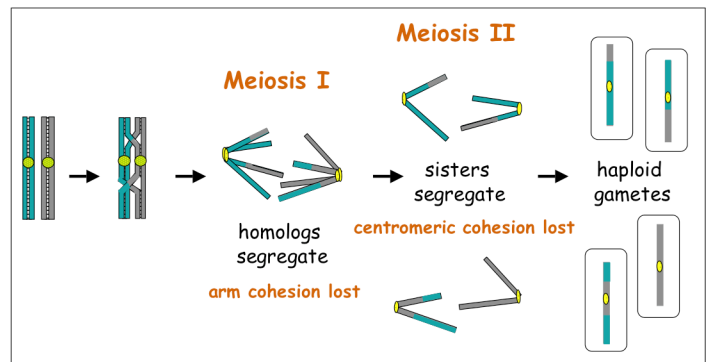




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Regulation of Chromosome Segregation During Meiosis
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One of the most critical aspects of cell division is the accurate partitioning of genetic material into the daughter cells. During DNA replication, connections between the newly formed sister chromatids are established. “Cohesion” between sisters is required for proper orientation of chromosomes on the mitotic spindle and when cohesion is released during anaphase, the sisters are able to segregate to opposite poles. Regulation of cohesion (establishment, maintenance and release) is a critical part of every cell cycle.

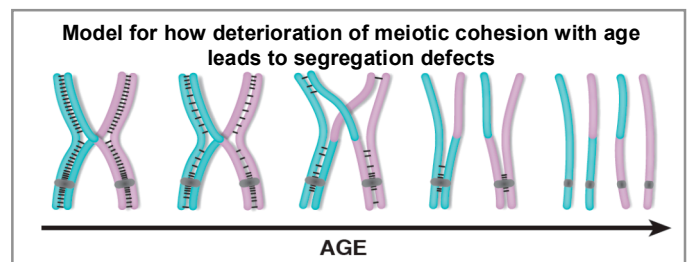
During meiosis, cohesion not only holds sisters together, but also plays an essential role in meiotic recombination and maintaining the association of recombinant homologues until anaphase I. The release of cohesion during meiosis is also unique—arm cohesion is dissolved during anaphase I but centromeric cohesion must be maintained until anaphase II. Therefore, normal regulation of meiotic cohesion requires additional control mechanisms that are not present during mitosis.



Defects in meiotic cohesion lead to the production of aneuploid gametes. In humans, approximately 15% of conceptions spontaneously abort because of aneuploidy and the leading known cause of mental retardation is trisomy 21. In addition, the incidence of meiotic segregation errors increases dramatically as women age. Although the correlation between increased maternal age and segregation errors is well-established, the underlying molecular defects that cause reduced fidelity of chromosome segregation in older oocytes are largely unknown.

The long-term goal of my lab is to define the pathway of events necessary for the proper regulation of sister-chromatid cohesion and chromosome segregation during meiosis and to understand the molecular events that cause reduced fidelity of meiotic chromosome segregation in older oocytes. We are using the model system *Drosophila melanogaster* to understand the mechanisms that govern meiotic cohesion and chromosome segregation. Analysis of meiosis in fruit flies allows us to capitalize upon a number of genetic techniques to identify proteins required for normal segregation and cytological methods to monitor the morphology and behavior of meiotic chromosomes. Because the process of meiosis is so highly conserved, our research provides a basic framework to understand the defects in meiotic chromosome segregation that lead to disease in humans.

In the last few years we have delineated a number of critical roles that cohesion plays during meiosis including chiasma maintenance (Bickel et al., 2002) and how chromatids preferentially choose a homologue (and not their sister) during recombination (Webber et al., 2004). We have characterized the localization and dynamics of several proteins involved in meiotic cohesion (Khetani and Bickel, 2007). In addition, we have used fruit flies to develop a model system to study why older oocytes are more susceptible to meiotic segregation errors (Jeffreys et al., 2003). Our recent work supports the model that weakening of normal meiotic cohesion with age is a major determinant of age-dependent



nondisjunction. Future studies in the lab will investigate why cohesion deteriorates with age. In addition, we will continue to define the role of chromatin modifiers/remodelers in the regulation of meiotic sister-chromatid cohesion during prophase I.

Potential Rotation /Thesis Projects:

Project 1: Test the hypothesis that oxidative damage contributes to age-dependent NDJ.

Oxidative damage accumulates with age and may lead to segregation errors in human oocytes. Given the difficulty of demonstrating a causative effect of reactive oxygen species on meiotic segregation defects in human oocytes, our ability to mimic age-dependent NDJ in flies and to genetically manipulate *Drosophila* oocytes provides a powerful approach to address this question. In *Drosophila*, mutations that reduce the levels of SOD2 (Superoxide Dismutase 2) increase oxidative damage and decrease life span. We will assay for age-dependent NDJ in oocytes with either reduced or elevated SOD2 activity. Determining whether the level of oxidative damage has a direct effect on the level of age-dependent NDJ will greatly inform our understanding of how/why cohesion becomes weaker as oocytes age.

Project 2: Test the hypothesis that re-establishment of cohesion during prophase I is required for chiasma maintenance.

One major unresolved issue regarding meiotic cohesion is whether the original cohesin molecules used to establish cohesion during meiotic S phase are sufficient to maintain cohesion throughout prophase I. This is a critical question given that meiotic cohesion must be maintained for decades in human oocytes. An alternative possibility is that meiotic cells (at least in metazoans) utilize a mechanism to “rejuvenate” cohesion during the extended time period that cohesion must be maintained. We will use genetic and cytological techniques to determine whether the activity of the cohesion establishment protein Deco is required during prophase I to maintain meiotic cohesion. These experiments will provide fundamental information about the normal mechanisms that ensure cohesion maintenance during meiotic prophase.

Project 3: Investigate the role of chromatin modifiers/remodelers in the regulation of meiotic sister-chromatid cohesion during prophase I.

Our search for interactors of the meiotic cohesion protein ORD has led us to two proteins, dRING and Mi-2, that are both conserved in metazoans and function within complexes that regulate chromatin structure. Virtually nothing is known about the function of these proteins or their respective complexes during meiosis. Current work in the lab is exploring the role of the PcG protein dRING in the regulation of sister-chromatid cohesion during meiotic prophase. We will expand this analysis by using a combination of genetic and cytological techniques to examine the function of the chromatin remodeling protein Mi-2. These experiments will be critical to understand how chromatin modifiers/remodelers contribute to the maintenance of meiotic cohesion during prophase I.

Because I am also affiliated with the Genetics graduate program, students that work in my lab may choose to join the Ph.D. program in Biological Sciences or Genetics. Please feel free to stop by and chat in more detail about research in my lab and about potential rotation/thesis projects.

Recent publications:

- Subramanian, V.V. & Bickel, S. E. (2009) Heterochromatin-mediated association of achiasmate chromosomes declines with age when cohesion is compromised. *Genetics* 181:1207-1218.
- Subramanian, V.V. & Bickel S. E. (2008) Aging predisposes oocytes to meiotic nondisjunction when the cohesin subunit Smc1 is reduced. *PLoS Genet.* Nov;4(11):e1000263.
- Page S.L., Khetani, R.S., Lake, C.M., Nielsen, R.J., Jeffress J.K., Warren W.D., Bickel S.E., & Hawley, R.S. (2008) *corona* is required for higher-order assembly of transverse filaments into full-length synaptonemal complex in *Drosophila* oocytes. *PLoS Genet* 4(9): e1000194.
- Gause, M., Webber, H., Misulovin, Z., Haller, G., Rollins, R.A., Eissenberg, J.C., Bickel, S.E. & Dorsett, D. (2008) Functional links between *Drosophila* Nipped-B and cohesin in somatic and meiotic cells. *Chromosoma* 17:51-66
- Khetani, R. & Bickel, S.E. (2007) Regulation of cohesion and chromosome core morphogenesis during pachytene in *Drosophila* oocytes. *Journal of Cell Science* 120: 3123-3137.