Seeking truth on Monte Verita

Workshop on The Molecular Biology and Biochemistry of Septins and Septin Function

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The EMBO Workshop on The Molecular Biology and Biochemistry of Septins and Septin Function took place between 6 and 10 May 2007, in Monte Verita, Switzerland, and was organized by Y. Barral, S. Buvelot Frei and C. Field.

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dissection of models and planning of experiments focused on understanding the intriguing family of proteins called septins.

After the original identification of septins in *Saccharomyces cerevisiae* by L. Hartwell 40 years ago, they have been discovered throughout metazoans and mammals, although they are absent in plants (Hartwell, 1971; Longtine *et al*, 1996). J. Pringle (Stanford, CA, USA), the founding father of septin biology, coined the name 'septins' based on their function in cytokinesis and localization to the mother–bud neck. Experiments in various systems have shown that septins have many cellular functions such as acting as membrane barriers, directing exocytosis, positioning the spindle, and regulating cell cycle checkpoints and polarized growth. Aberrant septin function is increasingly associated with various neurodegenerative diseases and cancers, emphasizing the roles of septins in diverse cellular processes. Here, we attempt to capture the highlights presented at the meeting and raise the important open questions facing the field.

Septin structure and filament organization

Ever since Breck Byers first observed septin-dependent rings made of 10nm filaments encircling the mother–bud neck using electron microscopy, it was speculated that septins might be filament-forming proteins (Byers & Goetsch, 1976). In the intervening 30 years, fascinating discoveries accumulated about septin organization and function in many species; however, in early 2007, the community still faced a bounty of structural and functional questions. What is the structure of septin monomers? How do different septin proteins associate into filaments? What are the rules for assembling septin filaments? How do filaments assemble into higher order structures in cells? What is the role of GTP-binding and hydrolysis in filament formation and function? Do filaments have polarity? What are the dynamics of assembly and disassembly? Is there a role for non-filament-associated septins in signalling? Our understanding of septin function hinges on knowing the answers to many of these questions, and the work presented at this meeting indicates that swift progress is being made towards understanding the function and organization of septins.

In an historic moment on the first night of the meeting, F. Wittinghofer (Dortmund, Germany) unveiled the first crystal

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Introduction

Septin biologists recently gathered on a lush hillside called Monte Verita above the sparkling waters of Lake Maggiore in Southern Switzerland for the second international meeting on septin biology. Once a utopian community of artists and exiles, this proved to be an inspirational setting for the animated exchange of ideas,

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Fig 1 | Structure of the human septin complex. (A) Superimposition of the molecular replacement solution using the SEPT2 G domain onto the selenomethionine anomalous map contoured at 5σ to assign the location of the SEPT2, SEPT6 and SEPT7 subunits in the asymmetrical unit. (B) Ribbon model of the trimeric SEPT2-SEPT6-SEPT7 complex, with SEPT7 in cyan, SEPT6 in pink and SEPT2 in blue, with nucleotides in ball and stick representation. (C) Positive $F_o - F_c$ electron density map, contoured at 3σ , around the nucleotide-binding sites of the respective septins, and the resulting nucleotide models, as indicated. Reprinted by permission from Macmillan Publishers Ltd:Nature. © 2007 Sirajuddin M, Farkasovsky M, Hauer F, Kuhlmann D, Macara IG, Weyand M, Stark H, Wittinghofer A (2007) Structural insight into filament formation by mammalian septins. *Nature* **449**: 311–315.

structure of septins, obtained by crystallographers M. Sirajuddin and M. Farkasovsky, thus beginning to answer some of the open questions (Fig 1; Sirajuddin *et al.*, 2007). R. Garratt (Sao Paulo, Brazil) detailed some of the challenges in creating high-resolution structures of septins, making the work of Wittinghofer all the more heroic. For many of us, seeing the ribbon diagrams of septins in complex was similar to finally meeting an old 'pen pal' who had

only been known through letters (or in this case experiments!). Finally, there was high-resolution form to this family of proteins and many of us had to say farewell to our favourite models of septin organization.

After much effort but limited success in determining a high-resolution structure of *S. cerevisiae* septins, the Wittinghofer team turned to a human septin complex composed of SEPT2, SEPT6 and

SEPT7 proteins (Fig 1). They purified a hexameric complex of these proteins from *Escherichia coli* and resolved it to approximately 4.5 Å. Their work shows that the complex assembles into a dimer of trimers or a hexamer composed of two copies of each septin protein. The trimers are asymmetrical with SEPT6 bound to GTP, and sandwiched between GDP-bound SEPT2 and SEPT7. SEPT6 and SEPT2 interact through their GTP-binding face, creating an interface that is likely to be crucial for GTPase activity, as many GTPases hydrolyse GTP through dimerization. SEPT6 and SEPT7 interact in what is thought to be a stable association between their amino- and carboxyl terminals, rather than through the GTP-binding region.

How do these trimers assemble into hexamers and ultimately filaments? The hexamers purified under high salt conditions form linear filaments 24 nm long and 4–5 nm wide, which look similar to beads on a string, as seen by electron microscopy (Fig 2). By using SEPT2 fused to maltose-binding protein (MBP), it was shown that SEPT2 appears in the middle of the hexamer indicating, much to the surprise of many, that the filaments are apolar, with two SEPT2 proteins facing one another in the centre of the hexamer and with SEPT7 exposed on both ends. Intriguingly, a percentage of these linear hexamers had a slight curve emanating from the SEPT2 interface, giving a 25–30° bend that might facilitate ring formation (Fig 2). Thus, these proteins that are crucial for cell polarity assemble into apolar filaments. In collaboration with Y. Barral (Zurich, Switzerland), R. Hite (Boston, MA, USA) reported a similar electron microscopy analysis of the only two septins present in *Caenorhabditis elegans*. In this case, the basic filament unit is a dimer of dimers, which again is apolar (John *et al*, 2007). Finally, J. Thorner (Berkeley, CA, USA) presented a similar supramolecular architecture of *S. cerevisiae* septin complexes and derived filaments at the ultrastructural level, also determined by electron microscopy and obtained in collaboration with E. Nogales. There was remarkable similarity in the symmetrical organization of the worm hetero-tetrameric, the human hetero-hexameric and the yeast hetero-octameric septin complexes. The order and patterns of septin subunits in the filaments from yeast to humans fit well with the thorough and useful septin phylogeny presented in a poster by M. Momany (Athens, GA, USA), in which she predicted the different groups of septin orthologues across species (Pan *et al*, 2007).

Septin form and function in model organisms

In vivo support for the apolarity of septin filaments came from polarized fluorescence microscopy data presented by C. Field (Boston, MA, USA). She and colleagues at the Mitchison laboratory used both cell division cycle (Cdc) 12 and Cdc3 fused to a rotationally constrained green fluorescent protein (GFP), to assay the orientation of septin filaments relative to the mother–bud axis in *S. cerevisiae*, and to determine if these filaments have polarity (Steels & Trimble, 2006; Vrabioiu & Mitchison, 2007). This approach indicated that there is symmetry across the mother–bud collar, which is in agreement with the apolar character of filaments determined from the structural data. These data suggest that filaments are aligned parallel to the mother–bud axis, as opposed to the circular rings proposed by Byers & Goetsch (1976), who first visualized septin filaments in the yeast bud neck. The organization of septin rings in the filamentous fungus *Ashbya gossypii*, shown by B. DeMay and A. Gladfelter (Hanover, NH, USA), brings further complexity to the filament orientation scenario. The cells of this fungus, in which septin proteins are 60–80% identical to budding

yeast, form septin rings that appear as thick bars in high-resolution fluorescence images. The orientation of these bars suggests that individual septin filaments might be bundled together and aligned along the polar growth axis, similar to the arrangement proposed in *S. cerevisiae* by Field. Future analysis by electron microscopy of the *A. gossypii* septin rings, as well as septin rings in mutant *S. cerevisiae* cells, will potentially resolve this long-standing controversy about the orientation of septin filaments relative to the growth axis in fungi.

Septin dynamics and post-translational modifications

In budding yeast, new septin rings are assembled at the initiation of each cell cycle as the septin ring from the previous division is dismantled. M. McMurray (Berkeley, CA, USA) studied whether septin proteins are destroyed or recycled during this disassembly–reassembly cycle. By using a clever method of fluorescently labelling septins *in vivo*, McMurray performed a fluorescence pulse-chase experiment and showed that septins are indeed recycled instead of degraded. He proposed that specific modifications must mediate disassembly and reassembly, and that these modifications must be ‘reset’ each cell cycle.

A. Gonzalez-Novo (Salamanca, Spain) studied septin rings in *Candida albicans* hyphal cells and reported an intriguing observation about septin dynamics. By using fluorescence recovery after photobleaching (FRAP) to bleach septin-GFP proteins, he observed that not all septin subunits have the same dynamics even within the same ring, and that the variable dynamics are crucial for normal septa and hyphal architecture. Thus, in *C. albicans* hyphae, specific regulation of individual septin subunit dynamics influences what factors are recruited to septa and, ultimately, the maintenance of hyphal shape.

The amount of data on the role of septin post-translational modifications—such as phosphorylation and SUMOylation—is rapidly growing and this was echoed at the meeting. To address how septins coordinate growth and the cell cycle in budding yeast, D. Kellog (Santa Cruz, CA, USA) presented his analysis of Sep7 (Shs1) phosphorylation by a CDK–G1-cyclin complex, Pho85–Pcl1–Pcl2. He mapped the sites on Shs1 that are most likely to be phosphorylated by the Pho85 complex and generated septin mutants that lack these sites. He showed interesting functional consequences of these mutations, including a loss of interaction with the kinase Gin4. Thus, phosphorylation of at least one septin subunit by a CDK complex is necessary although not sufficient to recruit specific proteins to the yeast mother–bud neck.

Asymmetry and the septins

A series of talks from several model organisms presented data expanding the role of septins in establishing and maintaining cell asymmetry. F. Finger (Troy, NY, USA) showed that cultured motor neurons from *C. elegans* require septins to form one primary and asymmetrical process. Septin-deficient cells had many short processes all over their surfaces instead of polarizing along a single axis. In addition, septin-dependent asymmetry in the ingression of the cleavage furrow in early *C. elegans* embryonic divisions was shown by K. Oegema (San Diego, CA, USA; Maddox *et al*, 2007). In cells lacking septins or the septin-interacting protein anillin, the cleavage furrow ingresses symmetrically, leading to an increase in failed cytokineses that might have an impact on overall tissue architecture.

Fig 2 | Electron microscopy of the human septin complex. (A) Class averages after alignment of the human septin complex SEPT2–SEPT6–SEPT7 using only the lower trimeric part as a reference to align the raw images. The upper trimeric part adopts different orientations, indicating the high level of flexibility of the hexamer. Bending is observed in the 25–30° range around a hinge formed by the central SEPT2 dimer. Reprinted by permission from Macmillan Publishers Ltd: Nature. © 2007 Sirajuddin M, Farkasovsky M, Hauer F, Kuhlmann D, Macara IG, Weyand M, Stark H, Wittinghofer A (2007) Structural insight into filament formation by mammalian septins. *Nature* **449**: 311–315. (B) Septins acting as a cortical diffusion barrier at cytokinesis in budding yeast. Localization of a Spa2-GFP and the septin CFP-Cdc3 in budding yeast. Spa2 (green) and Sec3 (red) localization to the bud cortex during cytokinesis. From Dobbelaere J, Barral Y (2004) Spatial coordination of cytokinetic events by compartmentalization of the cell cortex. *Science* **305**: 393–396. Reprinted with permission from AAAS. (C) Localization of SEPT7 in neurons. Cultured hippocampal neurons (DIV7) immunostained for endogenous SEPT7 (red), F-actin (phalloidin staining, green) and PSD-95 (blue). Low magnification image (left panel) shows whole neuron, and higher magnification image (right panel) shows dendrite segments. Arrowheads indicate examples of SEPT7 at the base of actin-rich dendritic spines. Scale bars, 10 μm. Photographs courtesy of T. Tada (Cambridge, MA, USA). CFP, cyan fluorescent protein; GFP, green fluorescent protein.

Asymmetry exists between mother and daughter budding yeast cells on many levels. One manifestation of this is that daughter cells are always born ‘young’ with a full replicative potential, whereas

mother cells age. Work presented by Z. Shcheprova (Zurich, Switzerland)—from the Barral laboratory—examined the role of septins in maintaining young buds and ageing mothers. By using

FRAP experiments, she expanded on the observation that inner-membrane systems such as the endoplasmic reticulum contain a septin-based diffusion barrier between the mother and bud so that larger complexes such as the translocon cannot diffuse freely through the bud neck. She predicted that these barriers limit the migration of pre-synthesized material from the mother into the bud and hence favour the insertion of newly synthesized material specifically in the bud. She showed that this septin-based filtering of old and new is a mechanism for 'rejuvenating' or ensuring the youthfulness of a bud on birth. Thus, the septins function in yeast ageing by ensuring that mothers do not share their age with their buds.

Two talks and several posters described proteins that localize asymmetrically to the mother–bud neck in yeast cells. The septin collar recruits a multitude of proteins many of which specifically interact with either the mother or the daughter side of the collar. These observations have led to a model in which some intrinsic polarity in the septin filaments make up the scaffold at the neck. Although the structural and polarized microscopy data (see above) make this idea unlikely, the mechanism by which proteins discern between sides of the septin collar in yeast is still unknown. K. Tatchell (Shreveport, LA, USA) and D. Lew (Durham, NC, USA) characterized proteins that can 'read' the asymmetry present at the yeast septin collar. Bni4, a targeting subunit for the type I phosphatase Glc7, localizes to the 'inside' of unbudded septin rings and then to the mother side of the collar. No mutants have been found that perturb the asymmetrical localization Bni4; however, J. Larson—from the Tatchell laboratory—discovered that glucose starvation leads to symmetrical distribution of Bni4. Lew and A. Trott—from the Thorner laboratory—both discussed work on the kinase Hsl1, which localizes to unbudded cell rings but is found only on the bud side of the septin collar after bud emergence. Hsl1 is inactive on the unbudded ring and its activation coincides with the transition in the septin collar, suggesting that it might somehow sense and react to different septin organizations. Lew speculated that the change in septin organization leads to a conformational change in the Hsl1 protein that relieves some kind of autoinhibition. His group has mapped possible regulatory domains that would allow this kinase to be sensitive to changes in septin organization.

Septins and cytokinesis

The founding father of septin biology, John Pringle and one of his academic progeny, E. Bi (Philadelphia, PA, USA) presented surprising results and provocative hypotheses for the role of septins in cytokinesis. Bi showed that the tail domain of Myo1, the contractile ring type II myosin in *S. cerevisiae*, can supply many functions for cytokinesis without the head domain being present. The data support a model in which the 'motor' protein predominantly functions to tether the secretion machinery to the division site, rather than to generate an actin-based contractile force. Pringle presented an analysis of genetic interactions, septum morphology and contractile-ring dynamics to determine the functions of Hof1, Cyk3 (mutations in both of which are synthetically lethal if in combination with *myo1* mutations) in cytokinesis. The results suggest that either the localized deposition of chitin physically drives cleavage-furrow ingression or that the Hof1 and Cyk3 proteins are part of a conserved group of proteins that are recruited to the furrow by the septins and then link membrane remodelling and invagination to furrow ingression. Both talks inspired many possible future directions in the analysis of cytokinesis.

Septins in learning and neurodegenerative disease

A unique element of this meeting was the mingling of data, ideas and researchers working in model systems, mammalian cell culture and animal systems. As a result, unexpected parallels could be drawn between diverse cell types and hundreds of thousands of years of evolution.

The complexity of septin biology increases with the complexity of the organism. Fourteen septin genes—many with multiple isoforms—have been identified so far in mammalian cells. Strikingly, most of the mammalian septins are expressed in differentiated non-dividing cells of the brain, clearly indicating that, at least in neurons, septins have crucial cellular roles outside cytokinesis. For example, SEPT3 and SEPT5 are neuronal septins associated with the presynaptic membrane, and SEPT4 is associated with both neuronal and glial processes.

M. Kinoshita (Kyoto, Japan)—who opened the meeting with an engaging history of septin biology—is leading the efforts to characterize septin function in normal neuronal cells and in neurodegenerative disorders such as Parkinson disease. In Parkinson disease, α -synuclein aggregates in Lewis bodies that are characteristic of neurodegenerative synucleinopathies. Kinoshita showed that α -synuclein associates physiologically with Sept4 (Ihara *et al*, 2007). In mice lacking *Sept4*, the dopaminergic neurotransmission is impaired due to the lack of these proteins and, similarly, Sept4 is downregulated in sporadic Parkinson disease. A. Hagiwara (Kyoto, Japan) performed detailed electron microscopy analysis of mouse brain sections followed by three-dimensional reconstruction, and showed that Sept4 is expressed in Bergmann glia, where it forms C- and U-shaped clusters, each surrounding a dendritic spine neck of a Purkinje cell. Kinoshita suggested that clusters of septins might generate a scaffold and therefore form supporting structures, or that septins might constitute diffusion barriers to control the entry and exit of molecules from the dendrite—similar to that observed in yeast.

Kinoshita's model was supported by M. Kiebler (Vienna, Austria; Xie *et al*, 2007) and T. Tada (Cambridge, MA, USA; Tada *et al*, 2007), who discussed the role of septins as possible diffusion barriers in neuronal cells. In a talk that linked septins to the function of dendritic spines and learning, Kiebler showed that *Sept7* mRNA is transported along microtubules to dendrites and that the protein product is localized to the base of dendrites where it forms a collar that co-localizes with the postsynaptic marker PSD-95. Downregulation of *Sept7* by short interfering RNA (siRNA) resulted in reduced dendritic complexity such that cells had fewer spines and those present were short and had a reduced diameter. Complementing Kiebler's data, Tada showed images of enhanced GFP (EGFP)-Sept7 expression in the growth cones of incipient neurons and at the base of dendritic spines (Fig 2). She quantified Sept7 localization and showed that spines with septins at the base are bigger, have wider base diameters and are more stable. Neurons overexpressing Sept7 have increased dendrite branching and density of dendritic protrusions, whereas depletion of Sept7 leads to diminished formation and restricted enlargement of spines in response to stimuli that induce modifications similar to long-term potentiation (LTP). Dendritic spines are unique in their ability to generate synaptic inputs and thus are integral to learning and memory. The data from these two groups working on opposite sides of the Atlantic Ocean support a model in which Sept7 forms a diffusion barrier at the base of spines—similar to the barrier role septins have in yeast (Fig 2B; Dobbelaere & Barral, 2004)—which might help to

establish and maintain dendritic spines. This model places septins in a central role in neuronal network architecture and function.

K. Nagata (Aichi, Japan) studied the localization and distribution of five septin members—Sept6, Sept7, Sept8, Sept9 and Sept11—in the brain. Interestingly, Sept8 is distributed in the Golgi, soma, axon and dendrites in the immature neuron, while localizing at the synapse in mature neurons, which suggests a role of this protein in synapse formation. A two-hybrid screen designed to isolate Sept8 binding partners identified synaptobrevin as one such molecule. Synaptobrevins are small membrane proteins of the secretory vesicles that mediate exocytosis in synapses and are members of the SNARE complex. Nagata's data suggest that Sept8 might be involved in the maintenance of synapse functions—such as the release of neurotransmitters—through the interaction of synaptophysin and synaptobrevin with the SNARE complex.

Septins talking to the mammalian cytoskeleton

Several groups analysed the functional interactions of septins with both the actin and the microtubule cytoskeleton. B. Trimble (Toronto, Ontario, Canada) indicated that septins co-localize and interact directly with the heavy chain of myosin II. He proposed a model in which septins form a scaffold for the activation of myosin II by myosin kinases that is crucial for stress-fibre stability and for normal ingression of the cleavage furrow. Further links between septins and actomyosin function came from a lively talk by M. Krummel (San Francisco, CA, USA). While screening for polarity factors required for the formation of the immunological synapse, which is the contact between a T cell and an antigen-presenting cell, he 'fished' out a septin protein. Sept7 is enriched at the cortex in the middle zone of a migrating T cell, and depletion of Sept7 in T cells leads to marked effects on cell and uropod morphology, and subtle effects on migration. He proposed a model whereby septins act as 'corsets' to stabilize the midzone of polarized migrating cells. The septin cortical scaffold would thus stabilize the central part of the cell against the forces led by myosin II that direct contraction and extension during cell 'crawling'.

In a talk linking septins to signalling proteins that regulate actin, B. Kremer (Charlottesville, VA, USA) showed that depletion of the SEPT2–SEPT6–SEPT7 complex in HeLa cells leads to loss of polarity and abnormal morphology. He found that these phenotypes are connected by the NCK adaptor protein, which might act as an important functional link between actin and septins (Kremer *et al*, 2007). NCK, which regulates actin through several proteins—including p21-activated kinase (PAK)—accumulates in the nucleus of cells with depleted septins and also, intriguingly, in cells responding to DNA damage. These data suggest that septins might contribute to the regulation of the subcellular localization of NCK thereby influencing the regulation of both the actin cytoskeleton and DNA-damage-induced cell cycle checkpoint arrest.

E. Spiliotis (Nelson laboratory; Stanford, CA, USA) proposed that Sept2 has a role in polarized vesicle transport in epithelial cells, thus connecting septins to microtubules and cell polarity. In Madin–Darby canine kidney (MDCK) cells, Sept2 is found in filament structures emanating from the trans-Golgi network, it co-purifies with a subset of Golgi-derived vesicles and co-localizes with a subset of microtubules. Depletion of Sept2 leads to slower kinetics of vesicular transport to the plasma membrane and it had been described that septins could influence microtubule dynamics by sequestering mitogen-activated protein 4 (MAP4), a microtubule-stabilizing protein (Kremer

et al, 2005). A new twist proposed by Spiliotis is that Sept2 has higher affinity for and binds to polyglutamylated microtubules, which are 'faster' tracks for the motors that deliver vesicles to the cell surface. He suggested that septins might act to ensure that there is an adequate population of polyglutamylated microtubules that are free of MAP4 in order to promote and maintain efficient polarized secretion.

Septin dysfunction in human diseases

Septins have been reported to be misregulated in various human diseases. The groups of H. Russell and P. Hall (Belfast, Ireland) have been actively working on deciphering the consequences of altered SEPT9 expression in cells, and the role that septin over-expression might have in tumorigenesis and other diseases. The possibility that septins might have oncogenic function or at least are especially sensitive to the alterations in cell physiology that are seen in cancer is supported by the observation that SEPT9 is overexpressed in various types of tumour and by C. Montagna's (Bronx, NY, USA) findings that Sept9 undergoes genomic amplification in the form of double minute chromosomes in mice. In addition, SEPT2, SEPT6 and SEPT9 have been reported as fusion partners of mixed lineage leukaemia in patients. As Hall pointed out during his presentation, understanding the role of septins in human diseases has an additional layer of complexity owing to the high number of isoform variants of the septin genes. SEPT9 is overexpressed in breast and ovarian carcinomas, leading to misregulation of the six isoforms examined by the Russell and Hall groups. Deciphering the mechanism underlying this aberrant regulation is crucial to understanding the role of septins in cancer. Russell presented a series of experiments suggesting that different levels of SEPT9 between normal and tumour cells arise from different internal ribosome entry site (IRES) elements in the 5' untranslated region. Naturally occurring mutations alter the IRES to favour translation under hypoxia. Another mechanism that could alter the expression of SEPT9 isoform variants in cancer cells is epigenetic regulation through the methylation of CpG islands at alternative promoters (Burrows *et al*, 2003). Data by Montagna, as well as a poster by Lesche, on DNA methylation analysis of tumour and matched normal patient samples provided further support for this idea in a clinical context. The mechanisms that control septin expression in normal and cancer cells are extremely complex and are likely to involve intertwined regulation at genomic, epigenetic and translational levels. The cell might control not only the amount of septin protein available but also the specific balance of the different isoforms needed to perform a given function. Deviation from this complex assortment clearly manifests itself in many diseases.

Conclusion

The variety of organisms, disciplines and biological problems presented at this meeting are a testimony of the exciting future that lies ahead for septin biology. With this diverse array of approaches, the questions that emerge are not likely to remain unresolved for long. How does the cell regulate filament assembly and use these symmetrical filaments for cell polarity? What is the physiological role of GTP binding and GTP hydrolysis for filament assembly and disassembly? What are the direct binding partners of septins? Why do mammalian cells generate such a variety of septin splice variants? What are the conserved and new functions of septins in mammalian cells? These are a few of the questions that no doubt will be answered at the third meeting of septin biologists in a few years.

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