1st Hong Kong RNA Club Symposium (2017)

(CityU, AC3, 19/F, 8:30am-12:30pm)

8:30-8:45	REGISTRATION	
8:45-9:00	OPENING REMARKS BY SYMPOSIUM ORGANIZERS **Dr. Chun Kit KWOK and Dr. Minh LE, CityU**	
9:00-10:00	**KEYNOTE TALK** **Prof. Harvey LODISH, MIT** Lineage-specific long non-coding RNAs (lncRNAs) that regulate development of erythrocytes, brown and white adipocytes, and probably every tissue.	
10:00-10:30	**Prof. Edwin Ho Yin CHAN, CUHK** RNA and Diseases: from basic mechanisms to therapeutic development	
10:30-11:00	COFFEE BREAK	
11:00-11:30	**Prof. Tuan Anh NGUYEN, HKUST** Molecular mechanism of miRNA biogenesis	
11:30-12:00	**Prof. Minh LE, CityU** The tale of microRNA-125b in cancer	
12:00-12:30	**Prof. Xin-Yuan GUAN, HKU** Recoding RNA editing of antizyme inhibitor 1 predisposes to hepatocellular carcinoma	
12:30-12:35	CLOSING REMARKS AND SPEAKERS' PHOTO	

Speakers' Lunch (12:30-2:00) CityU, 9/F

Biography of Keynote Speaker

Harvey F. Lodish, Ph.D.

Dr. Lodish is a Founding Member of the Whitehead Institute for Biomedical Research and Professor of Biology and Professor of Biological Engineering at the Massachusetts Institute of Technology.

He is a Member of the National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences. Dr. Lodish is a member of the Board of Trustees of Boston Children's Hospital, where he is Chair of the Board of Trustees Research Committee. From 2008 to 2016 he was the Founding Chair of the Scientific Advisory Board of the Massachusetts Life Sciences Center, the group charged with oversight of the state's 10- year $1 billion investment in the life sciences. He was a founder and scientific advisory board member of several companies including Genzyme, Inc., and Millennium Pharmaceuticals, Inc., and has served on the scientific advisory boards of numerous biopharmaceutical companies.

Dr. Lodish is the lead author of the textbook *Molecular Cell Biology*. The eighth edition was published in April 2016; the book has been translated into 12 languages. During 2004 he served as President of the American Society for Cell Biology.

Prof. Harvey F. LODISH, MIT

Lineage-specific long non-coding RNAs (lncRNAs) that regulate development of erythrocytes, brown and white adipocytes, and probably every tissue.

I will discuss recent work from my laboratory and others showing that many lncRNAs are expressed only in a single type of cell or developmental pathway and are essential for normal differentiation of these cells. Focusing on formation of red blood cells and fat cells, we will see that multiple and diverse types of lineage- specific lncRNAs participate in the regulatory circuitry underlying lineage-specific development.

To obtain a comprehensive view of how lncRNAs contribute to erythropoiesis, we' performed and analyzed data from high depth RNA-sequencing on RNAs from erythroid progenitor cells and terminally differentiating erythroblasts. We focused on differentiation-induced lncRNAs, including novel erythroid-specific lncRNAs conserved in humans that are nuclear-localized and identified 13 erythroid-specific lncRNAs that are greatly induced during erythroid terminal differentiation. Importantly, shRNA-mediated loss-of-function assays revealed that all 13 are important for red cell formation. One intergenic lncRNA, LincRNA-EPS, prevents the apoptosis of progenitors that is normally induced by erythropoietin deprivation and represses expression of several proapoptotic genes including Pycard, a caspase activator.

An enhancer lncRNA, Bloodlinc, is transcribed from the erythroid- specific super enhancer of the erythroid- specific Band3 gene. But Bloodlinc diffuses beyond its super-enhancer domain of origin; it localizes to *trans*-chromosomal loci encoding critical regulators and effectors of terminal erythropoiesis and directly binds chromatin-organizing and transcription factors, including the chromatin attachment factor HNRNPU. Inhibiting Bloodlinc or *Hnrnpu* compromises the terminal erythropoiesis gene program, blocking red cell production, whereas expressing Bloodlinc ectopically stimulates this program and can promote erythroblast proliferation and enucleation in the absence of differentiation stimuli. Thus, Bloodlinc represents a novel type of trans-acting, super-enhancer lncRNA that potentiates erythropoiesis.

To uncover brown adipose tissue (BAT)-specific long non-coding RNAs (lncRNAs), we used high depth RNA-sequencing on RNAs from mouse brown, inguinal white, and epididymal white fat. We identified ~1500 lncRNAs, including 127 BAT-restricted loci induced during differentiation and whose promoters are often targeted by the key adipocyte transcription factors PPARγ, C/EBPα and C/EBPβ. One such lncRNA, lnc-BATE1, is required for establishment and maintenance of BAT identity and thermogenic capacity. lnc-BATE1 inhibition impairs concurrent activation of brown fat and repression of white fat genes, and inhibition is partially rescued by exogenous lnc-BATE1 with mutated siRNA-targeting sites, demonstrating a *trans* function of lnc-BATE1

Thus diverse types of intergenic, enhancer, and antisense lncRNAs are expressed only in specific types of hematopoietic and adipose cells and are essential for their proper development. They are a significant component of the regulatory circuitry underlying lineage-specific development.

Prof. Edwin Ho Yin CHAN, CUHK

RNA and Diseases: from basic mechanisms to therapeutic development

Individual types of RNA, such as messenger, structural and regulatory RNA, are known to play distinct roles in the cell. Recently, a large number of RNA-mediated toxicity pathways that play significant pathogenic roles in numerous human disorders, including neurodegenerative and neuromuscular diseases. Common RNA toxicity pathways are beginning to be elucidated in recently years. Molecular details of disease pathogenesis will help us develop new therapeutic strategies to intervene RNA-mediated diseases.

Prof. Tuan Anh NGUYEN, HKUST

Molecular mechanism of miRNA biogenesis

MicroRNAs (miRNAs), short and non-coding RNAs ~22 nucleotides in length, can find and silence the expression of a specific set of mRNAs, thereby regulating a variety of vital cellular processes, including stem cell differentiation and cancer maturation. The aberrant miRNA expression resulting from irregular miRNA biogenesis might lead to erroneous downregulation of mRNAs, subsequently causing cellular abnormalities. Thus, miRNA biogenesis must be accurately executed and regulated. This process is initiated by human Microprocessor, or the DROSHA-DGCR8 complex, that associates with various transacting factors to precisely and efficiently cleave the primary precursors of miRNAs (pri-miRNAs). Though Microprocessor has been studied for more than a decade, a molecular mechanism underlying its proper miRNA initiation remains elusive. In this seminar, I will present the latest model for pri-miRNA processing of human Microprocessor that is built by using multiple approaches, including biochemistry, biophysics, and X-ray crystal structure. The model demonstrates the complex stoichiometry and assembly, illustrates how the complex recognizes and interacts with the various secondary structures and primary sequencing motifs of the RNA substrates. The model not only clarifies a long-standing discrepancy over pri-miRNA processing mechanism but also substantially changes our current view of this mechanism. I will also talk about a molecular mechanism of trans-acting factors coordinating with Microprocessor in order to regulate pri-miRNA processing.

Prof. Minh LE, CityU

The tale of microRNA-125b in cancer

microRNAs (miRNAs) have emerged in the last decade as an important class of gene expression regulators in all tissues. Dysregulation of many miRNAs are associated with cancers. The miR-125 family, including miR-125a and miR-125b, are the mammalian homologues of lin-4, the first miRNA discovered in C. elegans, which regulates developmental timing. Our pioneer work on miR-125b uncovered the important role of this miRNA in neural differentiation and embryogenesis. Loss of miR-125b triggers massive neural cell death in zebrafish embryos. miR-125b also suppresses apoptosis in human fibroblasts and tumor cells. We found that miR-125b directly inhibits the expression of p53 and multiple genes in the p53 network. By modulating the expression of these genes, miR-125b buffers and fine-tunes p53 activity to regulate apoptosis and proliferation of normal and malignant cells. Indeed, miR-125b is a bona fide oncogene in leukemia, lymphoma and prostate cancer. miR-125b also mediates drug resistance in breast cancer, lung cancer and glioma. We found that inhibition of miR-125b significantly suppresses the survival of leukemia and breast cancer cells. We have developed a novel method for delivery of antisense oligonucleotides to leukemia and breast cancer cells for efficient knockdown of miR-125b and suppression of cancer progression in vitro and in vivo.

Prof. Xin-Yuan GUAN, HKU

Recoding RNA editing of antizyme inhibitor 1 predisposes to hepatocellular carcinoma

A better understanding of hepatocellular carcinoma (HCC) pathogenesis at the molecular level may facilitate the discovery of the tumor initiating events. By comparing transcription profiles between 3 paired HCC (tumor vs non-tumor) specimens generated from deep transcriptome sequencing (RNA-Seq), an adenosine (A)-to-inosine (I) RNA editing at codon 367 (causing S367G substitution) of *Antizyme inhibitor 1* (*AZIN1*) was detected more frequently in tumor specimens. Clinically, hyperediting of *AZIN1* was detected in about 45% of human HCC samples and significantly associated with liver cirrhosis (P=0.02), tumor recurrence (P=0.019) and disease-free survival rate (P=0.029) of HCC patients. Functional study found that the edited *AZIN1* possessed stronger tumorigenic abilities compared with the wild-type *AZIN1*. *Adenosine deaminase acting on RNA-1 (ADAR1)*, one of the members of ADAR family that mediates A-to-I (G) edit, was responsible for the hyperediting of *AZIN1*. Further study demonstrated that the edited AZIN1 protein, having stronger affinity towards antizyme-1 than wild-type AZIN1, promoted cell proliferation via attenuating antizyme-mediated degradation of oncoproteins cyclin D1 and ODC. Collectively, our study indicates that hyperediting in *AZIN1* gene might be a "Gain-of-Function" event, which is a potential driver in the pathogenesis of human cancers, particularly in HCC.

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