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## **Decoding dynamic molecular interactions in cells**

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Visualization of specific molecules and their interactions in space and time is essential to investigate how cellular plasticity and dynamics are regulated, as perturbation of these processes is detrimental to health. The 1<sup>st</sup> International Conference on Cellular Dynamics and Chemical Biology (CDCB), which was held in Hefei, China in 2008, united scientists in the fields of photonics, chemistry, and biology, to provide synergism between these different disciplines (Yao & Fang, 2009; Yao, 2013). The 8<sup>th</sup> CDCB conference was held in Hefei, China from July 23 to 26, 2024, in a joint meeting with the Chinese Society for Cell Biology, the American Society for Cell Biology, and the Asian Pacific Organization for Cell Biology (Figure 1). About 200 scientists and students gathered in Hefei to discuss the recent advances in cellular dynamics, mesoscale imaging, and chemical interrogation of cell fate plasticity.

### **Chromatin plasticity, genomic stability, and chromothripsis**

Chromothripsis, an event that involves chromosome shattering, which is commonly followed by massive chromosomal rearrangement, drives circular extrachromosomal DNA formation, subsequent oncogene amplification, and evolution of the genome in cancer. In his opening keynote lecture, Dr. Don Cleveland, the 2018 Breakthrough Prize winner from the University of California-San Diego, shed light on the recent advances made by his laboratory in understanding the causes and consequences of chromothripsis. He shared insights into a recently discovered protein complex composed of MDC1, TOPBP1, and CIP2A that mediates the survival of chromothriptic cells by tethering shattered micronucleated chromosomes, to enable intact inheritance into a single daughter cell (Figure 2a) (Trivedi et al., 2023). By combining proximity ligation-based mass spectrometry and single-particle tracking, Dr. Cleveland and colleagues concluded that spatiotemporal dynamics of the CIP2A network play a role in controlling cell division, stabilizing the genome, and controlling genomic instability in tumors, for synthetic therapeutics.

Chromatin undergoes dramatic reorganization during the cell cycle, and the centromere is a key regulator for accurate cell division. One of the long-standing challenges in the cell biology field has been the chemical code of centromere organization. Dr. Xuebiao Yao (USTC, China) envisions the centromere as an important molecular environment involved in cell cycle dynamics. In this context, he investigated the material properties underlying human centromere dynamics and plasticity (Yao et al., 2000). By combining mass spectrometric identification of the centromere protein network with molecular real-time imaging (Xia et al., 2014), his team solved the molecular

architecture of the centromere-kinetochore core complex CCAN (Tian et al., 2022) and identified several metazoan centromere-kinetochore proteins such as ACAP4 (Fang et al., 2006), TIP150 (Jiang et al., 2009), and Apolo1 (Xu et al., 2021), which support his early working model that metazoans had evolved an elaborate centromere machinery to ensure faithful chromosome segregation in mitosis (Dou et al., 2024).

Dr. Dan Liu (USTC, China) presented his unexpected findings of WDR5 in centromere function. WDR5 was identified as a core component of the mixed-lineage leukemia 1 (MLL1) complex responsible for DNA methylation (Oh et al., 2020). Liu and colleagues found that WDR5 possesses the ability to undergo liquid-liquid phase separation (LLPS), which is responsible for its centromere localization (Figure 2b). LLPS-defective WDR5 perturbs H3K4me3, H3pT3, and CENP-A-pS7 localization, suggesting that LLPS of WDR5 serves as a signaling scaffold for centromere assembly and function. Given the fact that WDR5 exhibits multifaceted functions during cell fate decision (Oh et al., 2020), it is of great interest to delineate the code underlying context-dependent WDR5 networks using proximity ligation mass spectrometry.

Constitutive heterochromatin is of fundamental importance for transposon silencing and genomic stability in the eukaryotic nucleus. Dr. Kai Yuan (Central South University, China) presented his recent findings on H3K14ac, recruiting SetDB1 to create a repressive environment for the reinstallation of inactive heterochromatin (Tang et al., 2024), suggesting that H3K14ac is a crucial component of the embryonic machinery involved in maintaining genome integrity. Using a proximity labeling protocol, his team identified O-GlcNAcylation substrates in *Drosophila* and successfully mapped the O-GlcNAc interactome in major brain regions of *Drosophila* (Yu et al., 2024), which provides a critical stepping stone for delineating the chemical code of chromatin in *Drosophila*.

### **Cell fate determination and plasticity**

Accurate cell fate determination is largely governed by the precisely programmed cell cycle machinery, which in turn relies on a spatiotemporally controlled mitotic spindle apparatus, including the centrosome, the chromosomes, the spindle, and astral microtubules. Dr. David Burgess (Boston College, USA) summarized his work on astral microtubule assembly and spindle positioning mechanisms underlying the migration of the male pronucleus to the egg center, prior to mitotic entry. He provided several lines of evidence that different biological model systems use

either dynein-based pulling, or pushing forces from plus-end growth of astral microtubules, to move the male pronucleus towards the egg center (Meaders & Burgess, 2020). Dr. Zhenye Yang (USTC, China) shared his recent finding that cancer cells with high levels of reactive oxygen species (ROS) depend on a G6PD-mediated NADPH upsurge in mitosis to ensure accurate chromosome segregation (Cheng et al., 2023). These results open exciting perspectives, to delineate in the future how spatiotemporal dynamics of NADPH guide chromosome stability. Dr. Pierre Gonczy (EPFL, Switzerland) presented his work on the role of SAS proteins in the assembly and disassembly of the centriole. His team deployed photothermally-actuated off-resonance tapping high-speed atomic force microscopy to decipher mechanisms of centriole assembly and disassembly, and discovered that SAS-6 self-assembly is crucial for centriole assembly while SAS-1 protein removal from the central tube mediates centriole removal during oogenesis (Pierron et al., 2023).

Centrosome assembly starts with the recruitment of pericentriolar material (PCM), which contains hundreds of proteins, around centrioles. Decoding the spatiotemporal molecular dynamics of PCM assembly is a challenging task. Dr. Jordan Raff (University of Oxford, UK) revealed the role of Spd-2 in the dynamic assembly of pericentriolar material. His team used synthetic streptavidin-coated beads bound to a biotinylated anti-GFP-Nanobody, to capture the protein of interest (GFP-Spd-2) and other factors that it recruits to scaffold the assembly of PCM (Figure 2c) (Wong et al., 2024). In the future, it will be interesting to see how this technique revolutionizes the artificial synthesis of other non-membranous organelles. Dr. Zhe Feng (Fudan University, China) provided structural insights into molecular interactions required for PCM assembly (Feng et al., 2017). She shared supporting structural evidence of the molecular interactions underlying Spd-2 functioning. SP2D (Spd-2 domain of Spd-2/CEP192) forms a unique “extended cradle” structure, which was proven to be crucial for the PCM scaffold assembly.

### **Membrane organelles and dynamic interactions in cell physiology**

Tethered interactions between membrane organelles allow efficient transfer of ions and/or macromolecules and provide a scaffold for membrane fusion and fission during regulated epithelial cell secretion (Yao & Forte, 2003). However, uncontrolled membrane organelle fusion or fission leads to altered organelle plasticity, resulting in physiological disorders. For example, mutations in the outer mitochondrial membrane proteins mitofusins (MFN 1 & 2) result in

defective mitochondrial fusion that is associated with the onset of several diseases (Züchner et al., 2004). Dr. Quan Chen (Nankai University, China) described the potency of small molecules called S89 and S3 in reversing mitochondrial fragmentation. S3 targets deubiquitinase USP30, while S89 directly activates MFN1 to promote mitochondrial fusion (Figure 2d) (Guo et al., 2023). Indeed, Ke Liu (USTC, China) reported a previously unknown mechanism underlying how cells prevent excessive fission of mitochondria. Yta4 (AAA-ATPase) prevents mitochondrial fission by inhibiting the activity of the mitochondrial divisome made up of Fis1, Mdv1, and Dnm1 (Figure 2e) (He et al., 2023). Collectively, these findings offer great hope for the development of therapeutics by reversing aberrant mitochondrial morphology.

Dr. Xingguo Liu (Guangzhou Institute of Biomedicine and Health, CAS) revealed an astonishing discovery of the novel 14<sup>th</sup> mitochondrial protein named CYTB-187AA, encoded by mtDNA and translated through a previously unknown translational pattern of mitochondrial mRNA. CYTB-187AA is encoded by CTYB and translated by cytosolic ribosomes. Moreover, it regulates early mammalian development by modulating ATP production through interacting with SLC25A3 (Figure 2f) (Hu et al., 2023). It will be exciting to further decipher the dual translational pattern of mitochondrial mRNA. Dr. Da Jia (Sichuan University, China) shared the findings of his research group that set the first example of a sequence-specific recognition of cargo proteins downstream of the protein coat. The WDR11-FAM91A1 complex recognizes super acidic clusters (SACs) crucial for trafficking and neuronal development in zebrafish (Deng et al., 2024).

The PIWI/piRNA complex protects genome integrity in the animal germline by silencing transposons. Inter-mitochondrial cement (IMC) and chromatoid body (CB) are sites for piRNA processing and functioning, respectively. Dr. Mofang Liu (CEMCS, China) discussed the mechanism of translocation of MIWI (a member of the PIWI family) from IMC to CB. She proposed that piRNA loading is a prerequisite for the translocation of MIWI from IMC to CB (Wei et al., 2024).

### **Phase separation in orchestrating cellular dynamics**

During mitosis, the segregation of replicated chromosomes relies on the pulling and pushing forces from microtubules attached to the centromere. EB1 is a tracker of growing microtubule plus-ends and acts as an interactive hub for microtubule plus-end dynamics. Over the last decade, Dr. Xuebiao Yao and his colleagues decoded the chemical basis underlying microtubule plus-end

dynamics regulated by EB1 acetylation at Lys220 (Xia et al., 2012) and crotonylation at Lys66 (Song et al., 2021), respectively. Surprisingly, they also found that EB1 forms comet-like condensates *in vitro* and *in vivo*, which is essential for stable kinetochore-microtubule attachment (Figure 2b) (Song et al., 2023). Interestingly, they further uncovered how EB1 uses LLPS to contact the centromere-kinetochore core component CENP-R, to guide chromosome dynamics at the metaphase-anaphase transition (Figure 2b).

Purinosomes are the metabolons that represent a novel level of a metabolic constellation of enzymes involved in the regulation of purine metabolism. Dr. Ruey-Hwa Chen (Academia Sinica, Taiwan) presented her studies on the molecular mechanism underlying the assembly and the biological functions of purinosomes. Under stress conditions, PAICS, upon ubiquitination by ASB11-based Ubiquitin ligase, recruits ubiquitin-binding protein UBAP2, which through multivalent interactions drives phase separation to promote purinosome assembly. LLPS-dependent purinosome assembly is important for the tumorigenesis of melanoma cells (Chou et al., 2023). Dr. Chuanhai Fu (USTC, China) uses fission yeast as a model system to study the role of RhoGAP proteins in establishing cell polarity (Zheng et al., 2022). His group recently found that LLPS of F-BAR domain-containing proteins Rga7 and Rga8 guide their localization at the cell cortex for regulating the dynamics of the plasma membrane required for polarized cell growth. Considering that LLPS organizes epithelial cell polarity, it would be of great interest to evaluate how mammalian homologs of Rga7 and Rga8 guide polarity establishment.

### **Host-parasite interactome**

The major questions to completely understand virulence are: how the pathogens exploit the machinery of their host and what is the cellular response to microbial products. Dr. Dinshaw Patel (Memorial Sloan Kettering Cancer Center, New York, USA) discussed the previously unknown function of the transmembrane helix of a CARF domain protein, Cam1, which functions in prokaryotic type III CRISPR immunity against viruses. He predicted that Cam1 works through a novel second messenger mechanism to trigger defense against viruses by depolarizing membrane and growth arrest (Baca et al., 2024). His studies unfolded a novel pathway opted by the host to protect itself from viruses, and in the future, it will be interesting to see its therapeutic potential. Dr. Matthew Welch (UC Berkeley, USA) elaborated on how *Rickettsia parkeri* species escape the host membrane to avoid immune detection. Pat1 mediates *R. parkeri's* escape from the host

membrane and autophagy by avoiding galectins and polyubiquitin (Borgo et al., 2022). His team also revealed that the outer membrane proteins, OmpB and PKMT1, of *Rickettsia* protect it from ubiquitylation and thus autophagy.

Dr. Isabelle Tradieux (Institute for Advanced Sciences, Grenoble) discussed the strategy adopted by *Toxoplasma gondii* for high-speed motility. Using reflection interference contrast and expansion microscopy, she presented nanoscale evidence that only one apical anchoring contact of the parasite with the substrate is sufficient to slide over it. In addition, biochemical and biophysical quantitative assays further revealed that the interaction between the host's glycosaminoglycan (GAG) and the parasite is enough for the helical gliding of the parasite (Vigetti et al., 2024). Dr. Xinxing Yang (USTC, China) combines super-resolution imaging with single-molecule tracking to study bacterial cytokinesis. His findings provide evidence of successful direct real-time imaging of the cell division machinery using rhodamine-based fluorogenic probes (Yang et al., 2021). This study offers hope to directly visualize other cellular processes by using specific probes.

Dr. Sergio Schenkman (University of Sao Paulo, Brazil) showed that the *Trypanosoma cruzi* extracellular vesicles, EVs, also isolated from patients with chronic Chagas disease, possess the potential for being a biomarker and transducer (Madeira et al., 2024). It was proposed that EVs released by the parasite have the potential to induce cardiac fibrosis in the animal model. In the future, it will be interesting to examine how circulating EVs alter the system's physiology and elicit Chagas pathogenesis. This can be done by microscopic examination, using 3D organoids with microfluidic chips.

### **Cell biology in health and diseases**

Elucidating the molecular mechanisms involved in maintaining cellular homeostasis is crucial for individuals' health. Stem cell differentiation serves as a source for the foundation of all cell types, and their homeostasis plays a vital role in maintaining health. Dr. Ye-Guang Chen (Tsinghua/Nanchang University, China) delivered his keynote lecture on intestinal epithelial homeostasis and regulation. His team revealed that BMP represses Bcl11b expression, which is important for Lgr5<sup>+</sup> stem cell maintenance (Zhang et al., 2020). Surprisingly, Bcl11b regulates chromatin accessibility by repressing the NuRD complex to elicit specific gene expression. Thus,



it will be worth examining if Bcl11 is a useful target for examining gastrointestinal disease progression.

TDP-43 pathology is a hallmark of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). Dysfunction of TDP43 impacts the mRNA transcript of the human STMN gene, encoding for stathmin-2 protein, resulting in neurodegeneration in ALS. Dr. Jone López-Erauskin (University of California, San Diego) showed that stathmin-2 is co-transported with axon "survival factor" NMNAT2 and is required for its proper transport (López-Erauskin et al., 2024). These findings reinforce the restoration of stathmin-2 as an attractive therapeutic niche for treating ALS and other TDP-43-dependent neurodegenerative diseases.

Ninein, a centrosome protein, is implicated in microtubule anchorage and centrosome cohesion. Mutations in the human NINEIN gene have been linked to Seckel syndrome and a rare form of skeletal dysplasia. Dr. Andreas Merdes (University of Toulouse, France) described the role of ninein in osteoclast formation and bone ossification using a ninein knockout mouse model. He proposed that ninein is important for osteoclast fusion and for maintaining a functional balance between osteoblasts and osteoclasts (Gilbert et al., 2024). Dr. Duan-Qing Pei (Westlake University, China) reported his work on the reconstitution of human somitogenesis by direct reprogramming. His group reprogrammed human urine epithelial cells to a stable presomitic mesoderm progenitor cell line (UiPSM). They also demonstrated that UiPSM cells can differentiate into osteoblast and chondroblast cells *in vitro*, raising hope for future treatment of musculoskeletal disorders (Gao et al., 2024).

### **New techniques for modeling and delineating cellular dynamics**

One of the most exciting aspects of biology is to engineer cell regeneration and plasticity. Dr. Jinsong Li (CEMCS, Shanghai, China) reported in his keynote lecture exciting advances on "Sperm-like stem cell-mediated semi-cloning technology." Semi-clonal technology-based sperm-like haploid embryonic stem cell-mediated mouse models provide powerful tools to better simulate complex diseases involving polygenes and chromosomal abnormalities (aneuploidy), play a role in predicting and screening the high-risk groups, and provide more accurate diagnostic and prognostic tools for complex trait diseases (Lu et al., 2024).

Dr. Guo-Qiang Bi (USTC, China) discussed several imaging tools specially designed for visualizing neuronal architecture and dynamics. He shared an exciting discovery of a high-throughput technique called VISoR/SMART, a method developed by his group that combines optimized tissue sectioning of the brain and visualizing with ultrahigh-speed fluorescence microscopy featuring improved volumetric imaging with synchronized on-the-fly-scan and readout technique to visualize neuronal circuits of the entire brain (Xu et al., 2021). Dr. You Yu (Zhejiang University, China) reported an integrative structural study of the budding yeast Smc5/6 holo-complex (involved in DNA replication and repair). Using electron microscopy, cross-linking mass spectrometry, and computational modeling, his work revealed that intricate interactions among subunits (Smc5, Smc6, and the Nse1-3-4) of the Smc5/6 complex are essential to form a clamp that encircles DNA (Yu et al., 2022). Dr. Yingying Su (LUMICKS) showcased the applications of C-Trap to visualize the behavior of Smc5/6 on DNA with the help of correlative single-molecule fluorescence imaging (Chang et al., 2022). C-Trap is a newly emerging technology that makes it possible to manipulate and probe the dynamic biological process by allowing simultaneous manipulation and visualization of single-molecule interactions in real-time. Using transmission electron microscopy and ultrastructural *in situ* hybridization approaches, Dr. Luis F. Jimenez-Garcia (National Autonomous University of Mexico) revealed the presence of the nucleolus in an Archaeon for the very first time. Based on this discovery, he challenged the long-standing concept of the evolutionary origin of eukaryotes (Islas-Morales et al., 2023).

## **Perspectives**

Accurate determination of the spatiotemporal dynamics of interacting organelles within a cell is essential for understanding cellular dynamics. Combinations of advanced optical imaging protocols, such as lattice light-sheet microscopy with adaptive optics and photoactivatable complementary fluorescence, spectral imaging analyses, and correlative light and cryo-electron microscopic tomography, would increase our understanding of the dynamics of non-membranous organelles and inter-organelle communications. The newly developed lattice light-sheet microscopy with adaptive optics has enabled, for live organoids, noninvasive, aberration-free imaging of subcellular processes, including organelle contacts and remodeling during mitosis. This technology reveals the phenotypic diversity within cells of various organisms and at different developmental stages. Moreover, it is also useful for determining, in real-time and at the organelle

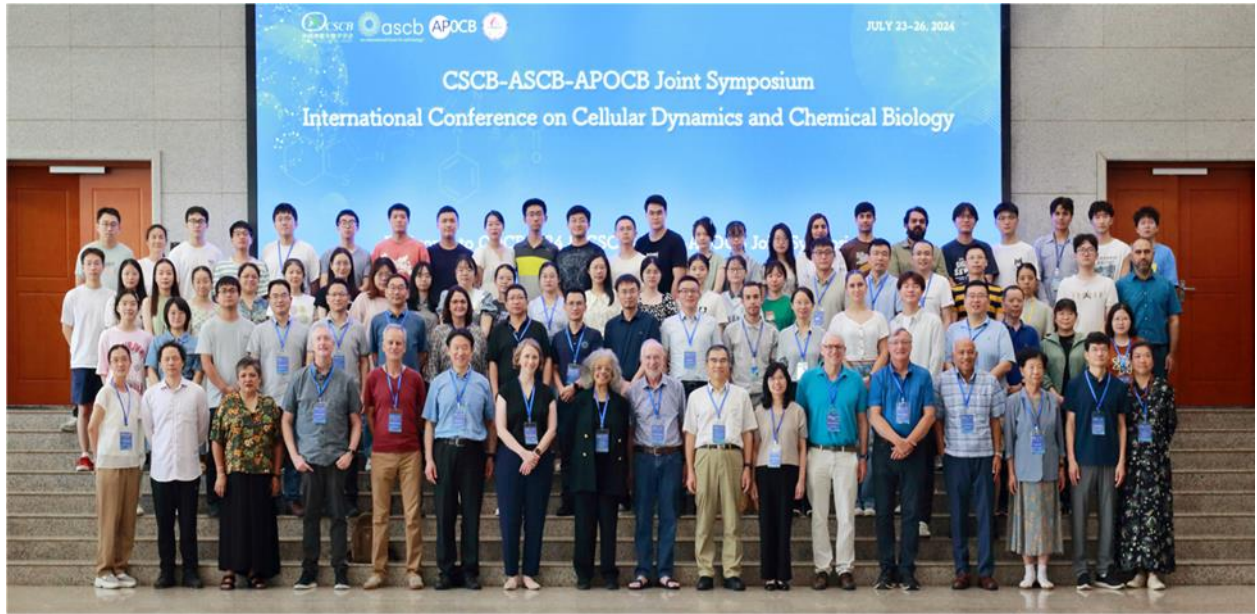
level, how host cells adapt to a physiological stimulus or in response to SARS-CoV-2 and *H. pylori* infections (Liu et al., 2020; Wang et al., 2022). In addition, it would be of great interest to examine whether fine-tuning the spatiotemporal dynamics of specific organelle-organelle communications in disease settings is sufficient for the cure. In both cases, small molecules targeting organelle-organelle contacts will be extremely valuable for investigating organelle dynamics in health and correcting aberrant organelle-organelle communications in diseases. There is no doubt that analysis of organelle-organelle interaction networks and circuitry combined with targeted chemical probes will enable us to delineate the molecular physiology and engineer targeted therapeutics for diseases.

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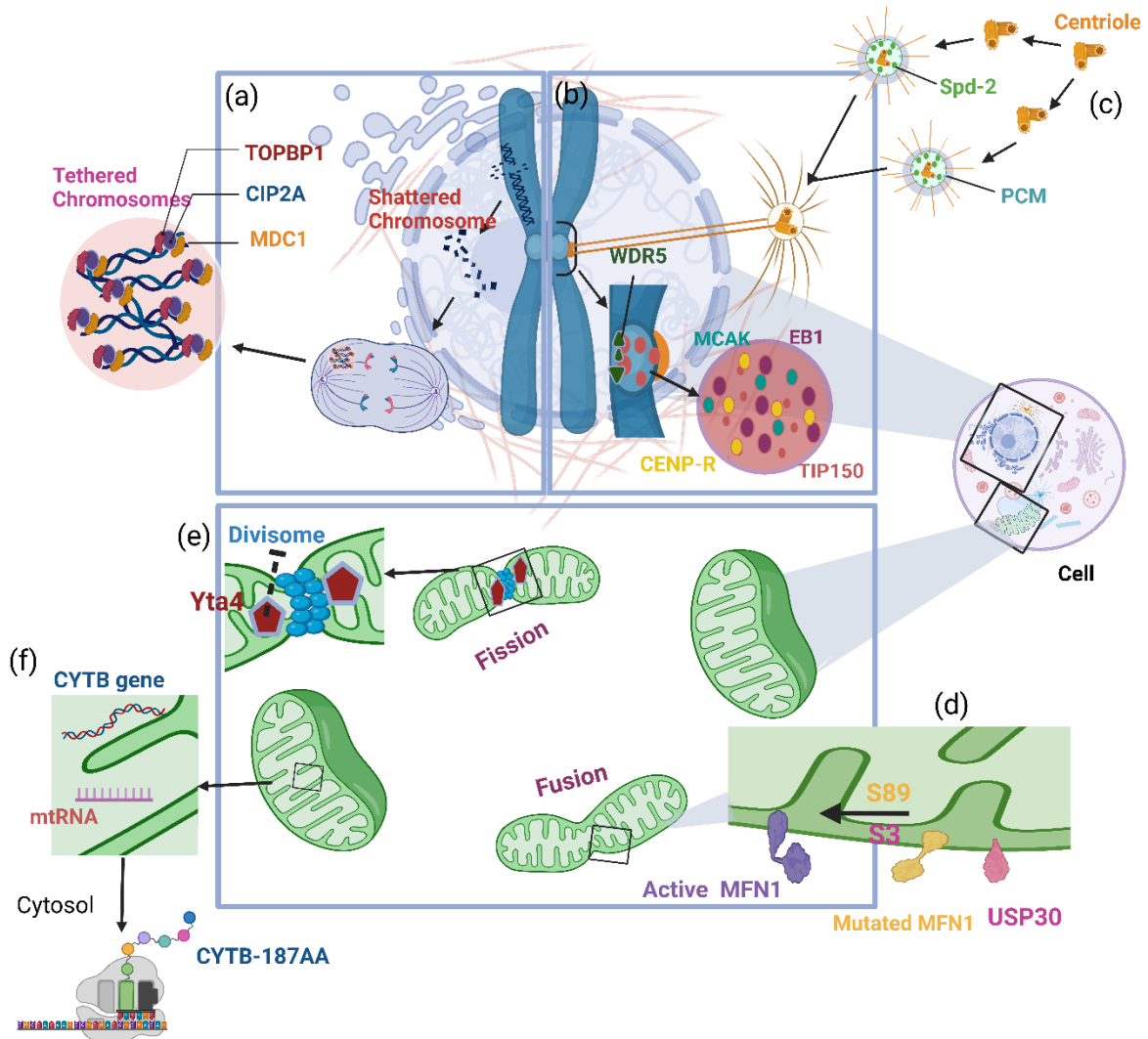
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**Figure 1**

**Group photo for the opening ceremony of CDCB2024.**



**Figure 2**

**Illustration of some key findings presented in the CDCB2024.**

(a) MDC1, TOPBP1 and CIP2A complex mediates the survival of chromothriptic cells by tethering shattered micronucleated chromosomes. (b) EB1, TIP150, MCAK, and CENP-R undergo liquid-liquid phase separation to orchestrate centromere-kinetochore organization. WDR5 activity at the inner centromere is also dependent on its LLPS ability. (c) Spd-2 recruitment and scaffolding initiates PCM assembly around centrioles. (d) S89 and S3 restore the



activity of mitochondrial MFNs and prevent aberrant mitochondrial fusion. (e) Yta4 halts excessive mitochondrial fission by inactivating the divisome. (f) CYTB-187AA is the 14<sup>th</sup> newly discovered mitochondrial protein, encoded by mtDNA (CYTB gene) and has cytosolic translation.