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The 2018 Annual Symposium of the Center for Life Sciences

2018生命科学联合中心国际学术交流会

2018.09.14

Venue

Zhong Hua Hall,
The Lakeview Hotel,
Sep 14, 2018
No.127,
Zhongguancun North Road
Haidian District, Beijing

北大博雅国际酒店B1层中华厅
(北京市海淀区中关村北大街127号)

会议日程 | PROGRAM

Morning Session — Chair: Chao Tang

9:00-9:40
Chris Sander
3D protein structure from evolution experiments in the laboratory

9:40-10:20
Linchong You
Microbial community dynamics

10:20-10:40
Tea Break

10:40-11:20
Hening Lin
Sirtuins and novel PTMs in cell signaling and cancer

11:20-12:00
Xinnian Dong
Live and let die: A defense strategy in plants

12:00-14:00
Lunch Break

Afternoon Session — Chair: Hongwei Wang

14:00-14:40
Victor Ambros
Developmental regulation and function of let-7a microRNA in C. elegans

14:40-15:20
Michael Karin
Metabolic and Immune Regulation of NASH-Driven HCC: From Basic Mouse Studies to Human Treatment

15:20-15:40
Tea Break

15:40-16:20
Dinshaw J. Patel
Structural Biology of cGAS-STING-mediated Immune Regulation

16:20-17:00
Robert Desimone
A causal analysis of the attentional network

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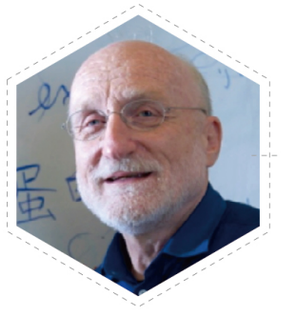

Chris Sander

Harvard Medical School and Dana-Farber Cancer Institute

3D PROTEIN STRUCTURE FROM EVOLUTION EXPERIMENTS IN THE LABORATORY

We have explored a fourth experimental method of protein structure determination using evolution experiments in the laboratory. For a protein of interest, the experiments involve sequence variation in a library of millions of sequences to which functional or structural assays are applied that select a performant subset of sequences. After one or more rounds of generation of variant sequence libraries and functional selection, the resultant sequence libraries of many thousands of sequences provide rich information about constrained residue-residue interactions. These interaction constraints can be used to compute correct protein 3D folds accurate to within a few Angstrom of positional variation of protein coordinates compared to static crystal structures. The interaction constraints also identify functionally important interactions that are informative for quantitative evolutionary biology, protein design and for the development of drug therapies. This genetic method of protein structure determination complements the classic methods of X-ray crystallography, NMR spectroscopy and cryo-EM electron microscopy and provides a tool for exploring molecular evolution extrapolated to the future. Collaboration with members of the Debora Marks and Chris Sander labs at Dana-Farber Cancer Institute and Harvard Medical School in Boston, including Mike Stiffler, Frank Poelwijk, Kelly Brock, and Nick Gauthier, as well as Nathan Rollins, John Ingraham, Adam Riesselman, Christian Dallago, Anna Green, Benjamin Schubert, Richard Stein and Thomas Hopf. Information at https://marks.hms.harvard.edu, http://sanderlab.org and http://EVcouplings.org

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Lingchong You

Duke Center for Genomic and Computational Biology, Department of Biomedical Engineering, Duke University

MICROBIAL COMMUNITY DYNAMICS

Microbes are by far the most dominant forms of life on earth. In every imaginable habitat, they form complex communities that carry out diverse functions. Microbial communities drive the geochemical cycling of diverse chemicals and through these activities shape the earth' s climate and environment. They are also intimately tied to human physiology and health. Members of each microbial community may compete for resources, collaborate to process the resources or to cope with stress. They communicate with each other by producing and responding to signaling molecules. And they innovate by exchanging genetic materials. These interactions raise fundamental questions regarding the evolutionary and ecological forces that shape microbial consortia. Our lab has adopted a combination of quantitative biology and synthetic biology to explore these questions. We engineer gene circuits to program dynamics of one or more Escherichia coli populations and use them to examine questions in cellular signal processing, evolution, ecology, and development. Analysis of these systems has provided insights into bacterial tolerance to antibiotics, developmental pattern formation, and scaling, as well as strategies to use bacteria to fabricate functional materials by exploiting programmed self-organization.

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Hening Lin

Howard Hughes Medical Institute, Department of Chemistry and Chemical Biology, Cornell University

SIRTUINS AND NOVEL PTMS IN CELL SIGNALING AND CANCER

Sirtuins are known as nicotinamide adenine dinucleotide (NAD)-dependent deacetylases. They regulate aging, transcription, and metabolism, and are considered important targets for treating several human diseases. There are seven sirtuins in humans, SIRT1-7. Four of them (SIRT4-7) have very weak deacetylase activity, which have caused many confusions and debates in the biological community. My laboratory discovered several novel enzymatic activities, such as desuccinylation and defatty-acylation, for several sirtuins with no robust deacetylase activity. This has led to the identification of previously unknown protein post-translational modifications (PTMs) and revealed new regulatory mechanisms of cell signaling pathways. Furthermore, these findings have enabled us to develop compounds that can inhibit particular sirtuins selectively. Some of the selective sirtuins inhibitors can kill cancer cells in cell culture and inhibit tumor formation in mouse models at least partly via the regulation of c-Myc and K-Ras. The roles of sirtuins and the new PTMs in cancer are being elucidated.

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Xinnian Dong

Howard Hughes Medical Institute, Department of Biology, Duke University

LIVE AND LET DIE: A DEFENSE STRATEGY IN PLANTS

Plants sacrifice infected cells through programmed cell death (PCD) as a defense mechanism against a pathogen once its effector is detected. This effector-triggered immunity is tightly controlled so that the intact tissue is protected. In my talk, I will first present data on how the PCD is executed and restricted to the infection site. I will also show how effector-triggered PCD could be used as an immune mechanism against biotrophic pathogens without making the host more vulnerable for necrotrophic pathogens which feed on death cells.

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Victor Ambros

Program in Molecular Medicine, Umass Medical School

DEVELOPMENTAL REGULATION AND FUNCTION OF LET-7A MICRORNA IN C.ELEGANS

let-7 microRNAs are one of approximately 40 evolutionarily ancient families of microRNAs that are conserved across all bilaterian animals. let-7 is unusual among these microRNA families, in that each bilaterian genome seems to have retained at least one let-7 (let-7a) that is almost perfectly conserved across all 22 nucleotides. This remarkable conservation of let-7a was discovered by Ruvkun 20 years ago, but we still do not understand it. The primacy of seed pairing (positions 2-8 of the microRNA) in target recognition accounts for evolutionary fixation of the seed sequence of a microRNA family, whilst permitting positions 9-22 to be less constrained. Indeed, positions 9-22 are poorly conserved for most microRNAs other than let-7a. We are systematically mutating individual nucleotides of C. elegans let-7a using CRISPR/Cas genome engineering and examining the impact of changing these sacrosanct nucleotides on the worm' s phenotype, and on the repression of let-7 targets. Our results to date indicate that certain non-seed nucleotides of let-7a may be critical for base pairing to sites in the 3' UTRs of evolutionarily conserved target mRNAs. We have also identified critical non-seed nucleotides at other positions which are not thought to be accessible for base pairing and hence may signify non-base-pairing interactions with currently unknown molecular partners.

Another evolutionarily conserved characteristic of let-7a is its pattern of developmental regulation; in most species, let-7a is upregulated at later developmental stages in association with transitions from proliferation to differentiation. The upregulation of let-7a is largely through post-transcriptional regulation of the processing of let-7a from longer transcripts; notably, the RNA binding protein LIN-28 plays a conserved role in blocking let-7a processing in stem cells and at early developmental stages. We are using CRISPR/Cas genome engineering of C. elegans to characterize what is emerging as a surprisingly complex web of LIN-28-mediated post-transcriptional mechanisms regulating let-7a expression, including a previously-unknown trans splicing event that cleaves the let-7a primary transcript downstream of the let-7a stemloop and inhibits Drosha processing. Moreover, the resulting trans spliced downstream let-7 transcript is actually an abundant small mRNA that contains let-7 complementary sites, enabling it to exert a negative feedback from the let-7a locus that inhibits other let-7-family microRNAs.

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Michael Karin

Department of Pharmacology, School of Medicine, University of California

METABOLIC AND IMMUNE REGULATION OF NASH-DRIVEN HCC: FROM BASIC MOUSE STUDIES TO HUMAN TREATMENT

Non-alcoholic fatty liver disease (NAFLD) is a common metabolic disorder whose incidence among US adults exceeds 30%. While NAFLD manifests as benign hepatic steatosis in most patients, in about 20% of patients it assumes a much more aggressive form – non-alcoholic steatohepatitis (NASH). The mechanisms that control the switch from benign steatosis to NASH are poorly understood, but were suggested to depend on ER stress. To query the role of ER stress in NASH development and establish a proper mouse model for studying the disease, we fed high-fat diet (HFD) to MUP-uPA mice, which are prone to liver ER stress due to hepatocyte-specific urokinase plasminogen activator (uPA) expression. Placing these mice on HFD triggered full-blown NASH within 3-4 months and most of the NASH-afflicted mice progressed to develop hepatocellular carcinoma (HCC), the most common form of liver cancer whose incidence and development rates greatly increase with steatohepatitis. Both NASH and HCC development in MUP-uPA mice depend on ER stress and are associated with persistent activation of sterol response element binding proteins (SREBP) 1 and 2. SREBP1 activation drives de novo lipogenesis (DNL) and cholesterol biosynthesis in HFD-fed MUP-uPA mice remains elevated without any sign of feedback inhibition mechanisms that control SREBP2 activation in tissue culture cells. DNL and cholesterol synthesis are also chronically elevated in NASH patients and the hepatic accumulation of free cholesterol was suggested to be a key switch from simple steatosis to NASH. While investigating the mechanism by which ER stress leads to persistent SREBP activation, we uncovered a previously unknown pathway in which caspase-2 (Casp2) leads to constitutive activation of site 1 protease (S1P), which initiates SREBP cleavage activating protein (SCAP)-independent SREBP activation. Of note, genetic ablation or pharmacological inhibition of Casp2 in MUP-uPA mice blocks NASH development by preventing hepatic steatosis. Casp2 ablation in both MUP-uPA and BL6 mice also prevents HFD-induced adipocyte hypertrophy and increases energy consumption. None of the effects of Casp2 on liver lipid metabolism are related to cell death. The NAFLD/NASH epidemic was also suggested to be associated with increased consumption of fructose, which is a major constituent of high-fructose corn syrup (HFCS), the main sweetener and a general food additive in the US. Increased consumption of HFCS has been linked to elevated risk of developing HCC, pancreatic and colon cancer. Indeed, feeding MUP-uPA mice a high-fructose diet (HFrD) results in NASH and HCC development even without the peripheral obesity that accompanies HFD consumption. Although fructose was believed to give rise to hepatic steatosis through preferential uptake and direct incorporation into the glycolytic pathway in hepatocytes, recent results indicate that the first site of fructose metabolism is the small intestine. Correspondingly, we found that fructose gives rise to NASH and HCC by first disrupting the intestinal epithelial barrier, evoking an inflammatory response that drives both NASH and HCC development.

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Dinshaw J. Patel

Structural Biology program, Memorial Sloan-Kettering Cancer Center

STRUCTURAL BIOLOGY OF CGAS-STING-MEDIATED IMMUNE REGULATION

One component of our research has focused on the field of pattern recognition receptors that sense double-stranded nucleic acids in the cytosol, thereby triggering a cascade of events that activate the innate immune response. Our efforts have focused on cGAS, the metazoan sensor of cytosolic dsDNA, the second messenger cGAMP and the adaptor STING. Our structural studies identified cGAMP, produced by DNA-activated cGAS from GTP and ATP, to be c [G(2’,5’)pA(3’,5’)p], that contained an unanticipated 2’,5’ linkage at the GpA step. Our group has made progress in the identification of small molecule inhibitors of mouse and human cGAS that target the same pocket as bound cGAMP. More recently, we have identified an additional human cGAS-DNA interface that contributes to cGAMP production and multivalency-induced phase separation. Our research has next been extended to homodimeric STING activation by cGAMP and targeting by the anti-viral agent DMXAA.

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Robert Desimone

McGovern Institute for Brain Research,
Department of Brain and Cognitive Sciences,
Massachusetts Institute of Technology

A CAUSAL ANALYSIS OF THE ATTENTIONAL NETWORK

The most behaviorally-relevant stimuli in scenes are selected for processing and control over behavior (“attention”). The effects of selection on neuronal responses are widespread, making it difficult to distinguish cause from effect in the attentional network. However, the flow of control can be inferred through the analysis of the relative timing of neural signals and the use of “causal” methods such as pharmacological inactivation, optogenetics, and feedback training to establish the impact of one circuit on another. This lecture will explore emerging new insights from human and animal data into the network that supports attentive vision.