NEW HORIZONS
SEMINAR SERIES

Kinetochore Microtubule Attachments and Accurate Chromosome Segregation

Mitosis is critical for the faithful segregation of genetic material among the two daughter cells. During mitosis, a eukaryotic cell assembles a bipolar spindle from dynamic microtubules. Chromosome segregation is accomplished by the concerted function of the mitotic spindle and kinetochores, mega-protein assemblies formed at centromeres of chromosomes. Kinetochores attach end-on to spindle microtubules and generate forces that orient and move sister chromosome pairs to the spindle equator at metaphase and segregate them to opposite spindle poles in anaphase. Kinetochores are also the sites of an efficient intracellular signaling mechanism called the spindle assembly checkpoint that has a major role in preventing inaccurate chromosome segregation. Unequal segregation of the chromosomes can have catastrophic consequences (chromosomal instability) leading to tumorogenesis and birth defects. Despite the progress we have made to characterize many of the molecules and mechanisms involved in mitosis, we are still lacking a completely mechanistic understanding of how kinetochores attach properly to spindle MTs and how they serve to move and segregate the chromosomes accurately. My research is focused towards understanding how kinetochores accomplish these key functions during mitosis.

ABOUT THE SPEAKER

Dr. Dileep Varma initiated his Ph.D. thesis research in Prof. Richard Vallee’s lab at the Dept. of Pathology and Cell Biology, Columbia University in 2002. He worked on the targeting and attachment of the microtubule motor protein, cytoplasmic dynein to kinetochores and membranous organelles. His research identified the mitotic checkpoint protein 2W10, previously shown to be involved in targeting dynein to mitotic kinetochores, as performing a similar function in targeting dynein to organelles. He also carried out an in-depth analysis of the cargo-binding N-terminal tail domain of dynein heavy chain and this study was instrumental in identifying novel functions for the dynein motor in maintaining proper kinetochore microtubule (kMT) attachments and kinetochore orientation. In another study, he developed a single molecule-based inhibition approach to study dynein light chains, the cellular function of which are yet to be clearly understood. In 2008, Dr. Varma moved to Prof. Ted Salmon’s lab in the Dept. of Biology, UNC Chapel Hill, to initiate his post-doctoral research. One of the main focuses of the Salmon lab has been to understand the function of the kinetochore-bound Ndc80 complex in kMT attachment and spindle assembly checkpoint (SAC). The Ndc80 complex possesses a flexible loop within its structure the function of which was unknown until recently. His work has demonstrated that this loop region is required for recruiting a DNA replication licensing protein, Cdt1, which in turn regulates the kinetochore functions of the Ndc80 complex. As a part of another study he used super-resolution microscopy to discover that, surprisingly, the SAC proteins are closely juxtaposed with the components of the core kMT attachment site at metaphase kinetochores. This study helps explain how checkpoint activity and kMT attachments are coordinated during mitosis to promote error-free chromosome segregation.

FRIDAY, SEPTEMBER 20, 2013
3:30 - 5:00 p.m., Kelly Hall 310