

The *Foxg1* suppressor and cortical cell fate. During normal mammalian development, neuronal progenitor cells first produce the earliest neurons, Cajal-Retzius (CR) neurons, which constitute layer I of the cerebral cortex (**top**). The progenitors then begin to express the transcription factor, *Foxg1*, resulting in production switching from CR neurons to ER81⁺ neurons of layers VI and V of the cerebral cortex (**middle**). If *Foxg1* expression is then silenced, production of neurons continues unabated but the neurons produced are CR neurons, not ER81⁺ neurons (**bottom**).

process of producing ER81⁺-layer V neurons switched fates, continuing neurogenesis unabated but producing CR neurons instead.

The progressive restriction of cell fate in progenitor cells embodies the most widely accepted mechanism for generating neuronal diversity elucidated in studies of the invertebrate nervous system (4), retina (5), and spinal cord (6, 7). According to cell culture and transplant experiments (2, 8–10), it seems that the cerebral cortex also uses

Of course, timing is everything. As such, one also can expect that future studies will determine the possible limits on retention of early cell fate potential by later progenitor cells. Is it possible that any progenitor cell, even when isolated from the last stages of tissue formation, can produce earlier born neurons in the absence of a suppressor? If so, this may necessitate a modified definition of the multipotent progenitor cell. And if one throws self-renewal into the mix, neuroscientists may turn their attention toward identifying the active molecular components of cell fate regulation and stem cell differentiation that fall on both sides of the activation-suppression dipole.

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neurons and deep-layer neurons were produced at appropriate times and migrated to their correct layers. Active removal of *Foxg1* in the rescued mice by administering doxycycline to inhibit the tTA system—after CR neurogenesis and concomitant with the normal timing of production of layer V (ER81⁺) neurons—caused the resumption of CR cell production from the progenitor pool (see the figure). In fact, cell-labeling experiments with bromodeoxyuridine confirmed that, indeed, progenitors in the

progressive restriction of cell fate to generate neuronal diversity. Implicit in the new work on *Foxg1* is the possibility that neuronal progenitors do not lose their capacity to generate multiple cell types. Rather, there is suppression of what is otherwise a program of transcriptional regulation that remains poised to guide different cell fate choices. The influence on this active molecular suppression of either an intrinsic timer or key environmental signals extrinsic to progenitor cells remains to be determined.

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Promiscuous Maize Chromosomes

Enrique Martinez-Perez and Graham Moore

Organisms exhibiting sexual reproduction carry two copies (homologs) of each chromosome. Meiosis is the specialized type of cell division that halves the number of chromosomes before sexual reproduction, thereby ensuring that chromosome number does not double with each generation. Before meiosis, each homolog is replicated, forming two sister chromatids that remain linked to-

gether (see the figure). During meiosis, the homologs are correctly segregated so that each gamete (that is, sperm and egg) carries only a single copy of each chromosome. The chromosome complement is restored in the zygote (fertilized egg) after the fusion of the two gametes. How is the complicated chromosome dance during meiosis achieved? A report on page 89 of this issue by Pawlowski *et al.* (1) goes some way toward answering this question.

At the start of meiosis, each chromosome must recognize its homolog from among all the chromosomes present in the nucleus. The homologs must then become

intimately aligned along their entire lengths and a proteinaceous structure known as the synaptonemal complex (SC) must be assembled between them, a process called synapsis. In this way, meiotic recombination (the exchange of DNA strands between the homologs) is completed, resulting in the formation of chiasmata, physical links that hold the homologs together after disassembly of the SC (see the figure). After the resolution of these physical links, the homologs separate during the first meiotic division. The two sister chromatids forming each homolog are then separated during the second meiotic division. Many components of the meiotic recombination machinery are known, especially in yeast, as well as some structural components of the SC. However, very little is understood about how homologs find each other in the first place and how this initial recognition is coordinated with synapsis and recombination. Enter Pawlowski and colleagues with their identification of a new key player, the *phs1*

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(*poor homologous synapsis 1*) gene, in maize that is necessary for the coordination of chromosome pairing, recombination, and synapsis (1).

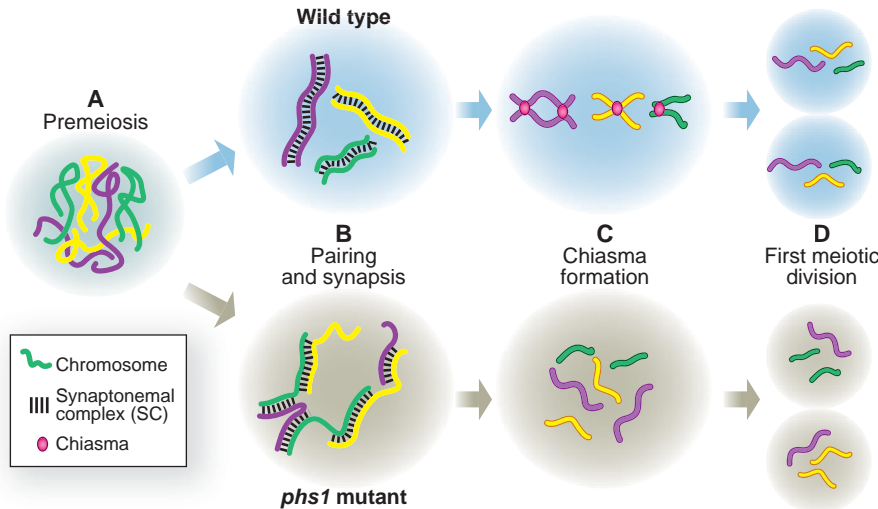
After SC disassembly in wild-type maize, the 10 pairs of homologs are present as 10 bivalents (each bivalent consists of a pair of homologs held together by chiasmata). However, maize plants carrying a mutation in the *phs1* gene have 20 unpaired chromosomes instead of 10 bivalents, suggesting that chiasma formation has failed. This could be due to a direct consequence of

homologs find each other in *phs1* mutants?

Two main mechanisms seem to be involved in the homolog search: the reorganization of chromatin in the nucleus, and the recombination machinery itself. In maize, as in many other organisms, the ends of chromosomes (telomeres) cluster in a small region of the nuclear envelope, forming a structure known as the telomere bouquet (6). This configuration is thought to facilitate homolog pairing by bringing all chromosomes into close proximity. In fact, chromosome pairing is affected in another maize mutant (*pam1*),

However, the presence or absence of DSBs can be indirectly assessed by monitoring whether RAD-51 is loaded onto meiotic chromosomes (in other organisms, mutants that do not make DSBs do not load RAD-51). Taking advantage of this feature, Franklin *et al.* (9) showed that in maize, only 5% of the total number of DSBs seen in early meiosis produce chiasmata. They proposed that the other 95% (or at least a large number of them) might be necessary for homolog pairing. If this hypothesis is correct, then maize would behave in a similar way to mice, yeast, and *Arabidopsis* in that DSBs would be needed for successful synapsis. This is also supported by a recent analysis of a collection of maize meiotic mutants showing a correlation between the reduction in the number of RAD-51 foci and the severity of synapsis defects (10). The number of RAD-51 foci in *phs1* mutants only reaches 1% of that in the wild type, supporting a correlation between RAD-51 loading and chromosome pairing. However, in *phs1* mutants, the severe reduction in RAD-51 foci does not seem to reflect a lack of DSBs, because a different assay indicates that DSBs are in fact being made.

Whether the number of DSBs made by *phs1* mutants is similar to that made by wild-type maize remains an open question. One possible explanation for the pairing defects in *phs1* mutants is that *phs1* is a component of the recombination machinery necessary for RAD-51 loading after DSB formation and that RAD-51 is needed for homolog pairing. However, this explanation may be too simple because RAD-51 disruption and even the absence of DSBs in other organisms does not lead to extensive nonhomologous synapsis. In *phs1* mutants, pairing and synapsis are completely uncoupled. Therefore, the function of *phs1* lies at the core of coordination between these two events. The *phs1* gene can now be used to identify new components of this coordinating mechanism. Obtaining maize mutants that lack different components of the recombination machinery will help to elucidate the relationship among recombination, pairing, and synapsis, as well as clarifying the exact recombination step that is impaired in *phs1* mutants.



Associating with the right chromosomes. Chromosome behavior in wild-type and *phs1* mutants. Three pairs of homologous chromosomes are shown in three different colors. (A) The three pairs of homologs are not associated before meiosis. (B) In wild-type maize, the chromosome homologs pair correctly and the SC forms between them. However, in *phs1* maize mutants, the homologs do not pair and the SC forms between nonhomologous chromosomes. (C) After the SC is disassembled in wild-type plants, the homologs remain attached through chiasmata (pink dots); in *phs1* mutants, chiasma formation fails and the homologs are unpaired. (D) At the first meiotic division, homologs segregate from each other in wild-type maize, whereas in the *phs1* mutants, the chromosomes segregate randomly.

problems in the late events leading to chiasma formation (2), defects in SC formation (3), or problems in initial homolog pairing (4). By following a single site on each homolog in *phs1* mutants, the authors found that the homologs were paired in only 5% of the cells at a time, whereas wild-type cells showed 100% pairing (see the figure). Surprisingly, SC formation appears normal in *phs1* mutants, resulting in the indiscriminate association of nonhomologous chromosomes in these plants. There are examples in other organisms of mutants that exhibit nonhomologous synapsis (5), but not to the same extent. Furthermore, the *phs1* gene does not appear to be related to any previously identified meiotic genes. In fact, it is the first gene shown to be involved in chromosome pairing and synapsis in the most important group of cultivated plants, the cereals. Thus, the *phs1* gene is clearly necessary for homolog pairing and its coordination with synapsis in maize. But why can't the

which is defective in the clustering of its telomeres (7). However, bouquet formation seems unaffected or very mildly affected in the *phs1* mutant and therefore cannot account for the severe disruption in pairing.

During meiotic recombination, double-strand breaks (DSBs) are created and processed to expose single-stranded DNA. After loading of the RAD-51 protein, single-stranded DNA can be used as a template to check for complementary DNA sequences. This homology search appears to be necessary for chromosome pairing and synapsis in yeast, mice, and the model plant *Arabidopsis*, because in all these organisms, the failure to produce DSBs results in the disruption of synapsis (8). However, in the worm *Caenorhabditis elegans* and the fruit fly *Drosophila*, synapsis between homologs is achieved even in the absence of DSBs. In maize, there are as yet no known mutants that fail to produce DSBs, so we cannot confirm whether DSBs are needed for synapsis.

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