MEIOSIS

Searching for a Partner

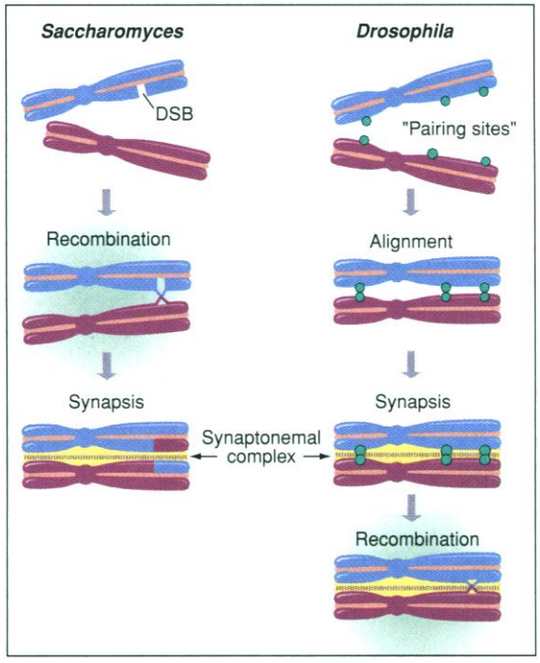
James E. Haber

The creation of a new organism starts with some preparatory work by its parents. Mother and father package their genetic material into eggs or sperm, which contain only one copy of each of the chromosomes rather than the usual two. When a sperm fuses with an egg, the offspring then starts life with the proper double dose of each chromosome. During this specialized cell division, called meiosis, recombination of the genetic material between pairs of parents' chromosomes (crossing over) ensures that offspring inherit an assortment of genes from all four grandparents. Crossing over is also necessary for the proper separation of chromosomes during meiosis.

Much of our understanding of meiotic recombination comes from research on the fruit fly *Drosophila* and the budding yeast *Saccharomyces*—genetics and cytogenetics from *Drosophila* and molecular mechanisms (often derived by genetics) from yeast. The structure characteristic of meiotic recombination—an elaborate ladder of protein between the homologous chromosomes called the synaptonemal complex (see the figure)—is highly conserved among most eukaryotes, and defects in recombination in yeast, flies, and mice all lead to similar failures of proper chromosome segregation.

Yet surprisingly, yeast have few meiotic genes and proteins in common with other organisms. Moreover, where homologs have been identified in yeast and flies, their mutation results in very different phenotypes. So does meiotic recombination proceed by a common mechanism among organisms or not? A report by McKim *et al.* on page 876 in this issue (*1*) now reveals that yeast and flies may have adopted quite different strategies to ensure recombinatorial crossing over, even while using apparently similar apparatus.

One of the most extraordinary aspects of meiotic recombination is that two regions of DNA that are destined to recombine must locate each other in a vast sea of nonhomologous sequences. This is difficult enough to achieve in yeast, with a haploid genome size of 12,000 kilobases of DNA, but seems incredibly daunting in fruit flies, let alone humans, where the genome is considerably larger. Moreover, the chromosomes of flies and mammals are riddled with repeated sequences, and recombination between ectopically located sequences on other chromosomes would create translocations or other chromosomal rearrangements. Finally, during meiosis there is not just one such event, but dozens, or hundreds. In yeast, meiotic recombination is initiated by double-strand breaks, and one is faced with the image of a hundred broken chromosome ends all waving about, each in search of a homologous sequence that can act as a template to repair the break.



Flies need it; yeast don't. (**Left**) During meiosis, pairs of replicated yeast homologous chromosomes synapse properly with the formation of the complete synaptonemal complex (yellow) only after they have been tightly aligned by recombination. (**Right**) As shown by McKim *et al.* (*1*), in *Drosophila*, meiotic recombination is not necessary for tight alignment and synaptonemal complex formation. Pairing of homologous chromosomes in flies may be facilitated through specialized pairing sites (green dots).

One solution to the problem of finding a proper partner would be to restrict recombination to regions of chromosomes that have already paired. Evidence for a set of "pairing sites" that would bring chromosomes together—independent of recombination—was first found in *Drosophila* by Hawley (*2*) and also seems likely to occur in the nematode *Caenorhabditis elegans* (*3*). Yet most data suggest that yeast do not have specific pairing sites. Yeast chromosomes transiently associate at apparently random homologous sequences before recombination (a process informally known as "kissing"), but at best this only loosely aligns homologous chromosomes before recombination (*4*). Consequently, in yeast there is only a 5- to 10-fold greater chance for recombination between true allelic partners than between even very short (1 kilobase) homologous sequences located elsewhere (*5*).

So the issue is this: In the absence of recombination, yeast cells may roughly align chromosomes ("pairing"), but do not bring them intimately together ("synapsis"). Synapsis—operationally defined as the appearance of the synaptonemal complex—tightly aligns homologous chromosomes along their entire length. A deletion of the yeast Spo11 endonuclease that creates meiotic double-stranded breaks not only abolishes recombination but also eliminates the formation of the synaptonemal complex (*6*, *7*). Conversely, yeast mutations that abolish synaptonemal complex formation, such as a deletion of the *ZIP1* gene, have modest effects on recombination, and chromosomes remain attached at a few discrete sites that are likely to be the sites of recombination (*8*). Thus, recombination appears to be a prerequisite for complex formation in yeast.

The new report by McKim *et al.* (*1*) suggests that the sequence of events is quite different in flies. In *Drosophila mei-P22* or *mei-W68* mutants that abolish meiotic recombination, chromosomes still synapse and form extensive synaptonemal complexes between each chromosome pair. This appears to be a key difference between flies and yeast: synaptonemal complexes can form in the absence of any recombination in flies. To be sure of this conclusion, it is critical to be certain that recombination—or even early molecular steps that might lead to recombination—has not occurred in the experiment. McKim *et al.* provide several lines of evidence to support this claim. There is no crossing over and no evidence of "invisible" recombination events (either gene conversions without crossing over, or exchanges between sister chromatids, or chromosome breakage resulting from recombination that was initiated but not repaired).

Of course, a yeast enthusiast might rejoin by pointing out that we don't yet know whether meiotic recombination in *Drosophila*

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is initiated by double-stranded breaks. One could also imagine that recombination events are initiated but aborted in ways that do not leave lethal DNA lesions or even genetic evidence of their previous existence. If double-stranded breaks in flies are made by a homolog of the yeast topoisomerase II–like Spo11 protein (*9*, *10*), there may be reversible cleavage of DNA. The cell might receive a signal that recombination has been initiated but, in the absence of a key subsequent step that is prevented by *mei-P22* or *mei-W68*, the cleaved DNA would simply be re-ligated. In this scenario, synaptonemal complex formation would then depend on the signal generated by transient double-stranded break formation, but not on recombination per se.

Moreover, the fact that the synaptonemal complex appears in the absence of recombination does not rule out the possibility that normally the complex forms in direct response to recombination. In meiotic mutants the establishment of the complex might be delayed for many hours, forming between unrecombined but well-paired chromosomes. Delayed complex formation between regions that cannot undergo recombination occurs in mice (*11*), and a similar event happens in yeast haploid cells tricked to undergo meiosis, even though there are no homologous chromosomes (*12*). This idea is lent some credibility by the existence of meiotic pairing sites that might bring *Drosophila* chromosomes into alignment (*2*).

In riposte, a drosophilist might note that there is already some evidence that the formation of double-stranded breaks in yeast is influenced by previous interaction of homologous sequences at "hot spots," although synaptonemal complex formation per se does not seem to be required. Also, the absence of some complex components significantly reduces double-stranded break formation (*13*).

The results of McKim *et al.* convince us that the events we normally think of as recombination—detectable crossing over or gene conversion—are not required to form the synaptonemal complex in a metazoan, even though this does seem to be the case for yeast. Whether synaptonemal complex formation is a prerequisite to initiate recombination in higher eukaryotes remains unknown. One may hope for a mutation in flies that eliminates a vital synaptonemal complex component to see whether recombination is also abolished.

Most organisms likely use a combination of recombination-dependent and recombination-independent mechanisms for homolog recognition and pairing, as they prepare to segregate their chromosomes. The reliance on one mechanism or the other may depend on genome complexity, the number of chromosomes, and the sites where recombination is initiated. For the moment, yeast and flies seem to be showing us two extremes.

References and Notes

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GEOSCIENCE

Sliding Skis and Slipping Faults

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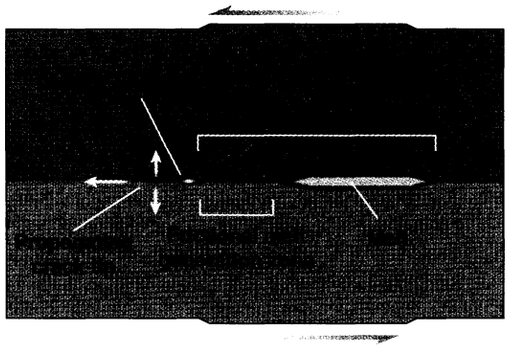
One of the first things taught in elementary physics is that friction increases with the force applied perpendicular to a sliding surface (the normal force). As innumerable high school experiments with sliding blocks attest, increasing the normal stress increases the forces resisting block movement. This property has long posed a quandary for understanding deep earthquakes, which occur as far as 670 km beneath Earth's surface (*1*). At such depths, the crushing pressure from many kilometers of overlying rock should hold faults locked tight; yet, deep earthquakes are common. Thus, some mechanism must be invoked to either eliminate the excessive normal stresses or explain the shear sliding without brittle frictional behavior. On the basis of analyses of the largest recorded deep earthquake, which occurred beneath Bolivia in 1994, Kanamori *et al.* (*2*) propose on page 839 of this issue that deep earthquakes may occur as a result of melting. They suggest that melting during such an earthquake forms a thin fluid layer that reduces friction in much the same way that a thin layer of water reduces the friction between a ski and the underlying snow (*3*).



Melting, slipping, and sliding. Model for faulting with lubrication induced by frictional melting, originally developed to explain geological observations of pseudotachylytes in exhumed fault zones [after Spray (*9*)]. As the active slip zone moves along the fault, melting is induced by friction. If rupture propagation is slow, some melt may be injected ahead of the main slip zone, perhaps facilitating crack propagation. Kanamori *et al.* (*2*) propose that a similar model may explain large deep earthquakes such as the 1994 Bolivia event.

There are several other ways to explain the shear motion associated with deep earthquakes in the presence of large confining pressures. Friction along an interface may be reduced or eliminated if a fluid is present at a pressure near the confining pressure. This mechanism is thought to weaken shallow faults and may provide a mechanism for deep earthquakes if water can be carried to such depths within hydrous minerals (*4*). Another proposal, transformational faulting, suggests that deep earthquakes are associated with solid-state phase transitions to denser phases of olivine (*5*). Laboratory experiments suggest that when such transitions have been kinetically inhibited, the metastable transformations occur suddenly and can be accompanied by shear dislocations (*6*). However, the fault widths of recent large deep earthquakes seem to be too large to be accommodated within the metastable olivine material (*7*).

Kanamori *et al.* (*2*) note that the Bolivia earthquake had several unusual properties, including a very slow rupture velocity, high stress drop, and a low ratio of radiated seismic energy to total strain energy (seismic efficiency). The high stress drop indi-

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