RESEARCH SYMPOSIUM 2023

Manipulating Cells through Synthetic Biology

Division of Molecular & Cell Biology

School of Biological Sciences

5th June 2023

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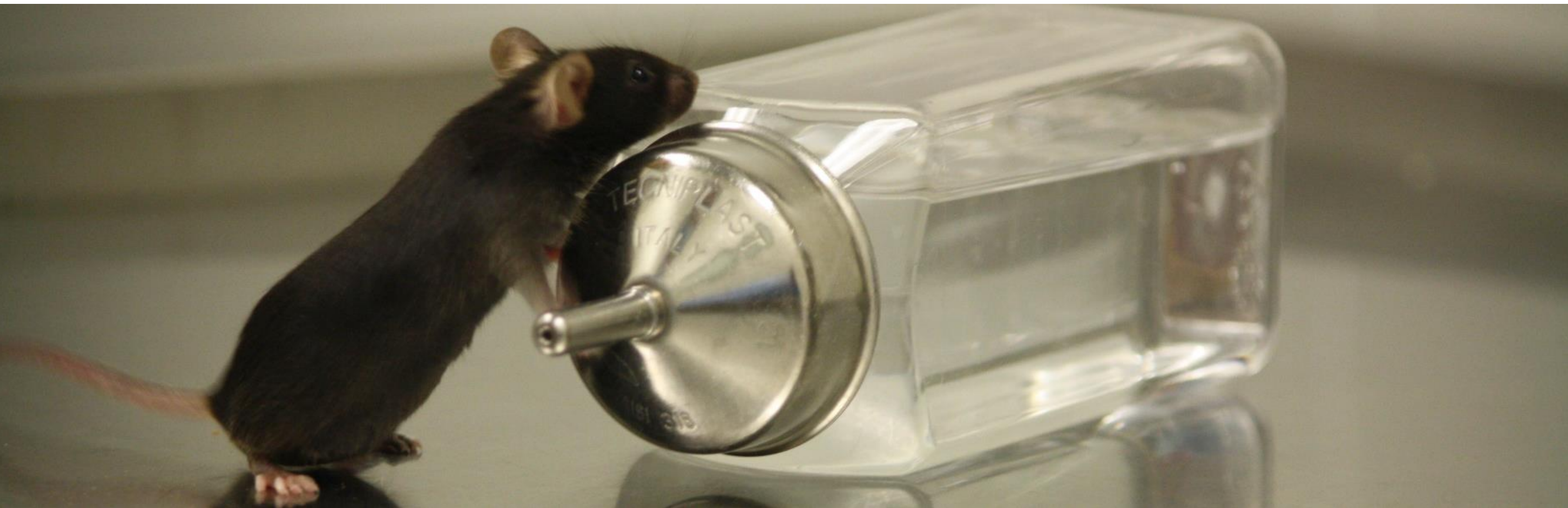

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SCHOOL OF BIOLOGICAL SCIENCES
THE UNIVERSITY OF HONG KONG
香港大學生物科學學院

WELCOME MESSAGE

Dear colleagues,

It is with great pleasure that we welcome you to the Molecular and Cell Biology Research Symposium 2023. We are delighted to host this event that brings together the brightest minds in our school to share their research and insights on various topics. Our symposium promises to be a platform for stimulating discussions and exchange of ideas that will foster collaboration and networking opportunities.

The meeting theme, *Manipulating Cells through Synthetic Biology*, has been carefully chosen to recognize the development of various tools to reshape the cells for a better understanding of various biological processes, disease mechanisms, and treatment options. We are honored to have Drs. Alan S.L. Wong and. Health E. Johnson as our symposium Keynote Speaker to share their thoughts and highlight the scientific advances in this field, and Dr. Colin Luk, a distinguished alumnus of our School, to convey his narrative as a startup creator. We encourage you to actively participate in the symposium by engaging in discussions, asking questions, and sharing your own perspectives. We believe that this event will be an opportunity for all of us to learn, grow, and contribute to the advancement of knowledge.

We would like to express our sincere gratitude to our keynote speakers, chairperson, judges, and all those who have contributed to making this event a success. We hope that your experience at the symposium will be informative, inspiring, and rewarding.

Once again, welcome to the one-day research symposium, and we look forward to an engaging and productive day.

Best regards,

Organizing Committee
Molecular and Cell Biology Research Symposium 2023
School of Biological Sciences

COMMITTEE

Organizing Committee

Dr. Chi Bun Chan

Dr. Ying Wai Chan

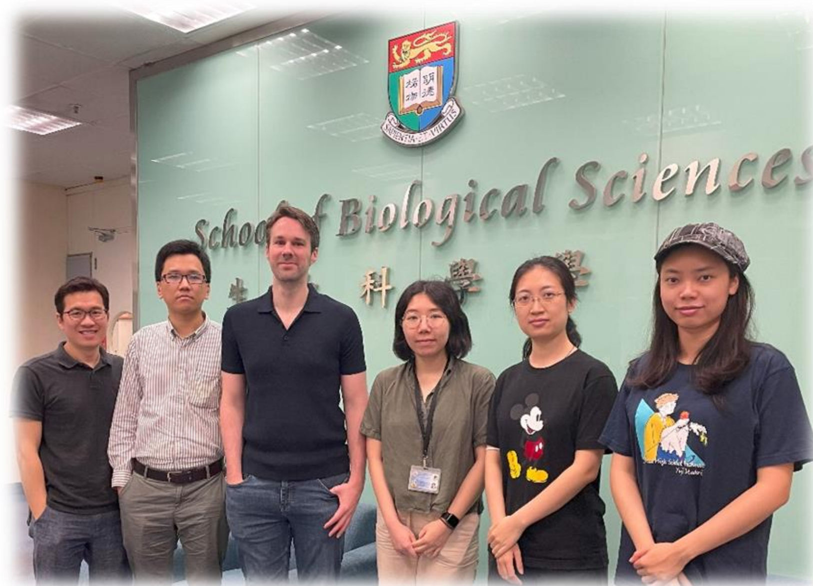
Ms. Marsena Jasiel Ismaiah

Dr. Heath Ellis Johnson

Ms. Hui Yuan Lim

Ms. Diwen Shi

Ms. Siyu Zhou



(Left to right: C.B. Chan, Y.W. Chan, H.E. Johnson, M.J. Ismaiah, D. Shi, S. Zhou)

Scientific Committee

Dr. Hani S. El-Nezami

Dr. Jetty C.Y. Lee

Dr. Clive S.C. Lo

Dr. Wing Yee Lui

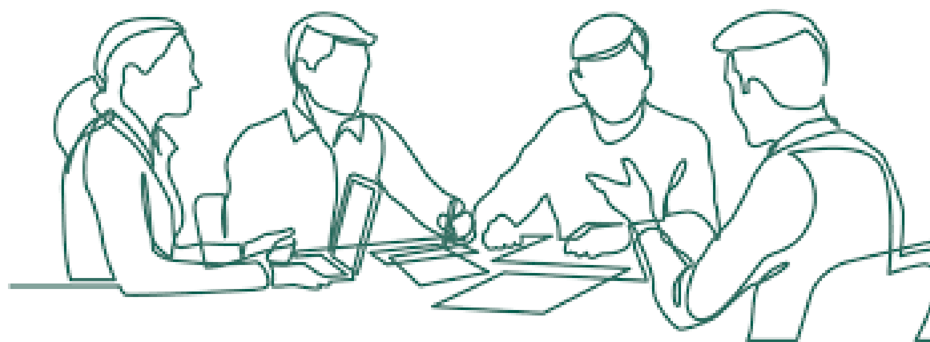
Dr. Simon Y.W. Sin

Prof. Aixin Yan

Dr. Karen W.Y. Yuen

Dr. Yuanliang Zhai

Dr. Chaogu Zheng



PROGRAM

09:55 – 10:00	**Opening message**
10:00 – 11:00	**Keynote Presentation 1**
	Optogenetic interrogation of developmental Erk signaling
	Speaker: Dr. Heath E. Johnson
	Chairperson: Dr. Karen Yuen
11:00 – 12:00	**Postdoctoral Fellow Presentation**
	Judges: Drs. Yuanliang Zhai and Chaogu Zheng
12:00 – 13:30	**Lunch Break**
13:30 – 15:30	**Postgraduate Student Presentation**
	Judges: Drs. Hani S. El-Nezami and Heath E. Johnson
15:30 – 15:45	**3Mins Presentation**
	Judges: Drs. Clive S.C. Lo and Chi Bun Chan
15:45 – 16:15	**Tea Break**
16:15 – 17:15	**Keynote Presentation 2**
	Enabling platforms for studying and engineering biological complexity
	Speaker: Dr. Alan S.L. Wong
	Chairperson: Prof. Aixin Yan
17:15 – 17:45	**Alumni Sharing**
	Dr. Colin C.L. Luk (isoFoodtrace)
	Chairperson: Dr. Jetty C.Y. Lee
17:45 – 18:00	**Prize Presentation**
18:00 – 18:05	**Closing Remarks**

KEYNOTE SPEAKER

Dr. Heath E. Johnson
Assistant Professor
School of Biological Sciences
Faculty of Science
The University of Hong Kong

Dr. Heath Ellis Johnson is an engineer-turned-biologist and microscopist. He completed his bachelor's degree at the University of Tennessee before going on to do his master's and Ph.D. at North Carolina State University in chemical engineering. There he performed his doctoral work on signaling and cytoskeletal interactions during cell migration in the lab of Jason Haugh. After completing his Ph.D., he worked in Jared Toettcher's and Stas Shvartsman's labs in the Department of Molecular Biology at Princeton University using Drosophila as a model system to study signaling using optogenetics. He received a Ruth L. Kirschstein Postdoctoral National Research Service Award for this work 2016. Last year he was appointed as an Assistant Professor at HKU in the School of Biological Sciences where he was denoted a HKU-100 Scholar. He uses live-microscopy and develops optogenetic approaches to study cell signaling and the mechanisms by which it dictates cell fates. His microscope images have been featured on the cover of Developmental Cell, the Wall Street Journal, and awarded by the Genetics Society of America.

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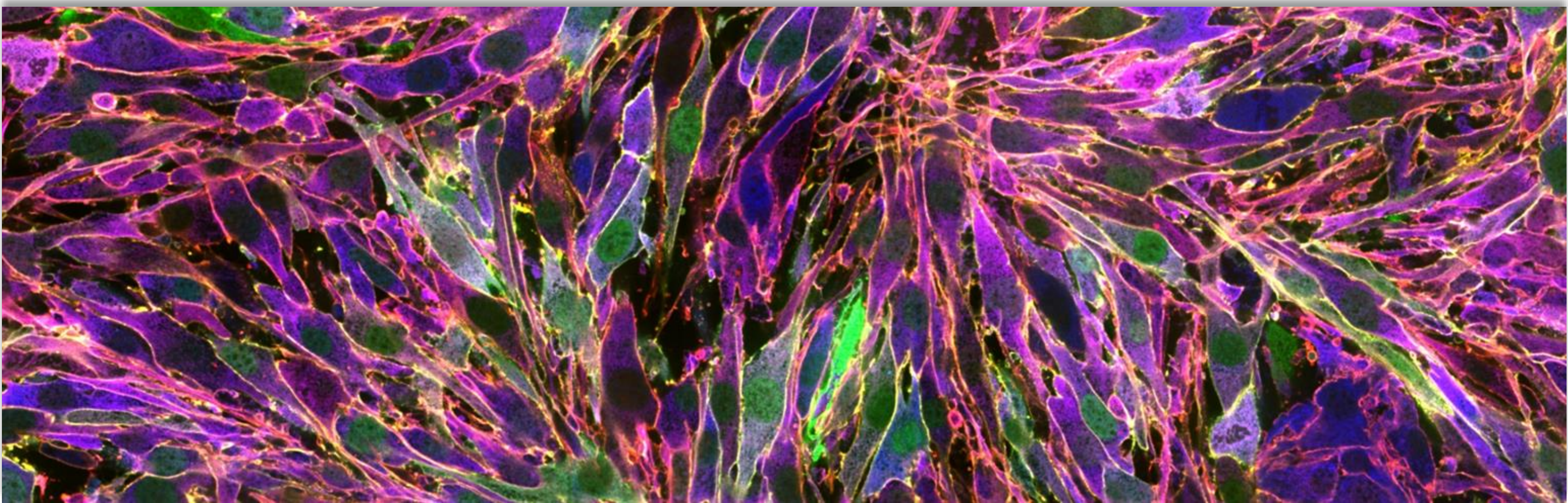
Keynote Presentation 1

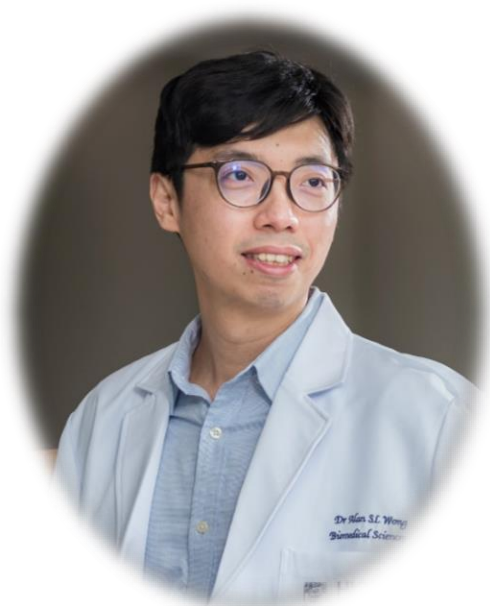
Optogenetic interrogation of developmental Erk signaling

Dr. Heath E. Johnson
Assistant Professor
School of Biological Sciences
The University of Hong Kong

Throughout development, signaling pathways must be activated at specific times locations to dictate cell fate. Yet in most cases it is unknown which pattern features are required to support normal development and how the underling cell fates are programmed. To understand this phenomenon, we developed optogenetic controls to allow for precise manipulation of Erk signaling in the fruit fly. We used these tools combined with classical genetics and live imaging we manipulate Erk signaling to understand how cell and tissue fates are set. This enabled us to discover a cell fate choice that depends on Erk dynamics by integrating the cumulative Erk signal load. Furthermore, we performed the first optogenetic "rescue" of an otherwise lethal signaling mutant, uncovering multiple duration thresholds of Erk which are read out by cells to set fates. We now continue to develop and apply these tools later in development to understand how signaling pathways integrate multiple cues dictate cell and organism level fates.



KEYNOTE SPEAKER



Dr. Alan S. L. Wong
Associate Professor
School of Biomedical Sciences
Li Ka Shing Faculty of Medicine
The University of Hong Kong

Dr. Alan Siu-lun Wong is an Associate Professor at School of Biomedical Sciences of The University of Hong Kong (HKU). Dr. Wong is also the Team Leader in Functional Genomics at Centre of Oncology and Immunology Limited, InnoHK, and is an Associate Member of Ming Wai Lau Centre for Reparative Medicine, Karolinska Institutet. Before he joined HKU in 2016, he obtained his B.Sc. and M.Phil. degrees in Biochemistry and Molecular Biotechnology from Chinese University of Hong Kong in 2005 and 2007 respectively, and completed his Ph.D. in Biochemistry at Hong Kong University of Science and Technology in 2011. He joined the Synthetic Biology Group at Research Laboratory of Electronics, Massachusetts Institute of Technology from 2012-2016 for postdoctoral training. His work has resulted in publications in prestigious journals including Nature Methods, Nature Biotechnology, Nature Cell Biology, Nature Neuroscience, Nucleic Acids Research, Cancer Research, PNAS, Cell Systems, Cell Reports, as well as PCT patents and patent applications on CRISPR-based screening methods and tools. He was awarded the Croucher Foundation Studentship (2008), Butterfield-Croucher Award (2008), Croucher Foundation Fellowship (2012), Hong Kong Institution of Science Young Scientist Award in Life Science (2011), RGC Early Career Award (2016), HKUMed Outstanding Research Output Award (2020), and NSFC Excellent Young Scientists Award (Hong Kong and Macau) (2020). His research takes an integrative approach leveraging on techniques in synthetic biology, CRISPR-based genome engineering, combinatorial genetics, and high-throughput functional genomics to decode the complex genetics of human diseases, as well as rationally engineer genetic circuits for providing new biomedical and biotechnological solutions.

KEYNOTE PRESENTATION 2

Enabling platforms for studying and engineering biological complexity

Dr. Alan S.L. Wong
Associate Professor
School of Biomedical Sciences
The University of Hong Kong

The specific sequences of DNA and protein code for the biological complexity and provide the templates for engineering. Harnessing the power of synthetic biology, genome editing, and next-generation sequencing technologies, we have developed high-throughput platforms to enable scalable assembly and parallel functional characterization of barcoded genetic and protein variants with high-order combinatorial modifications. In one example, multiplexed CRISPR screening can interrogate druggable targets to readily discover actionable combinations for cancer therapy. In another example, machine learning-coupled combinatorial mutagenesis of a library of protein variants can accelerate the identification of new CRISPR-based genome editors with more accurate and optimized genome-editing performances in human cells. The applications of these platforms, and among other high throughput enabling platforms under development in our laboratory, will be discussed.

ALUMNI SHARING

Dr. Colin C.L. Luk
Co-founder,
Project Development Lead
isoFoodtrace

Dr. Colin Chung Lim Luk is a Ph.D. graduate from the University of Hong Kong and the co-founder of isoFoodtrace (www.isofoodtrace.com). Dr. Luk works closely with the University of Hong Kong, the International Atomic Energy Agency, and the Food and Agriculture Organization on a food fraud project, utilizing stable isotope analysis to verify food attributes such as origin and farming practices. Before founding isoFoodtrace, Colin worked for NGOs and academic institutions, gaining expertise in large-scale project management, stakeholder engagement, and substantiability.

POSTDOCTORAL FELLOW PRESENTATION 01

Title:

Glycosylation of Insulin-like Growth Factor 1 Receptor (IGF1R): A functional role of sialic acids in resistance against IGF1R inhibitors in ovarian cancer

Authors:

Ayon Ahmed Hassan[a], Alice S.T. Wong[a]

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

Abstract

Glycosylation is the most complex and abundant post-translational modification of proteins. It involves enzymatic attachment of carbohydrate residues to specific amino acids. Although aberrant glycosylation is a universal feature of cancer cells that has been implicated in tumor progression, metastasis, and disease prognosis, the functional role of glycans in cancer biology remains largely elusive. In particular, the structure and function of specific glycoforms present on proteins remain unknown. Insulin-like Growth Factor 1 Receptor (IGF1R) is a receptor tyrosine kinase that plays a crucial role in ovarian cancer growth and progression. Preclinical studies have reported significant antitumor activity of IGF1R inhibitors in ovarian cancer patients, but with a variable response in advanced stage tumors. Here we found that IGF1R is heavily decorated with the sugar molecule neuraminic acid (sialic acid). Treatment of ovarian cancer cells with sialyltransferase inhibitor to prevent addition of sialic acids resulted in reduced spheroid formation, migration, and colony formation. Importantly, removal of sialic acid residues made ovarian cancer cells more sensitive to IGF1R inhibitor, suggesting a role of this modification in clinical resistance. We also found that the glycosylation status of IGF1R modulates signaling by its ligands IGF-1 and insulin. Using mass spectrometry, we have uncovered the structure of the glycans on IGF1R modified with sialic acid, which allows us to study the function of these specific glycoforms. Our work uncovers the functional role of glycosylation in IGF1R signaling and inhibition, and highlights the need to consider this post-translational modification in a clinical setting. Targeting IGF1R glycosylation may pave the pathway for development of efficacious therapies in the future.

Keywords: glycosylation, IGF1R, ovarian cancer, sialic acid

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POSTDOCTORAL FELLOW PRESENTATION 02

Title:

Human Endonuclease ANKLE1 Localizes at the Midbody and Processes Chromatin Bridges to Prevent DNA Damage and cGAS-STING Activation

Authors:

Huadong Jiang[a], Ying Wai Chan[a]

Affiliation:

[a] School of Biological Sciences, the University of Hong Kong, China

Abstract

Chromatin bridges connecting the two segregating daughter nuclei arise from chromosome fusion or unresolved interchromosomal linkage. Many of them can persist into cytokinesis or next interphase. These persistent chromatin bridges are trapped in the cleavage plane, triggering cytokinesis delay. Without the assistance from nucleases, the trapped bridges would be inevitably broken by the actomyosin contractile forces, inducing DNA damage and chromosomal rearrangements such as chromothripsis and aneuploidy. However, not all trapped bridges will undergo breakage. Recently, Caenorhabditis elegans LEM-3 and human TREX1 nucleases have been shown to process chromatin bridges to avoid chromatin bridges from catastrophic breakage induced by mechanical forces. Here, we show that ANKLE1 endonuclease, the human ortholog of LEM-3, accumulates at the bulge-like structure of the midbody via its N-terminal ankyrin repeats. ANKLE1 knockout cells display an elevated level of G1-specific 53BP1 nuclear bodies, prolonged activation of the DNA damage response, and replication stress, which can be rescued by expressing wild-type ANKLE1, but not N-terminal deleted or catalytic-dead mutants. Increased DNA damage observed in ANKLE1 knockout cells is also rescued by inhibiting actin polymerization or reducing actomyosin contractility. Importantly, we found that ANKLE1 acts on chromatin bridges by priming TREX1 nucleolytic activity and cleaving bridge DNA to prevent bridge breakage by actin-mediated mechanical forces, which results in the formation of micronuclei and cytosolic dsDNA that lead to the activation of cGAS-STING pathway. It is therefore proposed that ANKLE1 cooperates with other nucleases, such as TREX1, to resolve persistent chromatin bridges to avoid catastrophic breakage, thus preventing genome instability and autoimmune response.

Keywords: ANKLE1; chromatin bridge; midbody; micronucleus; cGAS-STING

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POSTDOCTORAL FELLOW PRESENTATION 03

Title:

Studying photosynthesis in mesophyll and guard cells using genetically encoded biosensors

Authors:

Shey-Li Lim[a], Boon Leong Lim[a]

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

Abstract

We are the first group to introduce ratiometric energy-related biosensors into Arabidopsis for visualizing the dynamic changes of subcellular adenosine triphosphate (ATP), reduced nicotinamide adenine dinucleotide phosphate (NADPH), and reduced oxidized and forms of nicotinamide adenine dinucleotide (NADH/NAD+) in living plant cells. By employing these genetically encoded fluorescent biosensors, we successfully solved two key issues in plant bioenergetics that have been debated for decades. First, what is the source of NADH for ATP generation in the mitochondria of mesophyll cells during photosynthesis? Second, could guard cell chloroplasts (GCCs) carry out photosynthesis and how important is it to stomata opening? When the sun rises, plant leaves require large amounts of energy (ATP) to open stomata to facilitate gaseous exchange and photosynthesis. While earlier studies suggested that GCCs do not undergo CO2 fixation, resulting in no or only limited photosynthesis in GCCs, some later publications reported contradictory findings. In this talk, I will illustrate how we employed genetically encoded fluorescent biosensors to solve these two important questions in photosynthesis.

Keywords: Photosynthesis, biosensors, guard cells, mesophyll cells

POSTDOCTORAL FELLOW PRESENTATION 04

Title:

Centromere plasticity and epigenetic regulation by RNAi pathway in the nematode C. elegans

Authors:

Charmaine Wong[a], Karen Yuen[a]

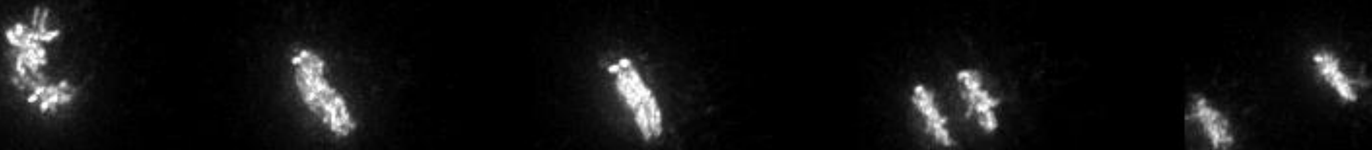
Affiliation:

[a] School of Biological Sciences, the University of Hong Kong, China

Abstract

The centromere is the single, dedicated region on a chromosome required for accurate chromosome segregation and stable inheritance of genetic materials. Among some other plants and insects, the nematode C. elegans contains long, diffused centromeres on non-repetitive sequences, which present a valuable model for studying epigenetic regulation of this conserved yet pliable structure. In this talk, I will provide you an overview on the challenges and our pursuit in developing strategies to investigate how RNAi pathway regulate centromere protein CENP-A organization. CSR-1 RNAi pathway expressed in the germline is important for mediating accurate chromosome segregation. This pathway targets endogenous germline genes, but the effect of this argonaute is perplexing - it does not suppress the expression of all its target genes. We found that CSR-1 and its components in the RNAi pathway regulate CENP-A level on the chromatin, concomitantly affecting the kinetochores and its binding to microtubules. Negative regulation of HCP-3 holocentromere loading by CSR-1 requires its slicer activity and the b isoform.From a previous CENP-A chromatin immunoprecipitation-chip, CENP-A scatters on different DNA sequences. These centromere-permissive regions rarely overlap with the germline and embryonic transcription regions. We hypothesize that CSR-1 recruits chromatin modifiers to deter CENP-A recruitment onto its targets' genomic positions. To test if CSR-1 bans CENP-A from occupying CSR-1-target genes, we probe for changes in CENP-A-binding, specifically at CSR-1 targets' gene regions, when CSR-1 is knocked down. The discovery of CSR-1 acting as an HCP-3 repressor for its chromosomal occupancy shed light on the role of RNAi pathways in specifying the centromere.

Keywords: Centromere biology, epigenetics, chromosome segregation, chromatin biology, RNAi pathway



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POSTGRADUATE STUDENT PRESENTATION 01

Title:

Exploring the roles of centromere RNA in maintaining chromosome stability in Saccharomyces cerevisiae

Authors:

Qiao Guo[a], Zhoubin Liang[b], and Karen W.Y. Yuen[a]

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

[b]Institute of Molecular Physiology and Gaoke Innovation Center, Shenzhen Bay Laboratory, Shenzhen, China

Abstract

Centromeric and pericentromeric transcription have been discovered, and are found to be regulated at an optimal level. In higher eukaryotes, including humans, it has been reported that centromeric RNAs (cenRNAs) are indispensable during the cell division process. CenRNAs may be involved in CENP-A deposition and kinetochore assembly. However, cenRNAs' functions in Saccharomyces cerevisiae are less understood despite their relatively conserved centromere sequences. Moreover, many centromere transcription variants and their functions are less characterized since centromere transcription could be initiated and terminated at different sites, followed by different post-transcriptional modifications, which is hard to profiled comprehensively until the emergence of 3rd generation of sequencing. Here, we try to explore the potential functions of budding yeast cenRNA in different approaches. We have identified the cenRNA binding proteins (cenRBPs) both in vitro and in vivo to study cenRNAs' function. We transcribed the cenRNA in vitro to obtain plenty of cenRNAs, and pull down with yeast cell lysate, followed by mass spectrometry identification. We also predicted some cenRBPs using computational methods and directly verify the protein-RNA interaction in vivo. Meanwhile, we have constructed strains with abnormal cenRNA levels to study impacts of cenRNA on the cells directly by phenotypic study and mRNA-seq. Our work will unveil the roles of cenRNAs in chromosome segregation and cell division in yeast, which might also be inspiring to research on genome stability in higher eukaryotes.

Keywords: Centromere, lncRNA, kinetochore, chromosome, genome stability

POSTGRADUATE STUDENT PRESENTATION 02

Title:

SBK1 promotes PPARα activity to enhance hepatic fatty acid oxidation through p21 inhibition

Authors:

Hang Miaojia[a], Bi Xinyi[a], Ng Chun Fai[b], Tse Chui Ling[c], Chan Chi Bun[a]

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

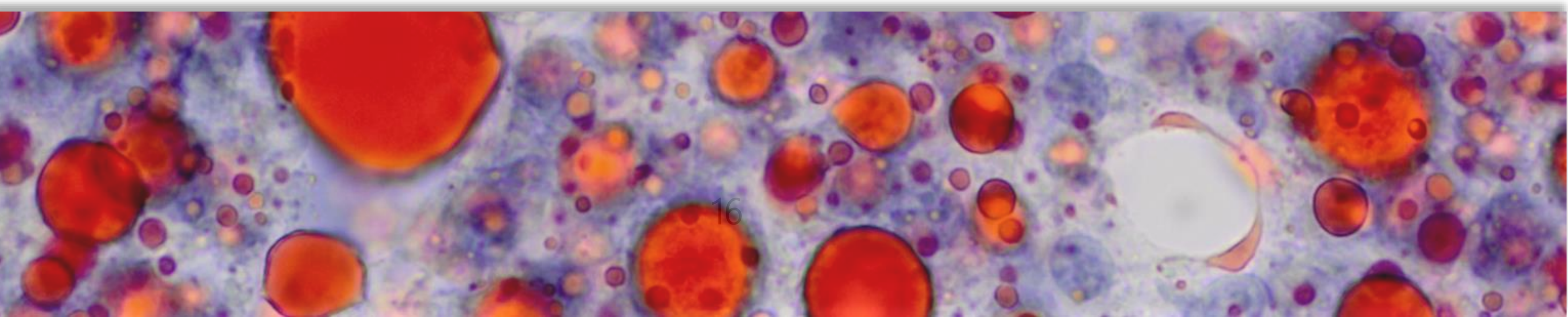
[b]Toronto General Hospital Research Institute, Canada

[c]School of Biomedical Sciences, the University of Hong Kong, China

Abstract

Mitochondrial fatty acid β-oxidation (FAO) in the liver plays a fundamental role in systemic energy homeostasis and redox balance. During nutrient challenges like prolonged fasting or overnutrition, hepatic FAO is reprogrammed to meet metabolic needs. Dysregulated FAO activity is associated with metabolic disorders like non-alcoholic fatty liver but the regulatory mechanism that controls the dynamic changes of FAO activity in the liver remains elusive. Recently, we found an uncharacterized kinase, SH3 domain binding kinase 1 (SBK1), that modulates FAO in the mouse liver. Using a combination of gene knockout, extracellular flux, and RNA sequencing analyses, we found an escalated SBK1 expression in the liver under various metabolic stresses, including excess energy supply, nutrient deprivation, or exhausted exercise. SBK1 knockdown in mouse liver cells impaired FAO and oxidative phosphorylation. Similarly, liver-specific SBK1 knockout mice displayed more severe hepatic lipid accumulation and lower expression of genes in FAO than the Flox/Flox control mice under fasting conditions. On the other hand, hepatic SBK1 overexpression enhances the activity of peroxisome proliferator-activated receptor α (PPARα), the master transcription factor of genes for FAO, in vivo and ex vivo. Mechanistically, SBK1 promoted PPARα activity by inhibiting the transcription of PPARα inhibitor, p21. Collectively, our data suggest that SBK1 is a novel regulator of metabolic adaption in the liver through the p21-PPARα pathway, which might provide insight into the development of new treatments for metabolic diseases.

Keywords: SBK1, Fatty Aicd Oxidation, Liver, PPARα, Energy Stress



POSTGRADUATE STUDENT PRESENTATION 03

Title:

Molecular Basis, Redundancy, and Developmental Remodeling of the Touch Response Circuit in Caenorhabditis elegans

Authors:

Haoming He, Wing Ka Lo, Martin Chalfie, Chaogu Zheng

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

[b]Department of Biological Sciences, Columbia University, New York, USA

Abstract

Deciphering the molecular basis of neuronal connections is critical to understanding the development of the nervous system. The nematode Caenorhabditis elegans offers an excellent model system to study the formation of neural circuits because its nervous system is relatively simple (containing only 302 neurons in adult hermaphrodites) and its connectome (neuronal wiring diagram) is completely mapped. In this project, we will use the C. elegans touch avoidance response circuit as a model to understand the principle of the circuit assembly. This circuit is composed of sensory neurons, interneurons, and motor neurons. Our focus is on the synaptic connections between the mechanosensory sensory neurons and the command interneurons, which control motor output. We plan to identify the genes involved in the formation of these synapses and understand how the circuit changes throughout development.

Our preliminary studies found that in the larval stage, electrical synapses formed by two innexin proteins, UNC-7 and UNC-9, mediate the connection between the anterior mechanosensory neurons and the interneuron that controls backward movement. At the adult stage, another chemical synapse-based neural pathway is added to the anterior circuit to create redundancy for the anterior response. Through fluorescent imaging, we also observed the pruning of certain synapses and the addition of new connections, which remodel the anterior circuit throughout larval development. Although the posterior circuit does not undergo significant remodeling during larval development, two gap junction proteins INX-1 and UNC-9 appeared to function redundantly in forming the connection between the posterior mechanosensory neuron and the interneuron that controls forward movement. Our results suggest prevalent redundancy built in the sensory reflex, either through multiple neural pathways or multiple genetic components. Further studies will focus on understanding the process of neural circuit remodeling and its behavioral consequences.

Keywords: neuronal circuit, Caenorhabditis elegans, redundancy, remodeling, mechanosensory

POSTGRADUATE STUDENT PRESENTATION 04

Title:

Muscle-generated brain-derived neurotrophic factor in torpor regulation

Authors:

Chit Yu Elsie Iu[a], Chi Bun Chan[a]

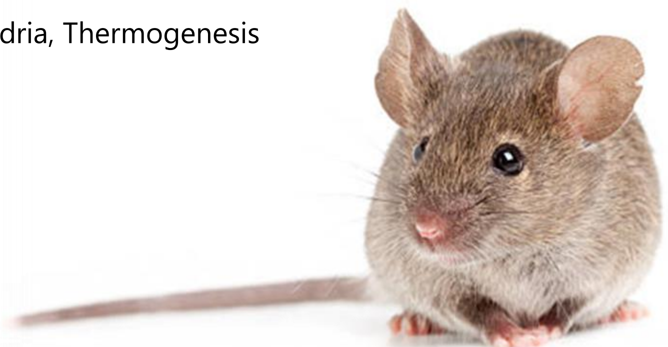
Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

Abstract

Torpor is a hibernation-like state in homeotherms to decrease the basal metabolic rate in response to food deficiency or low ambient temperature. Entry into torpor is characterized by marked reduction of body temperature via suppressing the mitochondrial uncoupling reaction of the brown adipose tissue (BAT). Torpor entry also induces a shift in fuel utilization from glucose oxidation to fatty acid oxidation in metabolically active organs to cope with the low glucose availability. Although it is an important strategy to conserve energy expenditure to deal with various challenges, the mechanism that initiates torpor remains largely unknown. In particular, the role of hormonal regulation of torpor entry and maintenance has not been explored. Our laboratory has recently reported that brain-derived neurotrophic factor (BDNF) is a myokine produced by the skeletal muscle during food deprivation. Increased BDNF expression in the muscle of fasted mice facilities the change of primary energy substrate from glucose to dominantly fatty acid. Since muscle-generated BDNF promotes the metabolic adaptation against energy paucity, we hypothesize that BDNF is a hormonal signal for torpor entry. Using the constitutive and inducible muscle-specific BDNF transgenic (MBTG) mice models, we found that muscle-generated BDNF increases tissue fuel utilization efficiency by modulating the mitochondrial activity. Moreover, the MBTG mice exhibit reduced locomotion and heat production in BAT via reprograming the metabolic gene expression, which resemble the metabolic phenotypes of torpid animals. Our in vitro study in T37i brown adipocytes further confirmed that BDNF is a direct regulator of BAT thermogenesis. Taken together, our results provide strong evidence that muscle-generated BDNF is an important hormone to prepare the body for stressful events via torpor induction.

Keywords: BDNF, Metabolism, Torpor, Mitochondria, Thermogenesis



POSTGRADUATE STUDENT PRESENTATION 05

Title:

RIF1 SUPPRESSES THE FORMATION OF SINGLE-STRANDED ULTRAFINE ANAPHASE BRIDGES VIA PROTEIN PHOSPHATASE 1

Authors:

Nannan Kong[a], Zeyuan Liu[a], Ying Wai Chan[a]

Affiliation:

[a]School of Biological Sciences, the University of Hong Kong, China

Abstract

Proper chromosome segregation is crucial for maintaining genome stability. Chromosome segregation defects induced by the persistent DNA entanglements connecting sister chromatids can lead to the formation of ultrafine anaphase bridges (UFBs) in anaphase. The resolution of UFBs must be completed before cytokinesis to prevent the breakage of bridge DNA. Otherwise, DNA damage can be induced in the following cell cycle. RIF1 was previously shown to be recruited by PICH to UFBs and is involved in UFB resolution with other UFB-binding factors by a yet unknown mechanism.

Here, we employ the auxin-inducible degron technology and CRISPR/Cas9 method to generate a cell line that allows rapid and inducible degradation of RIF1. We show that RIF1 functions in G2/M phase to inhibit the formation of 53BP1 nuclear bodies and micronuclei. Meanwhile, RIF1 localizes on PICH-coated double-stranded UFBs and prevents the formation of RPA-coated single-stranded UFBs mediated by BLM helicase. RIF1 interacts with protein phosphatase 1 (PP1) via its CI domain in anaphase when CDK1 activity declines. CDK1 negatively regulates RIF1-PP1 interaction via the CIII domain of RIF1. Importantly, depletion of PP1 phenocopies RIF1 depletion, indicating that PP1 is the effector of RIF1 on UFB processing. Furthermore, the phosphorylation-resistant mutant of PICH shows reduced interaction with the BLM-TOP3A-RMI1-RMI2 complex and bypasses the need of RIF1 in preventing the formation of single-stranded UFBs. Overall, our study reveals that RIF1-PP1 regulates UFB resolution by counteracting the actions of BLM.

Keywords: ultrafine anaphase bridges (UFBs), RIF1, PP1, UFB resolution

POSTGRADUATE STUDENT PRESENTATION 06

Title:

Targeting FANCM as a promising strategy for sensitizing cancer cells to PARP inhibitors

Authors:

Zeyuan Liu[a], Gary Yingwai Chan[a]

Affiliation:

[a] School of Biological Sciences, the University of Hong Kong, China

Abstract

Breast cancer and ovarian cancer are the first and the eighth commonest cancers in females for both incidence and mortality. Mutations in the BRCA1 or BRCA2 tumor suppressor genes predispose individuals to breast and ovarian cancer. In the clinic, these cancers are treated with inhibitors that target poly(ADP-ribose) polymerase (PARP) based on the concept of synthetic lethality. PARP inhibitors significantly improved prolonged progression-free survival in breast and ovarian cancer patients. However, despite a good initial response, many tumors develop resistance leading to aggressive tumor growth. PARP inhibitor resistance has proved to be a major problem in the clinic, We, therefore, sought to identify ways to enhance the efficacy of PARP inhibitors and overcome acquired resistance of cancer cells. Here we show that inhibition of FANCM, one of the core proteins in the FA pathway, aims to repair DNA interstrand crosslinks. potentiates the sensitivity of cells to PARP inhibitors (PARPi). The function of FANCM in PARP inhibitor resistance is independent of the FA pathway. Our studies showed that FANCM-depleted cells displayed a compromised ATR/CHK1 signaling but significantly increased the ATM-CHK2 signaling in response to S-phase DNA breaks in the second cell cycle. And the sensitivity can be rescued by deleting 53BP1 or PARP1. Together, we propose a model explaining how FANCM contributes to PARP inhibitor resistance: PARP inhibitor induces single-strand breaks in the first cell cycle, that would induce fork collapse in the second S phase. FANCM counteracts 53BP1 to promote proper repair of the collapsed forks to prevent chromosome abnormalities and cell death.

Keywords: PARP inhibitors, FANCM, DNA damage, Chromosome abnormalities

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POSTGRADUATE STUDENT PRESENTATION 07

Title:

Mechanistic study of Mcm2-7 Helicase Loading mediated by Orc2

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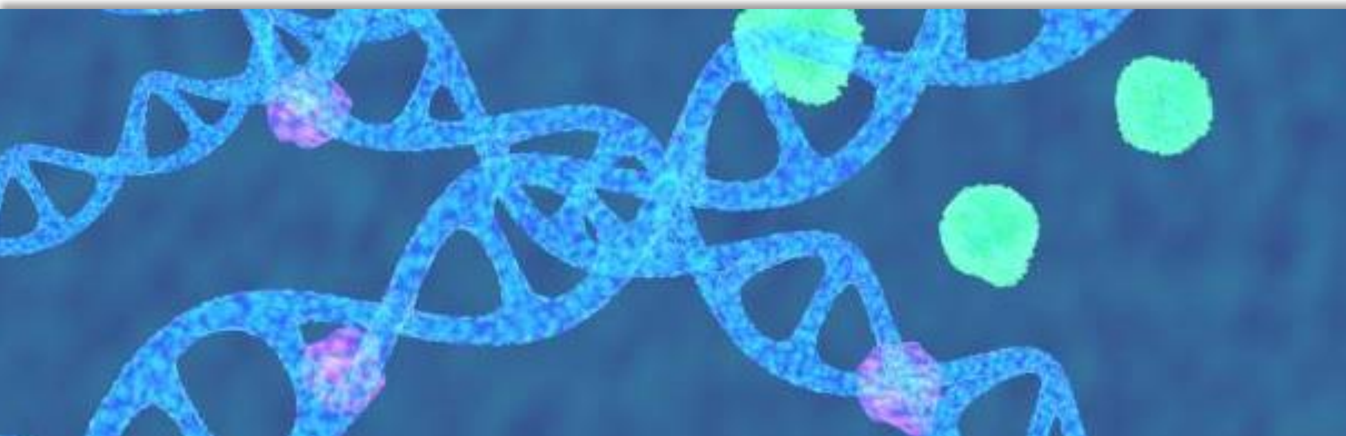
Abstract

Eukaryotic DNA replication initiation requires the origin recognition complex (ORC) to assemble abundant Mcm2-7 DNA helicase onto replication origins with the assistance of Cdc6 and Cdt1. The formation of the symmetric Mcm2-7 double hexamer (DH) is tightly regulated during the cell cycle to ensure a faithful genome duplication. Here we show that the Orc2 N-terminal domain (NTD) is essential for efficient genome replication firing. We managed to identify a conserved short α-helix in Orc2 NTD vital for origin firing by interacting with Mcm2 to promote Mcm2-7 DH formation through in vivo and in vitro approaches. The protein-protein interaction between Orc2 NTD and Mcm2, which can be inhibited by S-CDK, is able to facilitate Mcm2-7 ATPase activity. Our work reveals a novel mechanism of Orc2 NTD mediating Mcm2-7 helicase loading to support origin firing with rigorous control.

Keywords: DNA replication initiation; Orc2; Mcm2-7; EM



POSTGRADUATE STUDENT PRESENTATION 08

Title:

Stress adaptation to phosphate starvation leads to polymyxin resistance in E. coli through a Magnesium-Iron-BasSR signal transduction circuit

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Abstract

Phosphorus (P) is an essential element for building blocks of biomolecules and plays important role in vary biological processes. In bacteria, P is acquired mainly as inorganic orthophosphate (Pi), shortage of Pi can serve as a strong stimulus. Despite numerous works focused on how bacteria respond to Pi starvation, the whole process has not been fully understood. We now report that bacteria presented enhanced resistance to polymyxin during Pi starvation. We establish that the BasSR TCS were activated by Fe3+ signal and led to up-regulation of downstream arn operon when E. coli MG1655 experiences Pi starvation. Such response led to LPS modification and enhanced resistance to polymyxin. Further study proved that Mg2+ were disassociated from outer membrane (OM) during Pi starvation, which caused OM perturbation and charge imbalance. Charge driven iron to associate with OM even with low concentration, and iron together with iron induced modification stabilized OM. Our results proposed a nov el environment cue which could activate BasSR TCS and led to enhanced polymyxin resistance. Furthermore, we provided evidence of the connection between Pi, Mg and Fe pools.

Keywords: Stress response, Antibiotic resistance

3MINS PRESENTATION 01

Title:

RSU-1 Maintains the Integrity of Dense Bodies in the Muscle Cells of Aged Caenorhabditis elegans

Authors:

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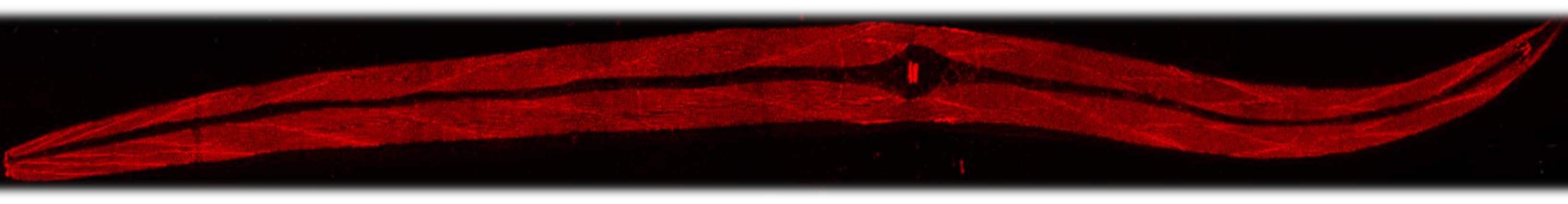
Abstract

Muscle contraction is a fundamental aspect of animal locomotion, enabling organisms to search for food, avoid predators, and locate suitable environments for reproduction and shelter. C. elegans is the foremost model to study muscles, which have a highly conserved structure when compared to vertebrates' muscles. The sarcomere, a highly ordered assembly of over a hundred conserved proteins, is the smallest functional unit of striated muscle. It is composed of dense bodies and M-lines, attached to actin filaments and myosin filaments respectively in the C. elegans body wall muscle. However, only some sarcomere proteins that null mutants cause obvious locomotion defects including "Unc" (uncoordinated) and "Pat" (paralyzed arrested at the twofold stage) are well studied, we need a more sensitive or appropriate assay to uncover the functions of remaining sarcomere proteins. Here, we demonstrate that the Ras suppressor protein (RSU-1), whose depletion doesn't show any obvious locomotion defect in young adults, primarily colocalizes with PINCH/UNC-97 and interconnects with PAT-3 at the dense body. And we observed an early onset of sarcopenia in rsu-1 mutant worms, wherein the locomotion ability of rsu-1 mutants significantly diminished in the old adult stage. Furthermore, remarkable dense body enlargement and elongation, as well as aggregation and distortion of the actin and myosin filaments were observed in the muscle cells of aging rsu-1 deletion mutant worms and mutants that lack interaction of RSU-1 with PINCH/UNC-97. Taken together, our results suggest that RSU-1 is required to maintain the structural integrity of the sarcomere in aging C. elegans, and its interaction with UNC-97 is crucial for this function. These findings also contribute to our understanding of the mechanisms underlying muscle function and its dysfunction during aging, providing insights for better treatment of muscle disorders such as muscular dystrophy and myofibrillar myopathies (MFMs).

Keywords: RSU-1, body wall muscle, dense body, aging



3MINS PRESENTATION 02

Title:
Effective delivery of imatinib by a bola-amphiphilic dendrimer to target cancer stem cells in treating metastatic ovarian cancer

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Abstract

Metastasis and chemoresistance driven by cancer stem cells (CSCs) are two major factors contributing to cancer mortality. The receptor tyrosine kinase c-Kit is a critical mediator of the ovarian cancer stem/tumor-initiating phenotype, thus making it a promising therapeutic target. However, imatinib (IM), a small molecule targeting c-Kit, has only limited clinical efficacy in treating ovarian cancer. In this study, we encapsulated imatinib in nanomicelles and demonstrated that Bola4A-amphiphilic dendrimer encapsulated imatinib (Bola/IM) outperformed IM alone both in vitro and in vivo, which effectively inhibited cell survival, stemness properties and metastatic spread. Bola/IM could significantly enhance the tumor accumulation and in vivo therapeutic index. The enhanced efficacy and application potential compared to IM alone were further demonstrated in patient-derived ascitic samples and organoids. Combination with cisplatin resulted in synergistic anti-cancer effect in patients' ascitic tumor cells with no adverse side effects and toxicity. These results show the potential use of this nanoformulation to empower IM for enhanced metastatic ovarian cancer treatment and chemosensitization.

Keywords: cancer stem cells, targeted therapy, nanoformulation, chemoresistance, ovarian cancer

3MINS PRESENTATION 03

Title:
Role of PICH in response to treatment of topoisomerase II inhibitors in colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third commonest cancer in the world, with a high death ratio and poor prognosis. In spite of some chemotherapy treatments being introduced, in particular 5-fluorouracil (5-FU), resistance emerges leading to tumor metastasis and recurrence. PICH is an SNF2 family DNA translocase that localizes to centromeres in prometaphase and binds to ultrafine anaphase bridges (UFBs) in anaphase. PICH is implicated in UFB resolution by recruiting other UFB proteins such as the BTR complex composed of BLM, TOP3A, RMI1 and RMI2, and RIF1. A deficiency of PICH leads to genome instability, apoptosis, and embryonic lethality in mice. Therefore, we propose that induction of UFBs using topoisomerase II inhibitors (known to induce a large number of UFBs) can be an anticancer strategy, particularly for cancer with low expression of UFB-processing proteins such as PICH. Here, we generated PICH knockdown and overexpression CRC cell lines to study whether PICH is important for maintaining genome stability and resistance to topoisomerase II inhibitors. And we found that PICH-depletion CRC cells showed increased sensitivity to ICRF-193 (a topoisomerase II inhibitor) compared to control cells. In the future, we will investigate the molecular mechanism of how PICH inhibition can lead to increased cell death, and to test if combination of PICH inhibition and topoisomerase II inhibitors can be an effective anticancer treatment for CRC.

3MINS PRESENTATION 04

Title:

Molecular Mechanisms in Cell Migration

Authors:

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Abstract:

The process of cell migration plays an essential role in the development and maintenance of multicellular organisms. To guide their motion through extracellular matrix (ECM), living cells use dynamic membrane projections known as filopodia, which are responsible for mechanical and chemical sensing of the surrounding microenvironment and formation of initial adhesion contacts with ECM or other cells. Numerous experimental studies suggest that abnormally high filopodia activity is a typical feature of aggressive cancer cells that results in their high motility, leading to formation of metastases. Thus, understanding molecular mechanisms responsible for the regulation of the filopodia dynamics and adhesion properties as well as investigation of filopodia-produced signals that guide cell movement may provide important insights into the cell migration and cancer development processes.

Recently, several proteins required for filopodia formation, growth and adhesion have been identified. However, there is still a large gap in understanding how their emergent collective behaviour results in the filopodia ability to guide cell migration, as the molecular mechanisms linking cell signaling pathways to the mechanosensitive function of filopodia remain largely unclear. Previously, it has been shown that mechanical forces applied to filopodia induce influx of extracellular Ca^{2+} through transmembrane channels, resulting in formation of intra-filopodial Ca^{2+} bursts that propagate to the cell body. It was found that such bursts are often followed by activation of lamellipodium propagation in the direction of stretched filopodia. Yet, the underlying activation mechanism are currently unknown.

To investigate them and gain better understanding of the key factors and processes responsible for integration of the mechanosensing behaviour of filopodia into the signalling network controlling cell migration, we plan to use a combination of in vivo and in vitro experimental approaches, including optogenetic tools, TIRF imaging and optical tweezers.

Keywords: Cell migration, Filopodia, Optogenetic tools, Mechanical forces

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