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THE KINETOCHORE: AN INTRINSICALLY DIVISIVE MOLECULAR MACHINE

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Chromosome bi-orientation is the pre-condition for successful cell division, but how it is achieved on the molecular level in settings as diverse as mitosis and meiosis remains poorly understood. Kinetochores play a decisive role in promoting chromosome bi-orientation and in imparting fidelity to the chromosome segregation process. In addition to binding microtubules, they recognize and correct improper microtubule attachments, and act as control centers to make the timing of cell division contingent on completion of bi-orientation through the spindle assembly checkpoint. How are these different activities regulated and integrated within the kinetochore's structure? To answer this question, our laboratory took up the long-term goal of reconstituting kinetochores and their functions in vitro, focusing on human kinetochores as model system. The reconstitution is challenging, because kinetochores consist collectively of ~35 core subunits [1], and several additional regulatory subunits, for a total of ~100 different polypeptides. The challenge is compounded by the embedding of kinetochores in the complex and incompletely understood environment of the centromere, a specialized chromatin domain whose organization promotes epigenetic propagation of the kinetochore assembly site through cell generations. As a summary of our work so far, I will present three large reconstitutions, comprising two major stable kinetochore sub-complexes (each with molecular mass ≥ 1 MDa), and the signaling ensemble of the spindle assembly checkpoint [1-3]. I will illustrate what organizational principles have emerged from this work, and how they are inspiring our current attempts to build the entire kinetochore and its functions in vitro. All three reconstitutions reflect stable interactions at thermodynamic equilibrium, and therefore cannot be considered "alive" by any means. The ultimate challenge for future in vitro work on the kinetochore, and a more general challenge for any in vitro reconstitution, is to ignite energy-dissipating reactions that subtend to regulation. We would like to build particles that, like their cellular counterparts, sense bi-orientation (or lack thereof) and turn the checkpoint on or off depending on context. This will require the addition of enzymes, most notably mitotic kinases and phosphatases, whose opposing regulation determines, at any given time, appropriate context-dependent signaling outcomes.

[1] Walstein K, Petrovic A, Pan D, Hagemeier B, Vogt D, Vetter IR & Musacchio A Assembly principles and stoichiometry of a complete human kinetochore module, Sci Adv. 2021, 7:eabg1037.
[2] Piano V, Alex A, Stege P, Maffini S, Stoppiello GA, Huis In 't Veld PJ, Vetter IR & Musacchio A (2021) CDC20 assists its catalytic incorporation in the mitotic checkpoint complex. Science 2021, 371:67-71.
[3] Singh P, Pesenti ME, Maffini S, Carmignani S, Hedtfeld M, Petrovic A, Srinivasamani A, Bange T & Musacchio A. BUB1 and CENP-U, primed by CDK1, are the main PLK1 kinetochore receptors in mitosis, Mol Cell. 2021, 81:67-87.

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