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Timm Maier trained as a biochemist at University of Tübingen, Germany. He completed his doctorate in structural biology with Wolfram Saenger at Freie Universität Berlin in 2003. He then moved as a Postdoc to the lab of Nenad Ban at ETH Zurich, where he was promoted to a team leader and lecturer position in 2006. He started his lab at Biozentrum in Basel in 2011 as tenure track assistant professor and is associate professor at Biozentrum since 2016. He and his team are best known for their work on giant multienzymes in primary and secondary metabolism, in particular fatty acid and polyketide synthases, as well as on metabolic regulation and mTOR complexes.

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Kira J Weissman holds a BS from Stanford University, California, and MPhil and PhD degrees from the University of Cambridge, UK, where she was a Churchill Scholar and an HHMI pre-doctoral fellow. Following receipt of several post-doctoral awards including a Royal Society Dorothy Hodgkin Fellowship and an Alexander von Humboldt Research Fellowship, she took up her current position as Professor of Enzymology at Lorraine University, Nancy, France in 2010. Research in Kira's group focuses on the mechanistic enzymology and structural biology of modular mega-enzyme systems, with work on protein-protein interactions gaining particular recognition.

## **Editorial overview: Macromolecular assemblies: Assembly, dynamics and control of activity**

Macromolecular assemblies of extraordinary size and complexity coordinate and execute many fundamental tasks in cells, including protein biosynthesis and chromosome segregation. In bacteria, gigantic multienzyme complexes are additionally employed to mediate intercellular communication and warfare. Understanding in detail how such complexes are assembled and act, and how they are regulated, critically depends on obtaining high-resolution structural information. Although X-ray crystallography has been the major source of such data, the recent resolution revolution in cryo-electron microscopy (cryo-EM) has been a major boon to these studies. Cryo-EM now allows, for example, for medium-to-high resolution structural determination of low-abundance complexes and assembly intermediates, as well as enabling the dissection of distinct functional states of macromolecular assemblies.

Nevertheless, understanding the role of large macromolecular assemblies across different length and time scales remains a critical challenge. It requires, on the one hand, the integration of structural data with detailed mechanistic and biophysical studies on intrinsic dynamic properties and, on the other hand, connecting atomic resolution structures to their cellular and multi-cellular environments. In this context, this special issue showcases eight different examples of multidisciplinary efforts to meet these challenges, as well as the role that super resolution optical microscopy is beginning to play in providing structural data at the molecular scale.

The fundamental architectures of bacterial, archaeal and eukaryotic cytosolic ribosomes have been revealed in ground-breaking studies by X-ray crystallography. However, the structures of the more divergent and less abundant ribosomes of chloroplasts and mitochondria have only recently been solved by cryo-EM. In this special issue, Bieri *et al.* compare the structures of yeast and mammalian mitoribosomes to bacterial ribosomes. The authors highlight the unusual integration of a tRNA element as a structural component of mitoribosomes and discuss the role of mitoribosome-specific proteins in mRNA interactions, as well as the specialization of the mitoribosome exit tunnel for membrane protein biosynthesis. In a companion piece, Barandun *et al.* focus on ribosomal assembly and review the structure of the small-subunit (SSU) processome, the first nucleolar precursor of the small ribosomal subunit in eukaryotes. In the SSU processome, extended peptides of flexible assembly factors form a meshwork of multivalent interactions, while rRNA domains are maintained in an accessible state for further processing. Thus, the multi-step maturation into a ribosomal small subunit requires coordinated and sequential RNA processing and large-scale conformational rearrangements.

Luo and Tong focus on the role of the separase in the opening of the cohesion ring that holds together the sister chromatids during cell division. Separase is a large cysteine protease which plays additional roles in other cellular processes. As a consequence, its activity is tightly regulated by association with the intrinsically disordered protein (IDP) securin, which acts both as a chaperone and a separase inhibitor. Recent crystal and cryo-EM structures have allowed the visualization of the separase-securin complex: extensive

interactions of securin with the different domains of separase provide the structural basis for the chaperone function of securin. The work also showed that separase inhibition by securin is mediated via a pseudo-substrate binding mode of a securin peptide. The role of IDPs in macromolecular complex assembly is further explored in the review by Fung, *et al.* Using three highly distinct examples (biomolecular condensates, the nuclear pore, and the cytoskeleton), the authors illustrate the critical role played by IDP multivalency (i.e. the possibility to simultaneously bind to multiple partners) in the formation of multiprotein assemblies.

Phosphatidylinositol-3-kinase like kinases (PIKKs) are a family of giant atypical protein kinase characterized by a conserved C-terminal kinase region and large numbers of N-terminal  $\alpha$ -helical repeats. PIKKs include the central regulator of growth, (m)TOR, as well as proteins involved in DNA repair and cell-cycle checkpoints. Imseng *et al.* review a wealth of recent structural data on PIKKs, largely obtained by cryo-EM. Although the core kinase regions of PIKKs adopt a conserved fold, PIKKs nonetheless exhibit a striking variety of assembly architectures, which are presumably linked to their specific mechanisms of activation by additional proteins and their modes of substrate recruitment.

Two reviews in this issue address macromolecular assemblies in bacteria. Nguyen *et al.* discuss current progress in deciphering the structure and firing mechanism of bacterial type VI secretion systems (T6SS) based on crystal and cryo-EM structures, as well as tomographic data. Recent structures of extended and contracted T6SS sheaths have yielded atomic-level insights into the conformational transitions underlying the power-drill mechanism of T6SS, which allows for injecting toxins directly into prey cell membranes or the cytoplasm. In their review, Reimer *et al.* provide a guide to understanding biosynthesis of nonribosomal peptides in bacteria by non-ribosomal peptide synthetases (NRPSs) – among the largest multienzymes in nature. The review examines in particular the recently-obtained crystal structures of four multi-domain NRPSs in multiple functional states, which, remarkably, model all of the sequential steps in the biosynthetic process. These data, in combination with analysis of several key didomain structures, have substantially enriched our understanding of NRPS architectures and interdomain interactions, as well as highlighting the dramatic conformational changes that underlie their function.

Protein-protein interactions and adaptability also take center stage in the review by Bule *et al.*, which emphasizes the unexpected complexity of cellulosomes from anaerobic cellulolytic microorganisms, as revealed in large-part by structural biology approaches. While assembly of the cellulosome core uniformly relies on high affinity interactions between cohesion (Coh) and dockerin (Doc) proteins, the architectures of the overall complexes and the molecular basis for the specificity and affinity of association of the various components, turns out to be species-dependent and surprisingly variable.

Finally, Sieben *et al.* provide an overview of current method development in super-resolution optical microscopy towards the study of macromolecular assemblies, using the examples of nuclear pore complexes and a helical filament of the yeast TOR complex to illustrate state-of-the-art averaging techniques for 3D-reconstruction based on fluorescence microscopy. The application of hybrid approaches to study cellular structures is additionally

exemplified by studies of centriole architecture, while strategies for the analysis of amorphous structures are also discussed.

Taken together, this collection of reviews amply illustrates the diversity and complexity of macromolecular assemblies, and the utility of interdisciplinary approaches anchored in structural biology – X-ray crystallography, but increasingly complementary approaches such as cryo-EM and optical microscopy – for dissecting and understanding their function.