Cell cycle, cell division, and cell death

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The Minisymposium on "Cell Cycle Regulation and Decisions" considered the relationship between cell cycle and cell growth, long, noncoding RNAs, a new mechanism of mRNA competition for subcellular localization, ciliogenesis, a clustered regularly interspaced short palindromic repeats (CRISPR)–knockout screen, and new insights into kinetochore–microtubule attachments and the spindle assembly checkpoint.

Kurt Schmoller (Skotheim laboratory, Stanford University) used single-cell microscopy combined with analytical and computational methods to understand cell size control. He described a size-independent increase in cell size throughout the cell cycle and a critical role for the concentration of the cell cycle inhibitor Whi5 in initiating cell division.

Hilary Coller (UCLA) presented findings from her laboratory about the transition between proliferation and quiescence in primary human fibroblasts derived from analysis of mRNA polyadenylation. She reported that quiescent fibroblasts express longer isoforms, whereas proliferating fibroblasts express shorter isoforms, and discussed the mechanisms underlying this transition and the functional consequences.

Yiqin Ma (Buttitta laboratory, University of Michigan) presented her analysis of quiescence in the pupal *Drosophila* wing. Ma described a flexible G_0 period during which cells can reenter the cell cycle, and a more robust state in which cells are more refractory to proliferative signals; the latter state correlated with more compact chromatin based on fluorescence in situ hybridization. A parallel genomic approach indicated that, upon entry into robust G_0, promoters of most genes involved in the cell cycle did not change their chromatin accessibility status, but the enhancers of cyclin E and cdc25c become occupied by nucleosomes, presumably blocking their accessibility to transcription factors.

Cheen Euong Ang (Wernig laboratory, Stanford University) turned the focus onto long, noncoding RNAs. Ang described research characterizing long, noncoding RNAs differentially expressed in different populations of cortical neurons. Comparison of these long, noncoding RNAs with a copy number variation map revealed candidate long, noncoding RNAs whose alteration may contribute to disease. In support of this notion, disruption of one specific long, noncoding RNA was associated with neurocognitive deficits.

Shambaditya Saha (Hyman laboratory, Max Planck Institute) presented a novel mechanism for the asymmetrical segregation of P granules, RNA–protein assemblies that are not membrane-bound. Saha described how a single protein, PGL-3, forms P granule–like droplets when mixed with mRNA in vitro and demonstrated competition between PGL-3 and MEX-5 for binding to mRNA (Saha *et al.*, 2016). Saha presented a model that shows how a gradient of MEX-5 would create a competition between MEX-5 and PGL-3 for mRNA, contributing to P granule assembly and subcellular polarization.

Eszter Vladar (Axelrod lab, Stanford University) described her research on cyclin-dependent kinase 2 (cdk2) in the generation of centrioles, which act as basal bodies for cilia, in multiciliated cells. In cycling cells, cdk2, with cyclins E and A2, controls precisely one centriole and DNA duplication event in S phase. In contrast, postmitotic multiciliated cells build hundreds of centrioles without DNA replication, and therefore must have a different mechanism to regulate centriole generation. Investigating a primary airway cell culture, Vladar and colleagues found that cdk2, together with cyclin A1, is essential for motile ciliogenesis, and it appears to act on both nuclear and centriolar targets. They concluded that cyclin A1, normally present in meiotic cell cycles, allows for the uncoupling of DNA and centriole duplication.

The discussion turned to the regulation of attachment of microtubules to kinetochores, with a presentation by **Ana Maria Dumitru** (Compton laboratory, Dartmouth University). Dumitru described her use of a systematic mass spectrometry approach to identify substrates of cyclin A/cdk1 that lower stability of kinetochore–microtubule attachments during prometaphase. She focused on one particular target, myosin phosphatase targeting subunit 1 (MYPT1), without which mitotic cells exhibited more stable kinetochore–microtubule attachments. Dumitru presented evidence that MYPT1 acts by dephosphorylating Plk1, thereby promoting detachment and providing the cell with an opportunity to correct erroneous connections.

Ajit Joglekar (University of Michigan) described work from his laboratory on the spindle assembly checkpoint. The spindle assembly checkpoint is activated when the Mps1 kinase phosphorylates the kinetochore protein KNL1, generating a diffusible signal for the cell to wait for anaphase. Joglekar and colleagues investigated the quantitative nature of this signaling mechanism by engineering an ectopic spindle assembly checkpoint activator that involves dimerizing a repeat-containing domain of the KNL1 and Mps1. By varying

DOI:10.1091/mbc.E16-11-0793
Molecular Biology of the Cell Volume 28 Page 693
MBoC is pleased to publish this summary of the Minisymposium on "Cell Cycle Regulation and Decisions" held at the 2016 ASCB Annual Meeting, San Francisco, CA, December 4, 2016.

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repeat number, Joglekar was able to describe quantitative response features that explain how the checkpoint acts as a rheostat.

Kara McKinley (Cheeseman laboratory, Whitehead Institute/MIT), the recipient of the Merton Bernfield Memorial Award, described the generation of a large-scale collection of CRISPR-inducible knockout cell lines for cell cycle genes. This collection promises to facilitate diverse phenotypic and structure/function studies. Analysis of the effects of knockouts across different cell types revealed that the p53 status of the cell line was an important determinant of the phenotypic severity of specific knockouts.

The session ended with a presentation by **Taekyung Kim** (Desai laboratory, Ludwig Institute, University of California, San Diego). Having previously reported that the Bub1/Bub3 complex, well studied as a central component of the spindle assembly checkpoint, also promotes anaphase onset in *Caenorhabditis elegans* embryos (Kim *et al.*, 2015), here Kim showed that Bub1 promotes APC/C-Cdc20 activation by recruiting Cdc20 to kinetochores. Kim presented data supporting a model in which Cdc20 at the kinetochore can either be dephosphorylated to promote APC/C activation or inhibit APC/C as part of the spindle assembly checkpoint. Kim speculated that microtubule attachment status modulates Cdc20 fate.

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