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MEETING REPORT

Meeting report – shining light on septins

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ABSTRACT

Septins are enigmatic proteins; they bind GTP and assemble together like molecular Lego blocks to form intracellular structures of varied shapes such as filaments, rings and gauzes. To shine light on the biological mysteries of septin proteins, leading experts in the field came together for the European Molecular Biology Organization (EMBO) workshop held from 8–11 October 2017 in Berlin. Organized by Helge Ewers (Freie Universität, Berlin, Germany) and Serge Mostowy (Imperial College, London, UK), the workshop convened at the Harnack-Haus, a historic hub of scientific discourse run by the Max Planck Society.

Septin proteins form an important component of the cytoskeleton and are conserved from yeast to humans (Nishihama et al., 2011). The emerging view today is that septins are not simply passive structural molecules that act as scaffolds, but rather that they function in a highly sophisticated and physiologically regulated manner. It is not surprising, therefore, that abnormalities in septin expression and function are associated with cancer, ageing, infectious disease, reproductive and neurodegenerative disorders (Dolat et al., 2014). The opening keynote lecture by Jeremy Thorner (University of California, Berkeley, USA) presented a resourceful historical overview of the discovery of septin proteins and their subsequent functional characterization over the past 45 years. During the four-day workshop, new evidence was provided for mechanisms of septin assembly and its regulation by interacting proteins, posttranslational modification, membrane interactions and membrane curvature. In the second keynote lecture, William Trimble (University of Toronto, Canada) discussed the role of septins as diffusion barriers and in cytokinesis. A wide variety of advanced microscopy, proteomic and structural tools were employed by the participants in the work they presented to query septin structure, assembly and dynamics in exquisite spatial and temporal detail. We summarize here the key findings, methodologies and developing hypotheses in the septin field that emerged from the meeting, and close with some of the remaining questions in the quest to understand the functional role of septins in health and disease.

Assembly of septin structures

Septin proteins follow certain rules of assembly; some we think we understand, while others remain paradoxical or unknown. How septin proteins assemble into filaments and disassemble, however, still remains to be elucidated. In most organisms, there are more available septin subunits than there are positions to occupy within septin hetero-oligomers, so how do cells decide which available septin protein will occupy which position?

Building on his recent work (Weems and McMurray, 2017), Michael McMurray (University of Colorado, Denver, USA) explored how some fungi assemble hetero-hexamers lacking the standard central homodimer. McMurray provided evidence that, in budding yeast cells, certain conditions favour a 'central homodimer bypass' assembly pathway involving an evolutionarily ancient molecular mode of septin homodimerization otherwise available only to GTPase-active septins. Stefan Raunser (Max Planck Institute, Dortmund, Germany) proposed a novel regulatory mechanism for septin filament formation and dissociation based on the interaction of septins with the GTPase Cdc42 and its effector Gic1 (Sadian et al., 2013). Through electron microscopy and cryo-electron tomography experiments, he showed that Gic1 acts as a scaffold for septins to form long filaments. Cdc42-GTP binds to Gic1, leading to the dissociation of Gic1 from the filaments. Cdc42-GDP is active and, in the absence of Gic1, directly interacts with septin filaments resulting in their disassembly. Iwona Mucha-Kruczynska from the Ewers group (Freie Universität, Berlin, Germany) presented stunning super-resolution images of cell lines engineered to express GFP-tagged SEPT2. Photobleaching experiments suggested that GFP–SEPT2 could actively exchange within pre-existing assembled filaments.

In a captivating talk that followed, Amy Gladfelter (University of North Carolina, Chapel Hill, USA) presented unpublished work analysing how septins sense micron-scale curvature. Her group has found that assembly on curved surfaces is highly cooperative, reflects differential affinity of septins for specific curvatures and may be mediated through a new mechanism of membrane association. Aurélie Bertin (Institut Curie, Paris, France) presented results from studies using biomimetic tools, such as artificial vesicles and supported lipid bilayers, to characterize the role of septins at the membrane. Bertin showed that septins induce significant deformations on vesicles, which seem to be closely related to their preferential organization on specific curvatures.

How yeast cells sculpt and use septin rings

Septins were first discovered in yeast in 1971 (Hartwell, 1971). The budding yeast remains today a useful system to understand the role of septins and their cellular organization. Jeremy Thorner (University of California, Berkeley, USA) presented a tripartite split-GFP method as a means to interrogate the interactome of the filamentous septin collar (Finnigan et al., 2016). During the cell cycle, septins first form a patch at the presumptive bud site. Activity of the small GTPase Cdc42, both directly, by recruiting septin oligomers, and indirectly, via the control of exocytosis, sculpts the yeast septin ring at the G1/S transition (Okada et al., 2013). Andrew Goryachev (University of Edinburgh, UK) presented new data showing that the septin collar is instrumental in maintaining the polarized segregation of Cdc42 activity not only in the bud, but also during bud growth in the S and G2 phases, thus extending the role that septins play during the cell cycle. Septins then assemble a

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highly ordered hourglass at the division site, which is remodelled into a double ring at the onset of cytokinesis (Ong et al., 2014).

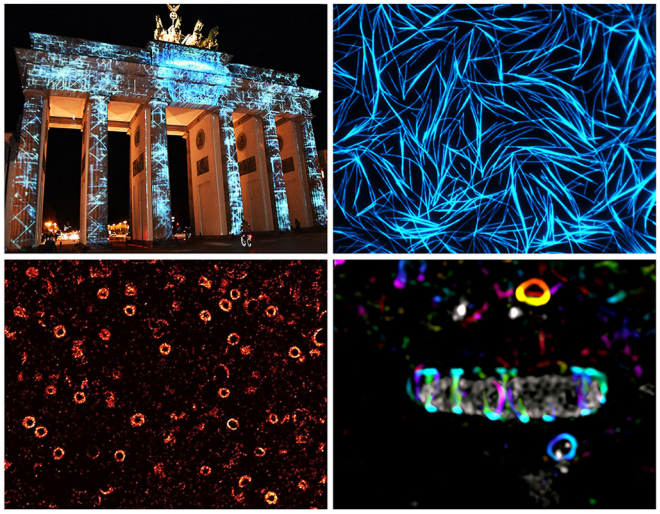
How septin filaments are organized at the bud neck is an ongoing debate. Through quantitative live imaging and platinum replica electron microscopy experiments, Erfei Bi (University of Pennsylvania, Philadelphia, USA) showed that the septin-associated kinases Elm1 and Gin4 control the hourglass assembly in a spatiotemporally manner, whereas a distinct set of proteins, including the anillin-related protein Bud4, are essential for the hourglass-to-double-ring transition. Yves Barral (ETH Zürich, Switzerland) introduced the role of septins in dictating the formation of a diffusion barrier in the membranes of the endoplasmic reticulum of asymmetrically dividing cells such as budding yeast, *Caenorhabditis elegans* embryos (Lee et al., 2016) and mouse neural stem cells (Moore et al., 2015). Septin-dependent diffusion barriers are involved in asymmetric cell division and retention of ageing factors in the mother cell. Barral presented his ongoing work testing a biophysical model of diffusion-barrier formation by a sphingolipid-rich domain (Clay et al., 2014) to understand how the cell regulates diffusion-barrier strength.

Cytokinesis

Septin 'cdc' mutants were originally identified as cytokinesis mutants in budding yeast (Hartwell, 1971). Their roles in cytokinesis are not limited to yeast division but appear to be conserved in mammals. Ulrike Eggert (King's College London, UK) presented the identification of Cdc42EP1, an effector protein of the GTPase Cdc42, as a protein involved in cytokinesis. She found that Cdc42EP1 was enriched at the ingressing furrow in dividing cells and interacted with SEPT9, but not SEPT2, SEPT6 or SEPT7. In the absence of Cdc42EP1, aberrant SEPT9 localization was observed during cytokinesis. Much remains to be learned about the temporal and spatial assembly and disassembly of proteins that occurs at the midbody or bud site leading up cytokinesis.

William Trimble (University of Toronto, Canada) described in his keynote lecture a hierarchical relationship between anillin, CD2AP, SEPT9 and Cin85 at the midbody during cytokinesis. He also showed that SEPT9 plays a critical role in the fission of mitochondria by mediating the activation of myosin motors, and presented studies examining the role of septins as diffusion barriers. Simonetta Piatti (CRBM-CNRS, Montpellier, France) showed that the septin collar in budding yeast must be displaced from the division site to allow for constriction of the actomyosin ring. Displacement of septins from the division site depends on the mitotic exit network (MEN) and is negatively regulated by ubiquitylation of a yeast centrosome component that recruits and activates MEN factors. Beyond their regulation by ubiquitylation, septins were the first proteins reported to be directly SUMOylated in yeast. In yeast, septin SUMOylation contributes to septin ring disassembly following cytokinesis, but whether SUMOylation regulates septin function in other eukaryotes was unknown. Arnaud Echard (Institut Pasteur, Paris, France) reported that his group, in collaboration with Pascale Cossart (Paris, France), found that several septins are SUMOylated in human cells and that expression of non-SUMOylable mutants of septins leads to aberrant septin bundle formation and defects in cytokinesis after furrow ingression (Ribet et al., 2017).

To study the role of septins in cytokinesis in an *in vivo* model, Manoj Menon (Medical School Hannover, Germany) presented the pan-septin depletion mouse models generated by conditional *Sept7* gene targeting, which also leads to depletion of other septins. Induced deletion of *Sept7* in primary fibroblasts leads to cytokinesis defects, but interestingly, SEPT7 was dispensable in the proliferation and maturation of B- and T-lymphocytes *in vivo*, and in the proliferation of splenocytes and myeloid progenitors *in vitro* (Menon et al., 2014), suggesting that septins have a tissue-specific role in cytokinesis.



Shining light on septins. Top left, the Brandenburg Gate, an 18th century neoclassical monument, appears to be lit with septin like filamentous structures during the festival of lights in Berlin, where the EMBO Molecular and Cellular Biology of Septins workshop was held (Courtesy: Smita Yadav). Top right, reconstituted septin filaments. Purified recombinant budding yeast septins diluted in 50 mM KCl solution were incubated on polyethylene glycol-coated coverslips to promote filament formation, and then imaged using total internal reflection fluorescence (TIRF) microscopy. (Courtesy: Gladfelter Lab, UNC Chapel Hill, USA). Bottom left, single-molecule localization microscopy reconstruction micrograph of SEPT2–GFP stained with nanobodies coupled to Alexa Fluor 647. Shown are latrunculin-treated cells. (Courtesy: Ewers Lab, Freie Universität, Berlin, Germany). Bottom right, Shigella in a septin cage. A structural illumination microscope (SIM) image showing a septin cage-like structure around the bacterial pathogen *Shigella flexneri*. HeLa cells were infected with *S. flexneri* tagged with mCherry for 3 h 40 min, immunostained for endogenous SEPT7 and imaged with an Elyra S1 microscope. Individual z-planes are temporal-color coded to create a 3D effect (Courtesy: Mostowy Lab, Imperial College, London, UK).

Septins in infectious diseases

One of the most exciting emerging functions of septins is their role in infectious diseases. Septins assemble into cage-like structures to entrap cytosolic bacteria and target them for autophagy, an intracellular degradation process (Mostowy and Cossart, 2012). Serge Mostowy (Imperial College, London, UK) presented new work describing the anti-bacterial activity of septin caging and discovered a fundamental link between mitochondria and the assembly of septin cages around *Shigella*, an important bacterial pathogen (Sirianni et al., 2016). To investigate the role of septins in host defence against bacterial infection *in vivo*, Mostowy utilized zebrafish (*Danio rerio*) as a model system. His group showed that septins restrict inflammation and protect zebrafish from *Shigella* infection, suggesting that septin dysfunction might be an underlying factor in cases of hyper-inflammation (Mazon-Moya et al., 2017).

Michael Way (The Francis Crick Institute, London, UK) presented the involvement of septins in the suppression of vaccinia virus spread. During viral egress, septins are recruited to cell-associated enveloped virus before clathrin and are then lost when the actin tail forms at the plasma membrane. In this way, the involvement of septins in pathogen infection has now been extended

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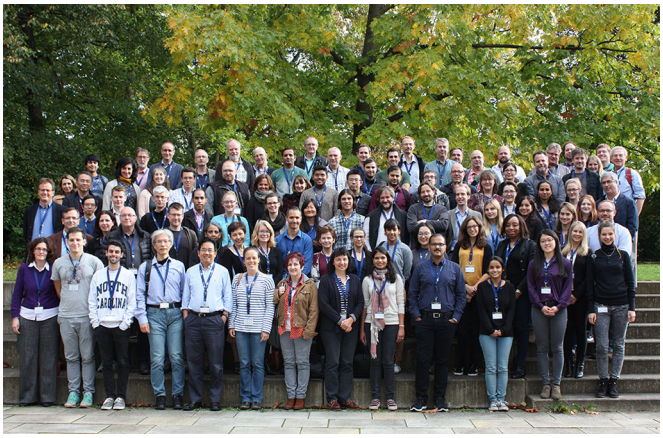

Participants from across the world at the 2017 EMBO Molecular and Cellular Biology of Septins workshop gathered at the Harnack-Haus of the Max Planck Society in Berlin.

to viruses. Nicholas Talbot (University of Exeter, Exeter, UK) introduced the role of septins in *Magnaporthe oryzae*, the rice blast fungus that is responsible for one of the most devastating and economically significant diseases of cultivated rice. During plant infection, the blast fungus forms a specialized infection structure called an appressorium. This process generates enormous turgor, focusing mechanical force to breach the rice cuticle, thus enabling entry of the fungus into plant tissue. Repolarization of the appressorium requires a 5.9 µm hetero-oligomeric septin ring that organizes a toroidal F-actin network at the base of the appressorium (Dagdas et al., 2012). Septins also play a key role in enabling the fungus to move between rice cells through plasmodesmata, which is mediated by septin-dependent hyphal constrictions.

Carsten Schwan (University of Freiburg, Freiburg, Germany) showed that the actin-ADP ribosylating toxin *Clostridium difficile* transferase affects the cortical actin cytoskeleton, which results in the formation of microtubule-based cell protrusions. Septins predetermine sites of protrusions and form collar-like structures at the base of protrusions. These accumulations function as a guide for incoming polymerizing microtubules through interaction with microtubule end-binding protein EB1 (Nölke et al., 2016). Whether septin function can be pharmacologically targeted to promote the cellular defence against pathogens is an exciting avenue for future research.

Septins in neuronal structure and function

Septins are involved in almost every step of neuronal development. Septins modulate dendritic branching and morphogenesis (Xie et al., 2007), spine formation (Tada et al., 2007) and diffusion of membrane-bound proteins into the spine (Ewers et al., 2014) as well as the excitability of neurons (Deb et al., 2016). Several interesting new results were presented at the workshop that broaden our understanding of how septins regulate neuronal structure and function. First, septins regulate neuronal activity by modulating the influx of Ca^{2+}. Gaiti Hasan (NCBS, Bengaluru, India) presented unpublished data showing that septins of the SEPT2 subgroup act as positive regulators of the Orai channel in *Drosophila melanogaster* neurons, expanding the previously reported role of SEPT7 as a negative regulator of Orai channels (Deb et al., 2016).

Second, septins mediate neuronal polarity. Septins are known to associate with microtubules (Spiliotis, 2010), but it is unknown whether they affect or modulate the motility of microtubule motors and their cargo. Elias Spiliotis (Drexel University, Philadelphia, USA) reported that microtubule-associated septins differentially regulate the motility of specific motors and their cargo. In addition, he presented unpublished data indicating that this role of septins is crucial for the axon-dendritic distribution of neuronal membrane proteins. In a poster presentation by Julian Falk from the Castellani laboratory (Institut NeuroMyoGène, Lyon, France), SEPT7 was shown to mark the site of process extension in bipolar neural crest progenitor cells, and this polarity information is inherited by the daughter bipolar dorsal root ganglia (DRG) neurons on differentiation. Disrupting septin function led to failure of correct polarity in DRG neurons (Boubakar et al., 2017). Septins therefore contribute to neuronal polarity through two independent mechanisms: differential trafficking of neuronal membrane proteins by affecting motility of motor proteins and through the inheritance of neuronal polarity from the parent cell after mitotic rounding.

Third, septin proteins act as scaffolds in the postsynaptic as well as perisynaptic glial membrane to recruit molecules that are crucial for their tripartite synaptic structure and function. Smita Yadav (University of California, San Francisco, San Francisco, USA) showed that phosphorylation of SEPT7 by TAOK2 kinase led to translocation of SEPT7 to the spine head and its interaction with the synaptic scaffold protein PSD95. In the absence of this phosphorylation at the septin C-terminus tail, synapses were mislocalized to the dendritic shaft (Yadav et al., 2017). Septin hetero-oligomers bind the Cdc42 effector molecule CDC42EP4 that is exclusively expressed in Bergmann glia that enwraps dendritic spines of Purkinje neurons. Unpublished data from Makoto Kinoshita (University of Nagoya, Nagoya, Japan) showed that configuration of the tripartite synapses comprising the parallel fibre boutons, dendritic spines of Purkinje cells and Bergmann glial processes is disrupted in *Cdc42ep4*$^{-/-}$ mice, indicating a requirement of the septin scaffolding function in maintaining the tripartite synapse.

Finally, septin filaments are an important component of myelin, the multilayered ensheathment of neuronal axons produced by oligodendrocytes that enables rapid nerve conduction (Buser et al., 2009). Hauke Werner (Max Planck Society, Göttingen, Germany) presented data showing that septins associated with myelin are regulated by phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] levels and assemble longitudinally along myelinated axons in the non-compacted adaxonal myelin compartment in a 1:1:2:2 ratio (SEPT2:SEPT4:SEPT7:SEPT8). Genetic disruption of these filaments in *Sept8*$^{-/-}$ mice causes myelin outfoldings, a frequent pathological finding in myelin-related disorders and normal ageing (Patzig et al., 2016).

Septins in cancer and stem cells

Various mechanisms for how septins contribute to cancer progression have been proposed, including their role in cell division, clustering of receptors at the plasma membrane, promoting apoptosis, and interaction with other cytoskeletal components to promote metastasis (Poüs et al., 2016). Another possible role for septins in cancer was presented by Olga Vagin (University of California, Los Angeles, USA), who showed that septins stabilize integral and membrane-associated proteins by attenuating their ubiquitylation-mediated degradation. In this case, septins were found to contribute to abnormal membrane persistence of the important pro-oncogenic receptor tyrosine kinase ErbB2/HER2 in cancer cells. Further understanding of how septins affect ErbB2 signalling might provide a potential target for aggressive malignancies.

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An oncogenic role for SEPT9 has long been proposed due to copy number gain at the *SEPT9* locus in tumours that results in gene upregulation. However, how increased SEPT9 expression alters biological functions in cancer cells remains elusive. New data presented by Cristina Montagna (Albert Einstein College of Medicine, New York, USA) suggests that SEPT9 overexpression activates secretory pathways, which leads to extracellular matrix remodelling during tumour invasion by matrix-metalloproteinase-mediated degradation. Septin-interacting proteins are also implicated in cancer progression and metastasis. Fernando Calvo (Institute of Cancer Research, London, UK) showed that the septin-interacting protein Cdc42EP5 is consistently required for melanoma cells to migrate, invade and metastasize. The presence of Cdc42EP5 favours the generation of SEPT9-enriched septin filaments, which in turn enhance the contractile properties of the cytoskeleton and thereby promote invasion and metastasis.

Katharina Senger from the Geiger laboratory (Universität Ulm, Germany) is investigating the functional role of SEPT7 in long-term repopulating hematopoietic stem cells (LT-HSCs). She presented unpublished data showing that SEPT7 displayed a polar distribution in young LT-HSCs. This was regulated by Cdc42 activity, and expression of *Sept7* mRNA was decreased in aged LT-HSCs. A direct interaction was found between SEPT7 and Cdc42EP4, as well as between Cdc42 and Cdc42EP4 in LT-HSCs. These interactions were dependent on Cdc42 activity. Ernst-Martin Füchtbauer (Aarhus University, Denmark) reported on a collaborative study with Kent Soe (Vejle, Denmark) about the role of septins in bone homeostasis. They have found that reducing septin function in human osteoclasts through treatment with forchlorfenuron or by genetic deletion of SEPT9 in murine hematopoietic stem cells reduces bone resorbtion *in vitro* and results in increased bone density *in vivo*.

Role of septins in membrane trafficking and tissue integrity

Septins are unique cytoskeletal proteins in that they can interact with other cytoskeletal components but also directly bind and remodel membranes. These properties allow them to regulate several aspects of membrane trafficking. Roberto Weigert (National Institutes of Health, Bethesda, USA) examines mechanisms regulating membrane remodelling in live rodents by using a novel imaging approach called intravital subcellular microscopy (iSMIC). Weigert's group has recently shown that, in exocrine glands, an actomyosin complex is recruited on the membranes of large secretory granules in order to control their exocytosis (Milberg et al., 2017). At the meeting, Weigert presented exciting new data showing that SEPT2, SEPT6 and SEPT7 are also recruited on the secretory granules and form a lattice-like cage that is required to control the assembly of the actomyosin complex. Michael Krauss (Leibniz-Institut, Berlin, Germany) identified SEPT1 as a Golgi-resident protein that is recruited to the Golgi membrane by coiled coil proteins called golgins. Loss of SEPT1 triggers a massive vacuolization of the Golgi, and impairs both anterograde and retrograde membrane trafficking. Based on a proteomic screen, Krauss found that SEPT1 is associated with a number of proteins involved in microtubule nucleation. His group found that depletion of SEPT1 inhibits the nucleation of Golgi-derived microtubules and that SEPT1 might assist in coordinating dynein activity at the cis-Golgi membrane.

Septins are also involved at the early stages of macroautophagy. In addition to their roles in cytokinesis, Gaurav Barve from the Manjithaya laboratory (JNCASR, Bengaluru, India) presented data uncovering a role for the yeast septins Cdc10, Cdc11 and Shs1 in autophagy and autophagosome biogenesis. During autophagy-inducing conditions such as starvation, Barve showed that septins relocate from the bud-neck ring to the cytoplasm as punctate structures, forming intriguing non-canonical rings that colocalized with autophagosomes.

Septins also localize to the cilium and contribute to its biogenesis (Palander et al., 2017). Cilia are important for a variety of cellular and physiological processes, such as kidney function and development of left–right symmetry. Sanna Lehtonen (University of Helsinki, Finland) presented data showing that suppression of *sept7b*, the zebrafish orthologue of human *SEPT7*, induced disruption of the glomerular filtration barrier and reduced fluid flow in the *sept7b* morphants. The length of the pronephric cilia was reduced and cilia were misoriented in *sept7b*-knockdown larvae, apparently due to misorientation of the basal bodies. Lehtonen also observed that depletion of *sept7b* leads to hydrocephalus and laterality defects, which are typical features of ciliary dysfunction.

Manos Mavrakis (Institut Fresnel, Marseille, France) reported on the role of septins in actin-driven cell shape changes *in vivo* by using the gastrulating *Drosophila* embryo as a model system for studying epithelial tissue morphogenesis. Mavrakis explored the function of septins in two actomyosin-driven morphogenetic events: mesoderm invagination powered by apically constricting cells on the ventral side and convergent extension on the ventrolateral side of the embryo driven by cell junction remodelling. Live imaging of septin mutant embryos revealed that septins play a major role in the remodelling epithelium. Mavrakis hypothesized that the actin cross-linking activity of septins (Mavrakis et al., 2014) contributes to cortical stiffness, which resists cell shape deformation during morphogenetic movements ensuring tissue integrity.

While the data presented in these talks together provide evidence for a important role of septins in regulating membrane trafficking, it seems that septins are in turn dependent on membrane trafficking events. Local translation of septin mRNAs on shuttling endosomes is a new mechanism for orchestrating septin assembly and transport in time and space (Baumann et al., 2014). Michael Feldbrügge (Universität Düsseldorf, Germany) presented work performed in the corn smut *Ustilago maydis* showing that local translation of all septin mRNAs is needed for the subcellular localization of septins on the surface of endosomes. Endosomal septin transport along microtubules mediated by molecular motors is needed to form higher-order septin filaments at the growth pole (Zander et al., 2016). Whether endosomal transport of septins is conserved in higher organisms remains to be investigated.

Future perspectives

The past 20 years have seen considerable progress in understanding mechanisms of septin assembly, in part through structural analysis of purified septin proteins. With the advent of new technologies, we now are poised to probe the nanoscale structure of septins *in vivo* in a spatiotemporally defined fashion. Localization and dynamics of septin assembly can be observed with unprecedented structural detail by using tools such as super-resolution microscopy, intravital subcellular imaging and platinum replica electron microscopy techniques described during the meeting. Investigating whether septins can be targeted to fight infection and understanding how dysregulation of septin function or expression leads to diseases such as neurodegeneration or cancer are important areas of future research. Harnessing our understanding of the cellular and molecular biology of septins will allow us to target them with specificity, whether it is for fighting pathogens or cancer.

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