circuits emerging prior to the onset of vision may use spontaneous activity, while those emerging later may require visual experience to reach their mature state [18]. This diversity of strategies moves the debate from does activity play a role or not, to why some circuits are 'hard-wired' while others are influenced by experience. This work also provides new insights into how activity influences the organization of synapses between two neurons. Future work based on super-resolution or electron microscopy (for examples, see [19,20]) is likely to provide a deeper understanding of how precise synaptic structures emerge during development.

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Genetic Conflicts: Stronger Centromeres Win Tug-of-War in Female Meiosis

Female meiosis presents unique opportunities for competition between chromosomes for evolutionary dominance. A new study reveals that centromere strength dictates meiotic success, driving karyotype evolution and reproductive isolation in mice.

Benjamin D. Ross[1,2] and Harmit S. Malik[2,3,*]

Budding biologists begin their genetics education by learning about the laws of inheritance proposed by Gregor Mendel, including the tenet that two alleles will randomly segregate from each other during the production of gametes and will be equally represented in the next generation. It is the near-universality of these 'laws' that has driven researchers to investigate any violations of random Mendelian inheritance for over 70 years [1,2]. New research that appears in this issue of *Current Biology* now provides compelling evidence for a widespread mechanism employed by some Mendelian scofflaws [3].

Violations of Mendel's laws come in two flavors. In the first, gametes representing different alleles are produced at equal frequencies during meiosis. However, selfish elements found on some chromosomes can 'poison' either gametic development or embryonic viability, ensuring their own evolutionary success at the expense of other chromosomes. Such post-meiotic dysfunction is seen in the Segregation Distorter system of *Drosophila*, the t-haplotype of mice, and the spore-killers of fungi [1,2].

A second violation of Mendelian inheritance occurs when selfish elements subvert the process of chromosome segregation. In female meiosis in plants and animals, only one meiotic product out of four becomes incorporated into the egg while the other three are discarded in polar bodies. Mendelian inheritance results when both homologous chromosomes are randomly represented in the egg. However, if a selfish element is able to skew the process of chromosome selection for the egg in its own favor, this results in biased inheritance known as meiotic drive [4].

Cheating in female meiosis can occur in either of two meiotic divisions. One of the best-studied examples of selfish elements that subvert female meiosis emerged from the study of knob elements in maize chromosomes. Pioneering work from Marcus Rhoades revealed that in appropriate genetic backgrounds, knob elements can recruit microtubules [5] and direct their orientation in meiosis II, thereby increasing their chances of inclusion in the oocyte nucleus [6].

Similar cheating behavior can also occur during the first meiotic division of female meiosis, in which the position of a chromosome on the meiotic spindle determines its fate. Meiotic chromosomes on the cortical side of the spindle are fated to end up in the polar bodies, while interior chromosomes will be incorporated into the egg. When meiotic inheritance is Mendelian, the frequency at which a chromosome finds itself on the internal side of the meiosis I spindle is expected to be random. In contrast, non-random positioning would result in meiotic drive. Such bias is thought to explain the higher transmission of B chromosomes in grasshoppers [7], and centromeric expansions in monkeyflowers [8].

Some of the most illustrative examples of female meiotic drive involve chromosomal fusions. In some species, telocentric chromosomes (with the centromere found at the chromosome end) can fuse to become metacentric (with the centromere in the middle). These fusion chromosomes (called Robertsonian fusions, or Rb) are found in many species and can exhibit biased transmission during female but not male meiosis [9]. Curiously, the fused chromosome appears to be favorably transmitted in species like chickens and humans, yet appears to be disfavored in mice [10]. Furthermore, karyotypic surveys of mammalian species have found non-random distributions of metacentric and telocentric chromosomes, suggesting that either one or the other are favored in separate species, and this preference has likely switched multiple times during mammalian evolution [10]. This survey further implies that a 'mixed' karyotype consisting of both metacentric and telocentric chromosomes must be disfavored.

From these types of studies, a very strong — albeit circumstantial — case has emerged for centromere configurations that dictate female meiotic success. Yet the cell biological evidence for this has been sparse. In addition, there has been no cogent model for why metacentrics are favored in some lineages but telocentrics in others. Taking advantage of wide variation in the frequency and persistence of Rb chromosomes in different European mice populations, Chmatal and colleagues address both these outstanding questions [3].

Chmatal *et al.* first characterized the meiotic positioning of heterozygous Rb chromosomes in a genetic background in which telocentric chromosomes are prevalent and favored in female meiosis. They found the internal positioning on the meiotic spindle for the Rb or the telocentric chromosomes to be highly non-random, strongly correlating with inclusion in the egg. They next investigated the cell biological determinant of this positioning by comparing kinetochore protein levels at Rb and wild-type (telocentric) chromosomes using antibody staining against both the CENP-A inner kinetochore protein, as well as the Hec1/NDC80 outer kinetochore protein. These analyses revealed that increased kinetochore protein levels at centromeres were directly associated with meiotic drive. Thus, Rb metacentrics recruited less CENP-A and Hec1/NDC80, and were only present in oocytes at 40% rather than expected Mendelian (50%) frequency. Next, turning to a genetic background in which metacentrics are favored in female meiosis, Chmatal *et al.* found the reverse trend to be true — Rb metacentrics recruited more kinetochore proteins and were preferentially transmitted. In both instances, differences in kinetochore protein recruitment were an intrinsic property of the centromeres themselves rather than reflecting different expression levels of kinetochore proteins [3].

These results provide the first cell biological evidence for previously proposed evolutionary models [10,11], which hypothesized that greater microtubule binding to the centromere of a driving chromosome (*i.e.*, increased 'centromere strength') directly affects positioning on the meiotic spindle, and meiotic success. Chmatal *et al.* not only provide a satisfying resolution to a large body of work on female meiotic drive but also provide a potentially universal currency — kinetochore protein recruitment — for meiotic success.

But how could centromere strength simultaneously explain the success of both telocentrics and Rb chromosomes? The authors propose a model in which the evolutionary success of Rb chromosomes depends on its relative centromere strength compared to other chromosomes. If the genetic background contains largely 'weak' centromeres, then an Rb chromosome is likely to be more successful. In contrast, the evolutionary success of an Rb chromosome would be diminished if it arose in a genetic background of 'strong' centromeres. Indeed, Chmatal *et al.* find that Rb fusions isolated from different populations of mice appear to be highly variable in their relative centromere strength [3]. One plausible explanation for this diversity is that it is genetic variation — each Rb fusion possesses differential retention of the centromeric DNA from the original telocentric chromosome [12], thus influencing centromeric strength.

Another source of variability in centromere strength of Rb chromosomes could be the result of epigenetic differences. For instance, centromeres are epigenetically defined by the centromeric histone H3 variant CENP-A in most organisms [13]. Despite its essential role in centromere specification, CENP-A itself evolves rapidly between species [14,15], which is believed to be due to recurrent cycles of female meiotic drive and suppression [16]. Therefore, subtle differences in CENP-A or other kinetochore proteins in different genetic backgrounds could affect kinetochore recruitment and centromere strength. This could potentially render an otherwise strong Rb chromosome to be weak depending on genetic background.

Even in situations where they have a significant advantage in female meiosis, Rb chromosomes face daunting prospects for fixation. Some may be fixed due to drift, which is especially powerful in small populations. However, male mice and

humans heterozygous for Rb chromosomes can incur fitness costs in the form of reduced fertility [17,18]. This sets up an intriguing tension in populations, in which Rb chromosomes are propagated because of their female meiotic advantage but are impeded because of the associated fitness disadvantages. Such fitness tradeoffs are likely to rapidly select for modifiers that act in centromere specification or meiosis to alleviate the fitness disadvantage. Indeed, many essential proteins involved in both these processes evolve rapidly between species, hypothesized to be a result of such recurrent cycles of female meiotic drive and suppression [14,16]. Thus, lowered fitness costs due to selection of modifiers could allow fixation of Rb chromosomes in certain populations. In these situations, hybrids between populations fixed for different Rb chromosomes could unleash deleterious effects in meiosis, resulting in chromosomal speciation [19].

The results of Chmatal *et al.* highlight the insight that can be revealed by cell biological approaches to old evolutionary questions. The establishment of Rb chromosomes as a cell biological model opens up the possibility of further insight into another poorly studied but necessary determinant for female meiotic drive — asymmetry of the first meiotic spindle in oocytes. It is this asymmetry that must be exploited by 'cheating' meiotic drivers. How this asymmetry is established, and how it can be exploited is practically unknown. Early studies in the grasshopper *Myrmeleotettix maculatus* found that the meiotic spindle was asymmetric — fibers from the egg pole to the equator were measured to be approximately three times as long as those from the polar body pole [20]. Taking advantage of this asymmetry, B chromosomes in this species drive by positioning themselves on the eggward side of the spindle. Similar to their insights into centromere strength, driving Rb chromosomes may help further dissect the mysterious cell biology of female meiosis in animal oocytes.

Even Mendel might have approved.

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Mitotic Kinesins: A Reason to Delve into Kinesin-12

The failure of kinesin-targeting cancer drugs is thought to result from functional redundancy of mitotic kinesins. A new study provides mechanistic insights into kinesin-12 that help to explain its targeting to kinetochore fibers and its ability to compensate for inhibition of kinesin-5.

William O. Hancock

The intricate dynamics of mitotic spindle morphogenesis involves many proteins that possess overlapping functions. While this redundancy is natural, given the vital importance of faithfully separating duplicated chromosomes, it hampers efforts toward a detailed understanding of spindle dynamics. Further, because targeting the mitotic spindle is an attractive approach for anti-tumor therapeutics, this functional redundancy reduces the probability of finding effective single-target drugs. One promising target is kinesin-5 (KIF11 or Eg5), a tetrameric kinesin that plays a key role in spindle formation by generating forces that separate the two poles. In cell culture, inhibition of Eg5 results in monopolar spindles and mitotic arrest [1]. The trouble is that in clinical trials, Eg5 inhibitors are less effective than hoped, and a principal reason is thought to be this problem of redundancy — other