own research team at The Hospital for Sick Children (SickKids) in Toronto in 1994 with a focus on gene therapy for sickle cell anemia. He subsequently developed MECP2 vectors for Rett syndrome, and vectors with reporter genes that mark specific cell types. For example, the EOS vectors express specifically in pluripotent stem cells and facilitate generation of patient induced pluripotent stem (iPS) cells.

Dr. Ellis' research theme is to define disease mechanisms using gene delivery to reprogram and manipulate human stem cells. His team uses these cells to study post-transcriptional regulation of gene expression. They develop vectors with reporter genes that mark specific cell types, such as our EOS vectors that express highly in pluripotent stem cells but extinguish during differentiation. Their focus is on modeling Rett Syndrome, autism spectrum disorder, and Williams Beuren syndrome using patient specific induced pluripotent stem (iPS) cells. They phenotype the affected cells in vitro and interrogate potential disease pathways using chemical compound screens to identify candidate drugs that may have therapeutic utility.

Poster Abstracts

1. Folding and unfolding of an alpha-helical lid govern target double-stranded DNA break in Cas12a

Aakash Saha[1], Isabel Strohkendl[2], Mohd Ahsan[1], Catherine Moy[2], Alexander-Hoi Nguyen[2], Rick Russell2, David W. Taylor[2], and Giulia Palermo[1]

[1]University of California Riverside

[2]University of Texas at Austin

CRISPR-Cas12a came to the limelight not only as a genome-editing scissor but also as a robust nucleic acid detection tool. In this system, the guide CRISPR RNA (crRNA) binds the target DNA to form an R-loop and generates double-stranded DNA cleavages using a single RuvC domain. Current Cas12a structures leave an important gap in knowledge as to how Cas12a coordinates rate-limiting R-loop formation with RuvC nuclease activation. An alpha- helical lid in the RuvC domain was captured in varying degrees of folding along the R-loop formation. To better understand the role and dynamics of this lid, we performed Replica-exchange Adaptively Biased Molecular Dynamics (ABMD) simulations in a well-tempered ensemble to compute the energetic cost of folding the lid into an alpha helix in different R-loop intermediates. While the 5-bp R-loop system prefers a loop form of the lid, a barrierless folding and unfolding of the lid allows the DNA non-target strand (NTS) accommodation in the 16 bp R-loop intermediate. Finally, the lid assumes a stable alpha-helical state in the 20bp R-loop structure. Furthermore, Umbrella sampling and free energy simulations illuminate how the alpha-helical lid chaperons the DNA target strand traversal toward the spatially distant RuvC active site while being aided by the REC2 and Nuc domains. These observations were in concordance with the biochemical DNA cleavage assay. Thus, RuvC nuclease activation ushers the lid to fold and unfold and chaperons the target double-stranded DNA toward catalysis.

2. Effect of prebiotic conditions and encapsulation on the activity of self-aminoacylating ribozymes

Alberto Vázquez-Salazar[1], Rebecca Lee[1], Ziwei Liu[2], Christy Cho[3], Neal Devaraj[3], Yei-Chen Lai[1], and Irene A. Chen[1]

[1]Irene Chen Lab, Chemical and Biomolecular Engineering Department, UCLA

[2]MRC Laboratory of Molecular Biology

[3]University of California, San Diego

How life originated is one of the fundamental questions in natural science. The RNA world hypothesis, based on the functional plasticity displayed by RNA, posits that this molecule played a fundamental role in the origin and subsequent evolution of life. In this model, RNA would carry genetic information as well as catalyze chemical reactions, and thus greatly simplify the metabolic architecture of the earliest cells (termed "protocells").

Of the set of chemical reactions that the protocell could have had, that of aminoacylation (i.e., charging an amino acid onto an RNA) is one of the most important. In the modern cell, the aminoacylation of transfer RNA (tRNA) is carried out by protein enzymes, aminoacyl-tRNA synthetases (aaRS), which map the information transfer between specific codons and specific amino acids. However, in an RNA world, catalytic RNA molecules (ribozymes) would have self-aminoacylated using activated amino acids to enable the synthesis of peptides and proteins, acting as tRNAs and aaRS at the same time.

In the present work we characterize self-aminoacylating ribozymes by exploring their catalytic capabilities under prebiotic conditions, i.e., at concentrations of ions that are compatible with those of the primitive earth, the effect of various small molecules that could have been present in the medium, and the effect that encapsulation inside vesicles has on their catalytic activity. The present results help to understand how the important reaction of aminoacylation could have evolved in an RNA world.

3. Single-Molecule Dynamics of VEGF mRNA Recognition by Human eIF4F

Alexandra Huang, Hea Jin Hong, Matthew Guevara, Rong Hai, and Sean O'Leary

Department of Biochemistry and Molecular Biology, University of California, Riverside

Translation is a key biological process that is highly regulated at the initiation step to control the efficiency of protein synthesis. Eukaryotic initiation factor 4E (eIF4E) binds to the mRNA 5' cap and is further bound by eIF4G, a scaffolding protein, and eIF4A, an RNA helicase, to form the eIF4F complex that initiates cap-dependent translation. mRNAs vary in their dependence on eIF4F for translation efficiency. How interactions of the eIF4F subunits confer this dependence remains poorly understood. Furthermore, why specific mRNAs show differential dependence on individual subunits remains unclear. Here we characterized cap-recognition dynamics on the vascular endothelial growth factor (VEGF) mRNA, which exhibits high translation-efficiency dependency on eIF4E that is linked to oncogenesis. Through a time-resolved single-molecule fluorescence approach that directly observes eIF4E-cap interaction, we dissected the contributions of eIF4F subunits to VEGF mRNA recognition dynamics. The kinetics of eIF4E-cap interaction were surprisingly insensitive to addition of eIF4G and eIF4A. This contrasts strongly with cap-recognition dynamics of the 5' UTR of the SARS CoV-2 genomic mRNA, which shows a strong dependence on eIF4A for translation initiation. For the viral UTR, decelerated cap recognition induced by eIF4G was mitigated by addition of eIF4A, restoring efficient cap recognition. Our results suggest the cellular function of an mRNA contributes to its recognition by individual eIF4F subunits and calls for further study of different functional mRNAs to better characterize the interactions and function of the eIF4F complex.

4. Small Cell Lung Carcinoma or Small Cell Carcinoma of Ovary of Pulmonary Type? What Can the Long non-Coding RNA Tell Us?

Allen Seylani

University of California, Riverside, School of Medicine

Nearly 10 million people die due to cancer globally. The U.S reports nearly 200,000 new lung cancer diagnoses and 150,000 deaths each year. Smoking remains the strongest risk factor for developing Small Cell Lung Cancer (SCLC). SCLC is highly aggressive with poor prognosis typified by a five-year survival rate of a mere 3.5% and a ten-year survival rate of a meager 1.8%. The pathoetiology of SCLC frequently implicates genetic aberrations such as deletion of the short arm of chromosome 3, the loss of thyroid transcription factor-1 (TTF1), mutations in the RB1 tumor suppressor gene, and TP53 mutations that attenuate pro-apoptotic activities in neoplastic cells. Importantly, SCLC exhibits a pronounced proclivity for metastasis, often affecting the brain, bone, liver, and adrenal glands. Pulmonary-type Small Cell Carcinoma of the ovary, a rare variant, represents less than 1% of all ovarian tumors. It necessitates meticulous differential diagnosis to discriminate between primary ovarian small cell carcinoma, metastatic SCLC, and small cell carcinoma originating in the cervix with ovarian metastasis. We present a case of a 36-year-old female presenting with widespread metastatic small cell carcinoma, involving the lung, liver, and ovaries, initially masquerading as acute cholecystitis with elevated tumor markers including CA 19-9 and 125 and SIADH. Tissue immunohistochemistry was positive for p40, p16, Mammaglobin, CK5/6 Synaptophysin, WT1, INSM1, and AE1/AE3. The tumor showed preserved BRG1/SMARCA4 staining, and wild type p53 expression. Screening for SCLC and SCCOPT can be achieved through their Long non-coding RNA profile.

5. The Role of RNA Binding Proteins in Mosquito Oogenesis and Embryonic Development

Breanna Jones and Karginov Fedor

Biochemistry and Molecular Biology (BCMB), University of California, Riverside

While mosquitoes are most commonly thought of as a mere nuisance, these insects are actually considered one of the most dangerous organisms in the world. This is because of their ability to act as an effective vector for diseases such as Malaria, Zika, Yellow Fever, Dengue Fever, and Chikungunya. My project focuses on finding RNA binding proteins (RBPs) involved in mosquito development, particularly that of the oocyte and embryo. Little is known about these processes besides broad knowledge of the critical role RBPs play in them, making this an exciting opportunity to expand our knowledge of this field. This research could also prove useful for those experimenting with gene drives, which aim to curb disease vector populations using a self-perpetuating Clustered Regularly Interspaced Palindromic Repeat (CRISPR/Cas9) knock-out of critical genes in development. I will be using the CRISPR/Cas9 gene editing system to knock-out genes in Aedes aegypti that would produce sterile or inviable progeny, either by mutating a maternal RBP involved in oocyte maturation or an embryonic RBP crucial for proper development and patterning. Alongside CRISPR knock-outs in embryos, RNAi will also be used to knock-down RBP transcripts in adults where immature ovarian phenotypes may be observed. The information gleaned from these experiments will help us better understand mosquito development and genetics as well as promote life-saving research to eliminate deadly diseases caused by these organisms.

6. Elucidating the role of Dicer in p53 activation of oncogenic-induced senescence

Corinne N. Dilsavor and Jesse R. Zamudio

Department of Molecular Cell and Developmental Biology; Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research; Jonsson Comprehensive Cancer Center; University of California, Los Angeles, Los Angeles, CA 90095, USA

The tumor suppressor p53 triggers a permanent cell cycle arrest, called senescence, when reactivated in mouse lung adenocarcinoma tumor cells undergoing oncogenic stress1. Our goal is to determine the roles of regulatory RNAs in this p53 response. We previously defined a distinct cellular senescence signature directly activated by p53 that includes functional long noncoding RNAs2. These experiments were performed in tumor cells with inducible p53 reactivation, resulting in oncogenic-induced senescence (OIS). Here, we report the establishment of conditional RNA interference (RNAi) mutants in this cell system, KRASG12D/+;p53LSL/LSL; Rosa26-CreERT2; hDicerHA/-, called KPRD. The evolutionarily-conserved RNAi pathway acts by small RNA guides that target protein complexes for the repression of RNA transcripts with complementary sequences3,4. In this pathway, the Dicer RNase III family endoribonuclease processes the mature guides5. In the absence of Dicer activity, guide RNAs are not processed, leading to a global loss of RNAi post-transcriptional regulation. By independently controlling p53 and Dicer activity, we aim to elucidate the critical interplay between the p53 transcriptional activation network and the post-transcriptional small RNA repression during OIS. We will present our preliminary data characterizing loss-of-function Dicer mutations in KPR cells and rescue with a tetracycline-inducible construct for Dicer expression in KPRD cells. We will also present preliminary data and plans to determine the consequences of induced Dicer activity on the p53 response to oncogenic stress. The outcomes of these experiments may determine how regulatory RNAs could be modulated to prime cells toward desired cellular outcomes in oncogenic stress conditions.

7. Single-Molecule Dynamics and Regulation of Ribosome Scanning on Eukaryotic Messenger RNAs

Hea Jin Hong, Antonia L. Zhang, Adam B. Conn, Gregor Blaha, and Seán E. O'Leary

Department of Biochemistry, University of California, Riverside

Faithful and efficient recognition of mRNA initiation codons is a key regulatory component of translational control. At the outset of initiation, the small (40S) ribosomal subunit, along with eukaryotic initiation factors (eIFs) first form a 43S pre-initiation complex (PIC). Cap-dependent PIC recruitment to the mRNA 5' end necessitates PIC movement along the 5' untranslated region (UTR) to locate and recognize the start codon. A linear, unidirectional 5'-to-3' "scanning" motion to locate the start codon, proposed by Kozak over 40 years ago, has been generally supported by intensive research. However, important mechanistic information on scanning kinetics and regulation remains unclear, not least due to the inherently dynamic nature of the process. We developed a multi-color single-molecule fluorescence assay to observe PIC dynamics on single mRNAs, in real time on the initiation timescale, in zero-mode waveguides (ZMWs). The assay employs fluorescently-labeled eIF1 as a reporter, first for stable PIC-mRNA recruitment, and then for arrival at the start codon when major conformational changes eject eIF1 from the PIC. These processes bracket the start and end of scanning, allowing us to quantitate its rate. To gain insights into cis-regulation of scanning, we contrasted scanning dynamics between RNAs with varying UTR length, structure, and uORF and near-cognate initiation-codon positioning, including the paradigmatic GCN4 UTR. We also gained quantitative insights into the extent to which RNA-binding proteins might regulate scanning dynamics in trans, using as an example the yeast poly(A)-binding protein Pab1p, which has been proposed to impact scanning on its own PAB1 mRNA. Our data reveal a complex interplay of cis- and trans-regulatory elements that underpin mRNA-specific scanning dynamics.

8. Solving pre-mRNA structures to understand the regulation of gene expression and discover new therapeutic targets

Jianhui Bai, Kongpan Li, and Zhipeng Lu

School of Pharmacy at University of Southern California

Alternative splicing (AS) is a complex mechanism that regulates gene expression and aberrant alternative splicing can lead to various neurological and muscular disorders. Increasing evidence has shown that pre-mRNA structures play a role in regulation of alternative splicing. However, studying these structures is challenging due to their low abundance, long length, and flexible structures. To overcome these challenges, we developed a new robust method called SHARCLIP, which achieves pre-mRNA enrichment by simultaneous immunoprecipitation of pre-mRNA binding proteins (RBPs) and structure analysis by chemical probing. SHARCLIP is highly efficient in crosslinking, proximity ligation, and crosslinking reversal, enabling us to determine pre-mRNA structures at a transcriptome-wide level. Importantly, we have identified structures that are associated with alternative splicing and gene expression. The integration of SHARCLIP with covariation analysis, disease-associated variants, and RBP binding motifs help identify functional structures. Targeting pre-mRNA structures provides a promising avenue for developing therapeutic approaches in the future to treat a variety of diseases caused by splicing defects, such as Spinal Muscular Atrophy (SMA).

9. Deciphering Rbfox Self-Assembly: A Novel Multiplexed Binding Assay

Kelechi Onwuzurike, Parham Peyda, and Douglas L. Black

Microbiology, Immunology & Molecular Genetics (MIMG), UCLA

The RNA-binding Fox (Rbfox) proteins are a highly conserved family of RNA-binding proteins (RBP) with important roles in the regulation of alternative splicing in multiple physiological processes. Rbfox in the chromatin compartment of the nucleus is bound to a large assembly of splicing regulators (LASR). The Rbfox/LASR complex can self-assemble into higher-order structures through Rbfox's C-terminal domain (CTD). This CTD contains a low-complexity domain characterized by tyrosine residues that are important for its self-assembly and its ability to activate splicing. However, other sequences within the CTD that mediate either its self-assembly or its splicing activity are not well defined. We are developing a novel multiplexed binding assay to determine the molecular drivers of Rbfox self-assembly. This method would allow the testing of hundreds of variants by linking each variant with a peptide barcode. As proof of concept, we have shown that proteins encoding peptide barcodes can be expressed, purified, and detected via mass spectrometry. In addition, a co-immunoprecipitation assay can distinguish binding between wildtype and mutant variants of the CTD. We are currently working on coupling the co-immunoprecipitation assay with the peptide barcode readout to test more mutants. This method can provide insight into the biochemical mechanism behind Rbfox's homotypic interactions and should be applicable to studies of other protein-protein interactions.

10. Knockdown of transcription factor C/EBPbeta suppresses triple negative breast cancer viability

Kevin Holm[1], Min-Sun Song[2], and John Rossi[2]

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Triple-negative breast cancer (TNBC) is a form of breast cancer characterized by low expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2). Therapeutics aimed at targeting these receptors are ineffective in cases of TNBC, which leads to a poorer prognosis. Consequently, there is a need for novel therapeutics at targeting this subtype. CCAAT-enhancer binding protein beta (C/EBPbeta) is a leucine zipper transcription factor with a traditional function in mammary gland development and macrophage differentiation. In tumors, C/EBPbeta is associated with metastatic and chemoresistant forms of breast cancer. Previous efforts at targeting this transcription factor in the tumor have been hampered by off-target effects and low penetrance into the intratumoral space. Furthermore, studies into C/EBPbeta knockdown in vitro have been mixed, owing in part to two distinct isoforms that are differentially expressed in healthy and cancerous tissues. Given that C/EBPbeta's function is closely tied to hypoxia factors such as HIF-1alpha, we hypothesized that the hypoxic intratumoral space may be driving specific isoform development, and consequently the pro-metastatic phenotype observed clinically. To this end, we have developed an aptamer-siRNA conjugate containing a transferrin receptor 1 (TfR1) aptamer (a receptor activated under hypoxic conditions) linked to a C/EBPbeta siRNA. We have measured C/EBPbeta's suppression of metastasis in traditional cell culture under hypoxic conditions, as well as in a spheroid model. These results point toward a novel approach to C/EBPbeta's contradictory role as a driver and mediator of metastasis, and a potential therapeutic for its treatment.

11. snoRNA-guided tRNA modifications control codon-biased translation and development

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Small nucleolar RNAs (snoRNAs) can be mainly classified into C/D box snoRNAs, H/ACA box snoRNAs, and small cajal RNAs (scaRNAs). While they are well-characterized in guiding the modification of ribosomal RNA (rRNA) by 2'-Oribose methylation and pseudouridylation, many so-called orphan snoRNAs have unknown target RNAs and functions. Here, we discover a global network of snoRNA-tRNA interactions revealed by PARIS and further validated by CLIP. We demonstrate that snoRNAs/snoRNPs are essential for cell growth and tRNA modifications, playing critical roles in protecting tRNAs against degradation. We reveal that snoRNAs D97 and D133 play important roles in regulating codon-biased translation in human HEK293 cells. More interestingly, the snoRNAs D97 and D133 can control mES self-renewal and differentiation, potentially by affecting the cellular metabolic process, with underlying mechanisms awaiting further investigation.

12. The physiological function of nonsense mediated mRNA decay in brain development

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Nonsense-mediated mRNA decay (NMD) has emerged as an essential post-transcriptional regulatory mechanism to shape a cell's transcriptomic identity. Genes involved in NMD regulation are implicated in multiple neurodevelopmental diseases such as autism and intellectual disability. How NMD regulation controls early brain development remains unknown. Here, we demonstrate that deletion of a key NMD factor Upf2 in embryonic neural progenitor cells (NPCs) results in perinatal microcephaly, but deletion in immature post-mitotic neurons does not. Upf2 depletion prolongs the cell cycle progression in radial glia cells (RGCs), the major neural progenitor cells in the brain. CRISPRi screening in Upf2KO NPCs identified Trp53 as the strongest modifier rescuing the growth defects induced by Upf2KO. Further, Trp53 is not a direct NMD target; instead, Trp53 transcriptional targets are targeted by NMD for degradation. Taken together, our study shows a novel mechanism to explain how NMD inhibition regulates RGC proliferation and cell cycle progression to influence neurogenesis and to shed light on cellular and molecular mechanisms in NMD-deficit related neurodevelopmental diseases.

13. Dynamic Molecular Reprogramming of Human and Viral Protein Synthesis by SARS-CoV-2 Nucleocapsid Protein

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Upon infection, SARS-CoV-2 must hijack host machinery to compete for translation of viral proteins. By mimicking 5'-capped eukaryotic mRNAs, the ribosome-lacking virus depends on the host factor eIF4F for recruitment of host ribosomes to its RNA genome. eIF4F contains the 5' cap-recognizing protein, eIF4E; scaffolding protein, eIF4G; and RNA helicase, eIF4A. Together with poly(A)-binding protein (PABP), this dynamic assembly is thought to functionally circularize mRNA 5' and 3' ends, forming a "closed loop." Circularization is hypothesized to enhance cap-dependent translation, yet previous research has never measured the real-time effects of forming a closed loop. Evidence suggests SARS-CoV-2 nucleocapsid (N protein) perturbs eIF4F–PABP interplay and suppresses initiation by dual mechanisms — direct association with eIF4G, disrupting the 4EG interface, and competitively binding mRNA poly(A)-tails. However, N protein effects on circularization remain unstudied. It is also unclear how the virus might escape N protein-mediated translational repression to advantage its translation over host mRNAs. To address this, we employed single-molecule approaches that directly quantify how PABP and N protein impact eIF4F-mRNA recognition, in real time, for both host GAPDH mRNA and the SARS-CoV-2 5' untranslated region (UTR). Our data suggest N protein acts as a viral PABP and targets the closed loop to specifically suppress eIF4F-cap recognition of host mRNA. Ongoing research will establish a real-time mechanistic model for circularization dynamics, and probe how N protein reprograms circularization to modulate translation. Our findings will provide new insights into eukaryotic translational control mechanisms and delineate a complex host-virus interplay central to pathogenesis.

14. The Function of Endogenous Retroviruses During Hematopoiesis

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Endogenous retroviruses (ERVs) are molecular remnants of ancient retroviral infections. Nearly 9% of our DNA is composed of identifiable ERVs. As being foreign genetic elements, ERVs are kept silent or under tight regulation to prevent their transcription and replication within the host genome. However, some ERVs can escaping silencing and impacting gene regulation. The activity of ERVs is in some cases associated with cancer progression and in others linked to the host's developmental and immune fitness that can be deleterious or beneficial to the host depending on when, where, and how is active. Therefore, it is important to understand how ERVs are regulated and how their activation may affect cell fate. Our work and others showed the chromatin assembly factor complex 1 (CAF-1) plays a major role in cell fate maintenance. Recently, we have demonstrated that CAF-1 suppression in hematopoietic stem and progenitor cells (HSPCs) leads to their differentiation into a mixed lineage state by activating fate genes. Given that CAF-1 is involved in heterochromatin regulation and has been implicated in ERVs silencing, we wondered CAF-1 probably also controls ERVs silencing in HSPCs. Our preliminary results show selective chromatin opening and transcriptional activation of specific ERV subfamilies upon CAF-1 suppression. We also find that one intriguing chimeric ERV transcript splicing into the Geminin gene and this novel ERV-Geminin transcript does not alter the open reading frame (ORF) of Geminin suggesting that it may control Geminin translation through potential upstream ORFs within the new 5'UTR.

15. Engineering oncogenic SF3B1 hotspot mutation via CRISPR-directed PRECIS mutagenesis

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RNA splicing factor SF3B1 is the most mutated splicing gene in cancers. Hotspot mutations on this gene drive aberrant splicing, impacting tumor suppressor functions and rewiring cellular circuitries to promote oncogenesis. Despite the significance of this splicing factor in cancer, the study of SF3B1 is severely limited by a lack of genetically faithful cell line model. Here, we use CRISPR prime editing to engineer SF3B1 mutant cells. We show that prime editing outperforms conventional Cas9 and AAV technologies and orthogonal base editors in installing the SF3B1 K700E hotspot mutation. We further demonstrate the versatility of prime editing by installing this hotspot mutation into a broad spectrum of cell lines spanning both solid tumors and liquid malignancies. To aid in prime editing, we next constructed an SF3B1 mutation-responsive reporter to fluorescently label prime edited K700E cells. When paired with prime editing, this reporter enables efficient isolation of SF3B1 mutant cells in an approach that we call prime editing coupled intron-assisted selection (PRECIS). As a proof of concept, we used PRECIS engineering to create isogenic SF3B1 K700E models in chronic lymphocytic leukemia (CLL) cell lines. Compared to primary patient samples, these novel CLL SF3B1 mutant cell lines accurately recapitulate the altered splicing profile and other features such as copy number variations (CNVs) of SF3B1-mutated CLL. Taken as a whole, we show PRECIS is a facile and simple approach that allows for rapid development of disease-relevant SF3B1 mutant cell line models.

16. Biophysical Origin of Adenine Base Editors' Improved Editing Efficiency

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Base editing is a type of genome editing that enables the direct and irreversible conversion of one base pair into another at a specific genomic locus. This technology holds remarkable promise in treating a myriad of genetic diseases associated with single nucleotide polymorphisms (SNPs) by correcting targeted A•T base pairs to G•C. At the molecular level, adenine base editors (ABE) comprise the engineered fusion of deaminating proteins with the CRISPR-Cas9 molecular machinery. Here, we establish the biophysical basis behind the DNA base editing efficiency of ABEs, and the synergistic role of their components – including the Cas9 nuclease, the deaminating proteins, and the DNA – through an integrative approach that combines extensive molecular dynamics (MD) simulations with enhanced sampling approaches, and biophysical experiments. An overall ensemble of >100 μs of MD simulations was collected on all-atom models of the CRISPR-Cas9–ABE complexes comprising > 500,000 atoms, revealing that the triad of interfaces between the deaminating units, Cas9, and the DNA is critical in the functioning of ABE complexes. Metadynamics simulations and FRET experiments also reveal that multiple rounds of directed evolution have stabilized the dimeric state of deaminating proteins, contributing to their increasing base editing efficiency when conjugated with Cas9. Finally, free energy perturbation simulations characterize the energetic gain/loss arising from point mutations throughout the evolutionary trajectory. Overall, our biophysical approach offers an in-depth understanding to improve the ABE function, aiding the foundations to design CRISPR-Cas9–conjugated base editors with enhanced specificity and improved base editing efficiency.

17. Splicing Regulation Through Combinatorial Recognition of Cis-Regulatory RNA Modules

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Alternative splicing, an essential component of the gene regulatory circuit, plays an important role in many cellular processes and its dysregulation can lead to a wide range of pathologies. This process is regulated by the combinatorial interplay between trans-acting RNA binding proteins (RBPs) and cis-regulatory elements on pre-mRNAs. The Rbfox protein family is a central splicing regulator, with mutations or abnormal expression of Rbfox associated with various aberrations such as familial epilepsy, pancreatic cancer metastasis, and heart conduction defects in myotonic dystrophy 1. Previous studies have primarily focused on how individual Rbfox proteins recognize cis-regulatory RNA elements and regulate splicing. However, Rbfox is part of a protein complex in the nucleus, the Large Assembly of Splicing Regulators (LASR), implying that its binding and activity might be influenced by other subunits within the complex. To understand this interaction, we mapped the transcriptome-wide footprints of LASR/Rbfox by sequencing nuclease-protected RNA fragments that co-purify with this complex. These RNA fragments contain motifs predicted to bind Rbfox and LASR subunits in tandem, indicating multi-subunit recognition of these elements. Analysis of the positions of motifs relative to each other reveals distinct binding configurations associated with Rbfox and LASR subunits. We identified sites directly bound by Rbfox using an RNA binding mutant Rbfox1(F126A). This mutant can still form a complex with LASR, but the nuclease-protected RNAs associated with LASR-bound Rbfox1(F126A) lack most sites containing the Rbfox binding motif, retaining sites bound by other LASR subunits. To understand the functional significance of these protected regions, we analyzed the protected fragments that lie in introns surrounding Rbfox-regulated exons. Many of these introns contain protected sites containing multiple regulatory motifs. Our findings indicate that Rbfox and LASR cooperate to recognize regulatory motifs in the transcriptome and have implications for deciphering the splicing code.

18. Disrupting MGA-MYC driven metabolic reprogramming in Richter's syndrome pre-clinical models via novel therapeutic approaches

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Richter's syndrome (RS) or Richter's transformation (RT) is an aggressive transition of chronic lymphocytic leukemia (CLL) to lymphoma; however, molecular mechanisms underlying CLL-to-RS transformation are poorly understood. MYC network alterations are observed in 70% of RS cases, and MGA (Max-gene-associated), a functional MYC suppressor, undergoes loss-of-function mutations in ~7-20% of RS cases. Using CRISPR-Cas9, we recently developed a B-cell restricted CLL to RS murine model by engineering loss-of-function Mga mutations in early progenitors (LSK) in the presence of commonly occurring CLL mutations 13q deletion (Mdr) and Sf3b1-K700E. MYC overexpression induces oxidative stress via reactive oxygen species (ROS) in several B-cell lymphomas. We found Myc and Nme1 (Nucleoside diphosphate kinase), both common targets of Mga, were upregulated, increasing oxidative phosphorylation (OXPHOS), leading to mitochondrial dysregulation. We sought to understand the molecular basis of mitochondrial dysregulation and determine if targeting the Mga-Myc-Nme1 axis is beneficial for RS in vivo.

19. Resistin-like-molecule alpha (RELMα)-mediated protection from obesity is associated with regulation of long non-coding RNA Gm47283 and hemoglobin in macrophages

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Over recent decades, obesity has emerged as one of the most pressing global challenges, with approximately 13% of the adult population being affected around the world. Obesity can cause range of complications including cardiovascular diseases, diabetes, and even cancer. Within the chronic inflammatory response in adipose tissue, macrophages serve a pivotal role. Macrophages can infiltrate adipose tissue and are responsible for producing the majority of inflammatory cytokines, subsequently influencing adipose tissue dynamics. In previous studies, we demonstrated the adipokine, resistin-like molecule alpha (RELMα) protects mice against high fat diet (HFD)-induced obesity and inflammation in a sex-dependent manner. RELMα levels were increased in the serum and adipose stromal vascular fraction (SVF) of females, and RELMα deletion led to increased weight gain, adipose tissue inflammation, and proinflammatory macrophage accumulation. Single-cell RNA sequencing of adipose SVF cells identified dysregulated macrophage activation and expression long non-coding RNA (lncRNA) Gm47283 and hemoglobin genes in HFD RELMα KO mice. These two genes that have not been previously associated with obesity nor macrophages, opening new potential pathways and targets for obesity. Monocyte-to-macrophage transition was also dysregulated in RELMα deficient animals. Based on these results, the focus of our studies is to determine the macrophage-intrinsic requirement for RELMα in protection from obesity, and the downstream function of lncRNA and hemoglobin in adipose tissue that leads to obesity pathogenesis.

20. Engineering Orthogonal Phase-Separated Compartments Using Modular RNA Motifs

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Recent biological advancements highlight the importance of protein and RNA-based condensates as alternatives to traditional membrane-bound organelles for organizing biochemical reactions. We demonstrate the controlled generation of pure RNA condensates using star-shaped RNA motifs, achieved through single-stranded nanostars with programmed interactions via kissing loops. These designed nanostars produce distinct, non-mixing condensates, individually traceable with fluorogenic aptamers. Successful cotranscriptional condensate formation hints at potential genetic encoding in living cells, and these condensates are able to recruit peptides and proteins selectively. Our library of orthogonal RNA condensates offers a platform for creating functional artificial organelle systems.

21. Investigation of PUM-AGO Interaction Using a Complex Library of Reporter Plasmids

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RNA Binding Proteins (RBPs) are an expansive heterogenous collection of proteins that bind & post-transcriptionally regulate RNA transcripts influencing the translation, stability, maturation, processing, and localization. Since RBPs form complex interaction networks, the resulting stability of a given mRNA results from a combination of different stabilizing and destabilizing RBPs. This study aims to investigate the relationship between 2 such RBPs: Pumilio and Argonaute. Pumilio proteins bind to the 3'UTR of RNA transcripts based on sequence-specific interactions, typically destabilizing their transcripts. Mammalian PUM proteins have been shown to influence several key cellular processes including embryogenesis, immunity, neurogenesis, motor neuron function, etc. Argonaute proteins (AGO) interact with various miRNAs transcripts to form a RISC silencing complex, which binds to the 3'UTR of RNA transcripts based on sequence specific interactions informed by the miRNA. Hundreds of diverse mammalian miRNAs have been identified with a wide range of functions. To study this potential interaction, we have developed a high throughput reporter assay to explore the global network of PUM-AGO interactions through the activity of a set of WT and mutated transcripts. Currently, we are working with a set of test fragments to validate our approach prior to high-throughput library evaluation. Protein impact will also be modulated at the cellular level, via knockout of the endogenous protein coupled with the stable introduction of the protein under a dox inducible promoter. Ultimately, each fragment's activity will be assessed using fluorescent reporters. The impact of each protein on activity will be determined, both separately and in concert.

22. Selective mRNA oxidation of the electron transport chain complex subunits dysregulate energy production in Multiple Sclerosis

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Mitochondria is the site of major cellular energy production. Any disruption in mitochondrial functions has deleterious effect on the cells, since it curtails energy supply essential for cell survival. Multiple Sclerosis (MS) is one of the neurodegenerative diseases associated with dysfunctional mitochondria. In addition to energy production, mitochondria serve as the primary source of reactive oxygen species (ROS) generation in cells. Decrease in complex I, III and IV activities in the neurons were observed in MS patients. Marked rise in ROS leading to oxidation damage to mitochondria and biomolecules, such as, DNA, proteins and lipids were widely studied, while very little is known about oxidation induced damage RNA. Subunits of the ETC complexes are encoded by both mitochondrial and nuclear genomes. Any potential oxidative damage to the mRNAs of these subunits will most likely have detrimental effects on subunit synthesis leading to mitochondrial dysfunction. Subjecting differentiated human neuroblastoma SH-SY5Y cells to 100 µM H2O2 treatment resulted in four mRNAs from the mitochondrial genome that are selectively oxidized leading to nearly 30-40% reduction in protein levels with concomitant decrease in complex I activity. Even though complex I activity is inhibited, still another pathway exists for the electrons to flow through and maintain the functioning of the ETC i.e., complex II□III□IV, albeit at a reduced level. However, oxidation of mitochondrially encoded mRNAs of complexes other than complex I were not detected. We performed RNA deep sequencing using nuclear encoded RNAs from oxidized SH-SY5Y and identified several nuclear encoded ETC subunit mRNAs particularly from complexes I, III, IV and V as oxidized with a fold change of □2. The KEGG network interaction analysis revealed that these targets are associated with many of neurodegenerative diseases including Multiple Sclerosis , Parkinson's and Alzheimer's. We also determined that there is nearly 50% loss in the mitochondrial membrane potential after 12 hrs following a 30 min H2O2 treatment. Taken together we hypothesize that deficiency of the ETC complex subunits due to mRNA oxidation can create a vicious cycle of ROS generation in the mitochondria, leading to enhanced mitochondrial dysfunction and neurodegeneration in MS and potentially other neurological disorders. We validated our results in post-mortem MS patient brain samples, where we observed the oxidation of the same set of mRNAs as was observed in SH-SY5Y cells. Therefore, RNA oxidation may play a role in mitochondrial dysfunction via affecting the energy synthesis (ETC) pathway causing neurodegeneration.

23. Universal rRNA Depletion for Transcriptome Analysis of Any Organism with a Streamlined, Autolaunch Bioinformatics Platform

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Depletion of ribosomal RNA (rRNA) is commonly adopted in total RNA-seq experiments to maximize the sequencing efficiency given its overabundance in RNA samples. Most existing rRNA depletion strategies are probe-based and thus species dependent, usually well-established for commonly studied human samples and mouse/rat models. Research utilizing other models and non-model organisms often lacks a simple and reliable rRNA depletion solution. To address such a need, Zymo Research developed a novel probe-free rRNA depletion technology that enables universal rRNA depletion for any organism and is integrated into the library prep procedure. Total RNA from eight species (mouse, rat, human, cow, tomato, wheat, yeast, and green algae) were used as input for the RiboFree total RNA library preparation workflow. The resulting libraries achieved an average unique alignment rate of 75.8% with > 90% uniquely aligned in samples from human. rRNA was effectively depleted to ≤ 9% across the tested species. Exceptional numbers of genes were detected: > 30,000 genes were detected in the human samples including > 16,000 protein coding and > 8,000 lncRNA genes; in the yeast samples, over 6,100 genes were detected among the ~ 6,260 annotated genes. Furthermore, Zymo Research deposited an RNA-Seq pipeline to a no-code platform called Aladdin to provide ready-to-use data analysis tools for the scientific community. By simply point-and-click, researchers can complete essential analyses including differential gene expression and gene set enrichment analyses. The powerful RiboFree technology and the streamlined Aladdin bioinformatics platform will greatly empower researchers from diverse backgrounds to make further impactful contributions.

24. A PPARγ-Lexis regulates adipose thermoneutral remodeling

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The intricate interplay between energy-storing white adipose cells and thermogenic beige adipocytes contributes to the development of obesity and insulin resistance. Irrespective of specialized niche, adipocytes require the activity of the nuclear receptor peroxisome proliferator activated receptor gamma (PPARγ) for proper function. Exposure to cold or adrenergic signaling enriches thermogenic cells though multiple pathways that act synergistically with PPARγ. However, the molecular mechanisms by which PPARγ licenses white adipose tissue to preferentially adopt a thermogenic or white adipose fate in response to dietary cues or thermoneutral conditions are not fully elucidated. In this study, we show that a PPARγ-long noncoding RNA (lncRNA) axis integrates canonical and noncanonical thermogenesis to restrain white adipose tissue heat dissipation during thermoneutrality and diet-induced obesity. Pharmacologic inhibition or genetic deletion of the lncRNA Lexis, enhances UCP1 dependent and independent thermogenesis. Adipose specific deletion of Lexis counteracted diet-induced obesity, improved insulin sensitivity, and enhanced energy expenditure. Single-nuclei transcriptomics revealed that Lexis regulates a distinct population of thermogenic adipocytes. By systematically mapping Lexis motif preferences, we show that it regulates the thermogenic program through the activity of the metabolic GWAS gene and WNT modulator TCF7L2. Collectively, our studies reveal a novel mechanism of communication between PPARγ and WNT, which serves to maintain the plasticity of white adipose tissue.

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