Mammalian SWI/SNF chromatin remodeler is essential for reductional meiosis in males

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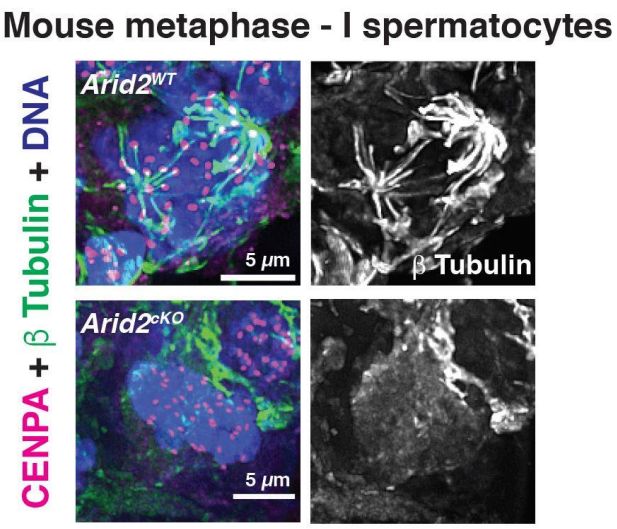

Gametogenesis is a process by which sexually reproducing organisms generate haploid egg or sperm from diploid progenitors by meiosis. Meiosis features critical biological processes such as homologous recombination and cell division. Genes governing these processes are therefore essential for genome stability and fertility. Interestingly, several known chromatin regulators have been implicated in meiosis. These include the SWI/SNF (SWItch/Sucrose Non Fermenting) family of ATP dependent chromatin remodeling complexes, known to regulate DNA accessibility. We have previously shown that BRG1, a catalytic subunit of SWI/SNF facilitates meiotic progression during spermatogenesis. In addition to BRG1, multiple subunits (~10-14) s ome of which are mutually exclusive, constitute biochemically distinct SWI/SNF subcomplexes, whose functions in spermatogenesis remain unknown. Here, we identify a role for the PBAF (Polybromo - Brg1 Associated Factor) complex in the regulation of meiotic cell division. The germ cell-specific depletion of PBAF DNA binding subunit, ARID2 resulted in a metaphase-I arrest. *Arid2*^{cKO} metaphase-I spermatocytes displayed defects in chromosome organization and spindle assembly. Additionally, mutant centromeres were devoid of Polo-like kinase1 (PLK1), a known regulator of the spindle assembly checkpoint (SAC). The loss of PLK1 coincided with an abnormal chromosome-wide expansion of centromeric chromatin modifications such as Histone H3 threonine3 phosphorylation (H3T3P) and Histone H2A threonine120 phosphorylation (H2AT120P) that are critical for chromosome segregation. Consistent with the known role of these histone modifications in chromosome passenger complex (CPC) recruitment, *Arid2*^{cKO} metaphase-I chromosomes display defects in CPC association. We propose that ARID2 facilitates metaphase-I exit by regulating spindle assembly and centromeric chromatin.

Speaker Bio:

Early on during my undergraduate training in microbiology, I was fascinated by classical genetic and biochemical studies that helped establish basic models of gene regulation. This sparked an interest in studying chromatin-based mechanisms that govern cell development. During my graduate studies in the lab of Dr. Victoria Meller (Wayne State University, Detroit), I investigated mechanisms of dosage compensation, a strategy employed by heterogametic species to accomplish balanced X linked gene expression between sexes. Using *Drosophila melanogaster* as a model system, we discovered roles for genomic imprinting and the siRNA pathway in dosage compensation. The latter observation led me to identify X linked repeat derived small RNAs as potent regulators of X chromosome recognition, a key feature of dosage compensation. My current work in the lab of Dr. Terry Magnuson (University of North Carolina at Chapel Hill) is focused on understanding how chromatin regulation impacts mammalian germline development. My studies have been focused on elucidating the functions of the SWI/SNF chromatin remodeling complex in spermatogenesis. I use genetic, genomic and proteomic techniques to investigate how SWI/SNF collaborates with various chromatin and meiotic factors to regulate germline development. Using these approaches, we have identified roles for SWI/SNF in the maintenance of undifferentiated precursor germ cells and regulation of meiotic progression. These studies have important implications in reproductive health.

Topic areas: Gene Expression, Genome Integrity & Transmission, Molecular & Cellular Genetics