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REVIEW

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The synaptonemal complex and meiotic recombination in humans: new approaches to old questions

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Abstract Meiotic prophase serves as an arena for the interplay of two important cellular activities, meiotic recombination and synapsis of homologous chromosomes. Synapsis is mediated by the synaptonemal complex (SC), originally characterized as a structure linked to pairing of meiotic chromosomes (Moses (1958) J Biophys Biochem Cytol 4:633–638). In 1975, the first electron micrographs of human pachytene stage SCs were presented (Moses et al. (1975) Science 187:363–365) and over the next 15 years the importance of the SC to normal meiotic progression in human males and females was established (Jhanwar and Chaganti (1980) Hum Genet 54:405–408; Pathak and Elder (1980) Hum Genet 54:171–175; Solari (1980) Chromosoma 81:315–337; Speed (1984) Hum Genet 66:176–180; Wallace and Hulten (1985) Ann Hum Genet 49(Pt 3):215–226). Further, these studies made it clear that abnormalities in the assembly or maintenance of the SC were an important contributor to human infertility (Chaganti et al. (1980) Am J Hum Genet 32:833–848; Vidal et al. (1982) Hum Genet 60:301–304; Bojko (1983) Carlsberg Res Commun 48:285–305; Bojko (1985) Carlsberg Res Commun 50:43–72; Templado et al. (1984) Hum Genet 67:162–165; Navarro et al. (1986) Hum Reprod 1:523–527; Garcia et al. (1989) Hum Genet 2:147–53). However, the utility of these early studies was limited by lack of information on the structural composition of the SC and the identity of other SC-associated proteins. Fortunately, studies of the past 15 years have gone a long way toward remedying this problem. In this minireview, we highlight the most important of these advances as they pertain to human meiosis, focusing on temporal aspects of SC assembly, the relationship between the SC and meiotic recombination, and the contribution of SC abnormalities to human infertility.

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The synaptonemal complex–50 years

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Tools of the trade

Three major technical developments were essential to the recent advancement in human meiosis research. The first of these occurred during the late 1980s to early 1990s and involved the application of molecular tools to the analysis of meiosis in lower organisms. Early studies focused on *Saccharomyces cerevisiae*, initially characterizing temporal aspects of meiotic prophase (Sun et al. 1989; Padmore et al. 1991; Weiner and Kleckner 1994) and subsequently identifying molecular players involved in the formation of the synaptonemal complex (SC) and SC-associated proteins important for the induction of double strand breaks (DSBs), DNA-damage checkpoints, cell-cycle progression, chromatid cohesion, chromosome pairing, and recombination and crossover interference (for review, see Roeder 1995; Kleckner 1996; Murakami and Nurse 2000; Roeder and Bailis 2000; Yamamoto and Hiraoka 2001; Solari 2002; Bishop and Zickler 2004; Krogh and Symington 2004). These analyses were followed by comparable studies in other model organisms, especially *Drosophila melanogaster* (Kerrebrock et al. 1992; Theurkauf and Hawley 1992; McKim et al. 1993) and *Caenorhabditis elegans* (Dernburg et al. 1998; Pasierbek et al. 2001; Siomos et al. 2001; MacQueen et al. 2002), facilitating the identification of homologous proteins involved in chromosome pairing, synapsis, and recombination.

Secondly, and initially somewhat unexpectedly, cancer geneticists played an important role in the development of mammalian meiosis research. Beginning in the mid-1990s, several groups generated mutant mice carrying null alleles (knockout mice) for cancer-causing genes. For several of

these (e.g., the mismatch repair genes Mlh1 and Pms2), homozygous knockouts were found to have severe meiotic defects, resulting in subfertility or infertility (Baker et al. 1995, 1996). Targeted disruption studies of other loci—some associated with human cancers, others not—have now provided a long list of mouse mutations exhibiting meiotic phenotypes (e.g., see Cooke and Saunders 2002; Wei et al. 2002; de Rooij and de Boer 2003; Scherthan 2003; Ashley 2004; Eichenlaub-Ritter 2005). The genes associated with these mutations were obvious targets in initial studies of human meiosis.

A third keystone was the recent development of straightforward antibody-based immunolocalization techniques. Earlier localization attempts were often time-consuming, labor intensive (e.g., immunogold staining using electron microscopy), and were limited by the reagents available at that time. Fortunately, the rapid maturation of fluorescence microscopy for immunostaining and fluorescence in situ hybridization (FISH) mapping, coupled with the dramatic increase in the number of antibodies recognizing epitopes of SC and SC-associated proteins, resulted in an array of cytological markers for the systematic probing and visualization of the kinetics of meiotic events in germ cells (Moens et al. 1987; Dobson et al. 1994; Moens 1995; Moens and Spyropoulos 1995; Offenberg et al. 1998; Plug et al. 1998; Schalk et al. 1998; Eijpe et al. 2000a,b, 2003; Revenkova et al. 2004). As discussed below, the application of this methodology now made it possible to visualize the important steps and structures in the human meiotic process.

Temporal aspects of SC assembly

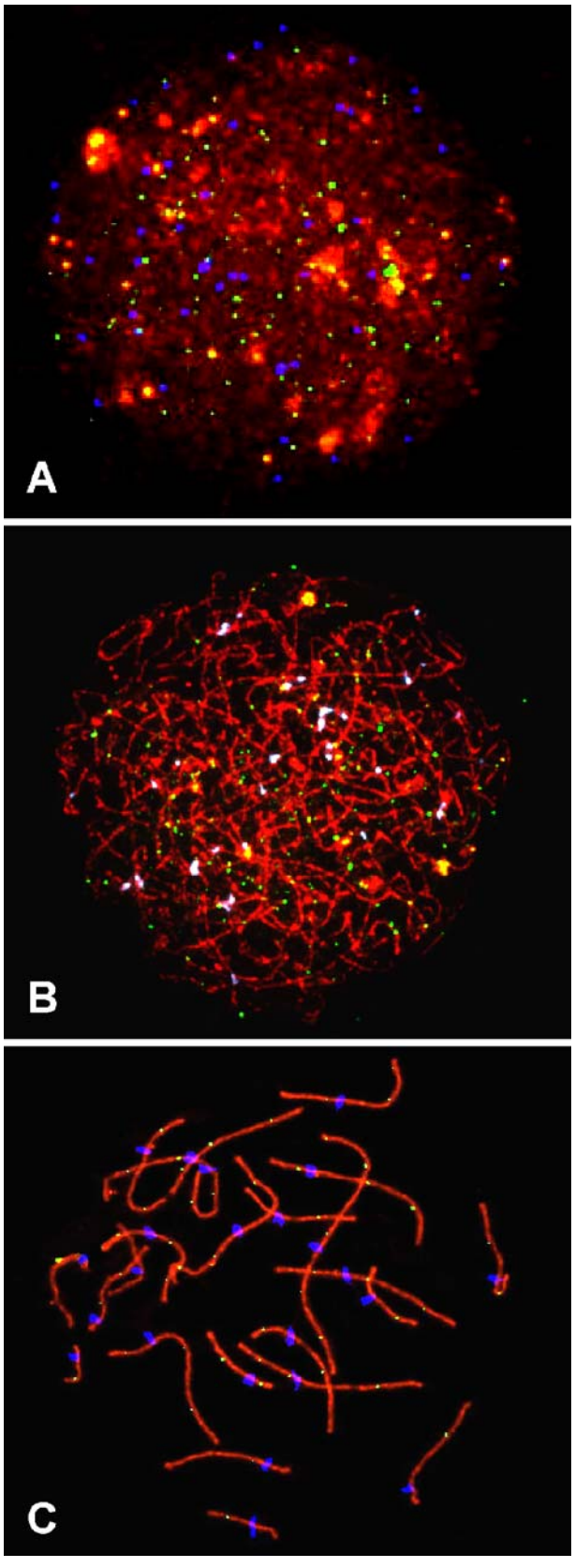
A hallmark feature of meiosis is the SC, the prophase-specific supramolecular proteinaceous structure that forms between and holds homologues together. The SC provides a favorable location for binding of recombination machinery proteins and is intimately associated with proteins involved in sister chromatid cohesion (cohesins). In addition, the SC serves as a reliable chronometer for substaging meiotic prophase based on its degree of formation or morphology (Fig. 1). One major structural template of the SC is the SC protein SCP3, which undergoes major transformations during prophase. At leptotene, SCP3 is initially visualized as well-distributed short linear segments (axial elements, AEs) forming along each chromosome with chromatin loops extending out from the protein backbone. These eventually lengthen and condense into a filamentous meshwork. At zygotene, the AEs appear as distinct full-length structures and are brought together by transverse filaments composed of the SC protein SCP1. At pachytene, completely synapsed chromosome cores are distinct and cells have 23 centromeres. The SC begins to disassemble at diplotene and homologous chromosomes move apart except at the sites of recombination (chiasmata).

Results of immunolocalization studies on the temporal expression patterns of SCP3 and other SC-associated proteins in human spermatocytes and oocytes are summarized in Fig. 2. To date, relatively few meiotic proteins were analyzed in humans but, nevertheless, they have allowed us to address a number of important questions regarding the chronology of meiotic processes. One of the more interesting of these was the relative ordering of events involved in synapsis with those associated with recombination. In yeast, plants, and mammals, induction of DSBs is a prerequisite to normal SC formation (Zickler and Kleckner 1999). In contrast, initiation of recombination is not required for SCs in *Drosophila* and *C. elegans* and presynaptic alignment appears to be mediated by specific chromosomal domains (McKim et al. 2002; MacQueen et al. 2002). Another investigation showed that expression of RAD51 recombinase, which attaches to processed DSBs and promotes homologous DNA exchanges, occurs much later in *C. elegans* than in *S. cerevisiae* (Colaiacovo et al. 2003), suggesting that homologue pairing, not SC formation, is required for DSB formation in *C. elegans*. Furthermore, in both *Drosophila* and *C. elegans*, the number of DSBs per cell is much lower than in *S. cerevisiae*, plants, and mammals, suggesting that recombination is not required for chromosome alignment (Jang et al. 2003).

In human meiocytes, preliminary data now indicate that we follow the yeast paradigm. That is, two protein families are evident early at prophase recombination-associated proteins (e.g., RAD51, γH2AX, RPA, MSH4, and MSH5) (Moens et al. 1998; Plug et al. 1998; Tarsounas et al. 1999; Cohen and Pollard 2001; Roig et al. 2004; Lenzi et al. 2005; Oliver-Bonet et al. 2005) and cohesion proteins (e.g., REC8 and STAG3) (Prieto et al. 2004). The appearance of DSB "markers" (e.g., RAD51 and γH2AX) occurs in advance of fully formed SCs and indicates that initiation of the human meiotic recombination pathway does not require homologues to be completely synapsed (Brown et al. 2005; Lenzi et al. 2005).

In other studies of DSB-associated proteins, it was suggested that RAD51 foci are of different sizes: large and bright in synapsed regions and somewhat smaller on asynapsed AEs (Barlow et al. 1997), possibly reflecting their short-term existence during synapsis. RPA and γH2AX appear to be maximally expressed at late zygotene/early pachytene, coincident with the completion of synapsis between homologous chromosomes and these proteins diminish at pachytene (Lenzi et al. 2005; Oliver-Bonet et al. 2005). The MutL homologues MLH1 and MLH3 appear on synapsed SCs (Lynn et al. 2002; Tease et al. 2002; Lenzi et al. 2005).

Sex-specific temporal patterns of protein expression were observed in around half of the proteins studied in human meiocytes. Generally, it appears that oocytes have more prolonged expression patterns than spermatocytes. For example, the MutL homologue MLH1 is observed in oocytes in zygotene and as early as leptotene (Vallente, Cheng, and Hassold, unpublished observations; Fig. 1a,b) while in males, it is not evident until pachytene (Lynn et al. 2002; Brown et al. 2005; Gonsalves et al. 2005; Oliver-Bonet et al. 2005). The number of MLH1-MLH3 foci are



◀ **Fig. 1** Visualization of prophase substages using immunofluorescence staining for SCP3 (axial elements, *red*), CREST (kinetochores, *blue*), and MLH1 (late recombination nodules, *green*) in human oocytes. **a** Leptotene oocyte with patchy SCP3 staining, approximately 46 CREST signals and small, dispersed MLH1 foci. **b** Zygotene oocyte with full-length axial elements and MLH1 signals. **c** Pachytene oocyte with SCP3 fibers showing complete synapsis of homologous chromosomes and distinct MLH1 foci

maintained during pachytene, yet there is an ~tenfold variation of MLH1-MLH3 foci numbers between oocytes, which is also evident at the chromosome level as frequent achiasmate chromosome arms and whole chromosomes and chromosome arms overloaded with MLH1 foci (Lenzi et al. 2005). Another protein that is variably expressed in oocytes is MSH4, a component of the MSH4-MSH5 heterodimer complex that is thought to act as a stabilizing clamp for recombination intermediates. MSH4 is detectable in leptotene in females but does not associate with SCP3 until zygotene (Lenzi et al. 2005), while it appears later at zygotene in males (Oliver-Bonet et al. 2005).

In oocytes, RAD51 remains associated with the chromosomes at high numbers until early pachytene (Lenzi et al. 2005), suggesting that these represent the late γH2AX events that have either failed to be processed or that are induced later during prophase. It is interesting to note that by late pachytene, the numbers of RAD51 foci and γH2AX foci are not statistically different, which suggests that all γH2AX sites are targeted by RAD51. Most of the γH2AX protein diminishes at pachytene, but some are expressed at a prolonged period in the XY body in males (Lenzi et al. 2005; Oliver-Bonet et al. 2005). In spermatocytes, RAD51 protein is depleted by late pachytene while γH2AX persists (Lenzi et al. 2005; Oliver-Bonet et al. 2005), possibly representing late-processing DSBs, improper dephosphorylation, or changes within the chromatin architecture from SPO11-independent damage (Hamer et al. 2003). Unfortunately, the cohesion proteins REC8 and STAG3 were only investigated in oocytes and these remain colocalized to SCP3 only until early diplotene (Prieto et al. 2004).

The SC and meiotic recombination

Until recently, all information on meiotic recombination levels in humans were based on one of two approaches: cytogenetic studies of chiasmata (the sites of crossovers) in diakinesis stage meiocytes (Hulten 1974; Laurie et al. 1981; Laurie and Hulten 1985a,b) or, more commonly, genetic linkage analyses using DNA polymorphisms (either restriction fragment length polymorphisms, mini- or microsatellite polymorphisms, or single nucleotide polymorphisms) to trace inheritance of alleles in family pedigrees and generate sex-specific or sex-averaged genetic maps (e.g., Broman et al. 1998; Nievergelt et al. 2004; Gibson et al. 2005; Serre et al. 2005). Each approach has advantages and disadvantages. The cytogenetic approach provides a useful tool for examining chiasma patterns on individual chromosomes and for estimating genome-wide chiasma frequencies. However, even under the best of circumstances, the morphology of diakinesis chromosomes is suboptimal, interfering with banding and thus with

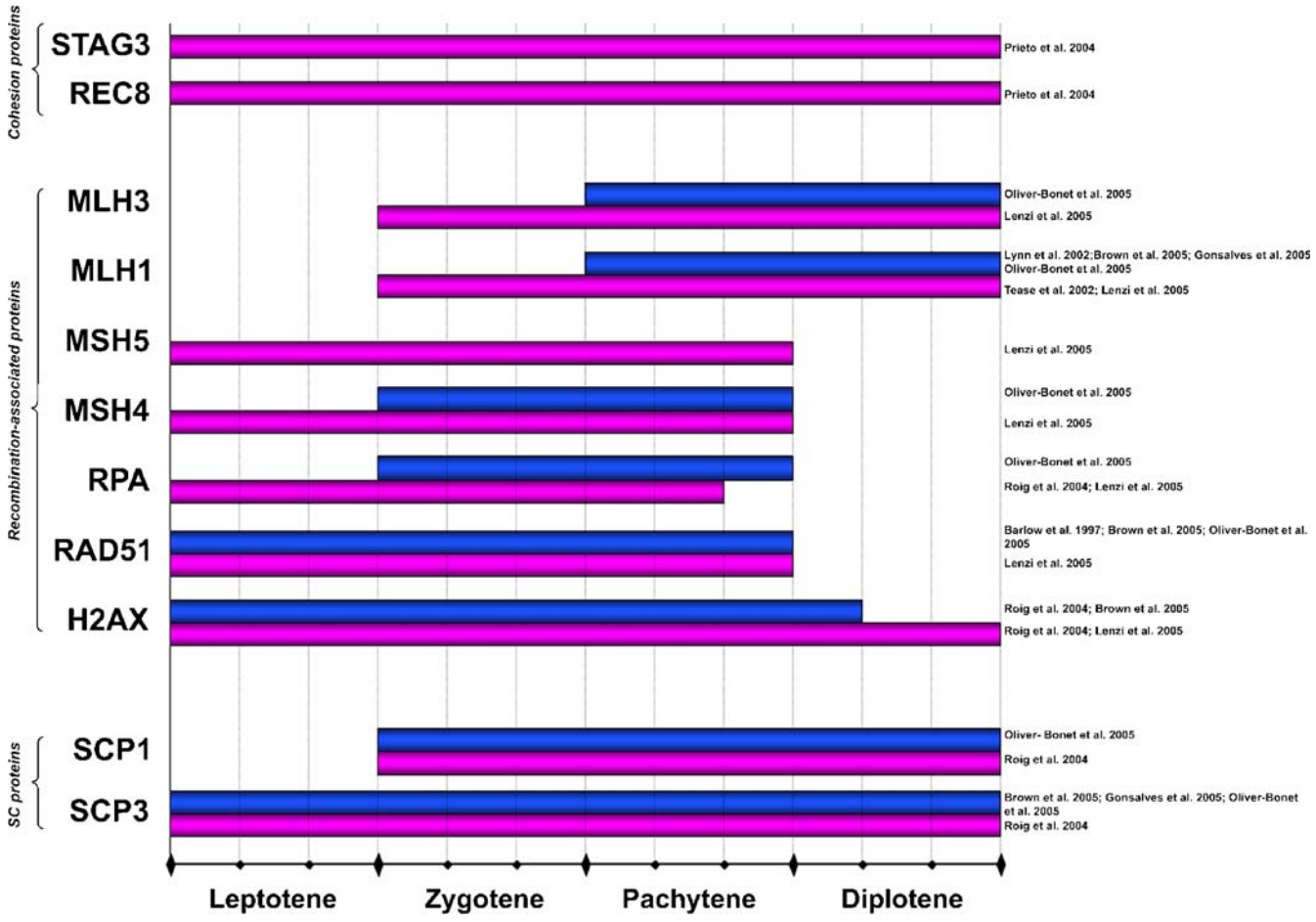


Fig. 2 List of immunofluorescence studies performed on human oocytes (*pink*) and spermatocytes (*blue*) showing expression profiles for cohesins, recombination-associated proteins, and SC proteins

chromosome identification. Further, the chromosomes are typically highly condensed, making localization of chiasmata to specific chromosome regions difficult. Finally, invasive techniques are required to obtain the cells of interest (fetal oocytes and spermatocytes) and there are relatively few cells at the appropriate stage, further limiting the power of the technique.

Genetic linkage analysis stands in stark contrast to the cytogenetic methodology because it provides a powerful, high resolution approach to studies of recombination. Highly detailed chromosome-specific genetic maps can be constructed and compared to physical maps, narrow hot and cold spots of recombination can be identified, and patterns of male and female recombination can be compared. However, genetic linkage analysis relies on studying transmitted haploid meiotic products rather than the cells undergoing meiosis; as a result, only one half of all exchanges can be detected (e.g., after a single exchange, only two of the four chromatids will be recombinant). Thus, any recombination-associated selection against gametes will be missed. Further, genetic linkage analyses are not well suited to analyses of genome-wide recombination events in individual meiocytes.

Recently, a third approach—immunolocalization studies of crossover associated proteins in pachytene meiocytes—has attracted considerable attention. The rationale for this approach is based on studies in mice, which indicated that a number of proteins, including the mismatch repair protein MLH1, had meiotic localization patterns that paralleled those of crossovers (Baker et al. 1995, 1996; Anderson et al. 1999). Thus, it was suggested that if applicable to humans, this approach had the potential to provide a "medium" level of resolution (higher than that using conventional cytogenetics but lower than that afforded by linkage analyses) and because pachytene stage cells are plentiful in fetal oocytes and testicular biopsies, a large amount of data on individual samples.

Accordingly, several groups initiated studies of MLH1 in human germ cells. Most of the initial data has come from males attending infertility clinics. Many such individuals are infertile for "mechanical" reasons (e.g., vasectomized males), making it possible to construct "control" genetic maps based on MLH1 localization patterns and to compare them with maps generated from cytogenetic or linkage studies. The results were remarkable because the maps are virtually identical regardless of the method used (Table 1).

Specifically, analyses of MLH1 foci indicate that there are approximately 50 exchanges per spermatocyte, translating to a genome-wide map of approximately 2,500 cM; this value agrees well with previous estimates from chiasma studies and with most genetic linkage analyses. Further, the distribution of MLH1 foci exhibits several features expected of crossover-associated proteins (Anderson et al. 1999). For example, consistent with genetic linkage data on human males (Kong et al. 2002; Mohrenweiser et al. 1998), MLH1 foci are preferentially distally located. In addition, MLH1 foci exhibit strong positive interference, the meiotic property that ensures "spacing" between adjacent crossovers on the same chromosomes. Finally, the number of MLH1 foci per chromosome is tightly regulated in human males with virtually all chromosome arms (except short arms of acrocentric chromosomes) having at least one focus, but seldom more than two foci; this agrees with previous data suggesting that "achiasmate" chromosomes are rare in humans (Hassold et al. 1995). Taken together, these results have demonstrated that MLH1 foci, indeed, do localize to sites of exchanges, providing a powerful surrogate for analyses of meiotic recombination events in the human male.

The initial results from human males also provide evidence of a role of the SC in mediating recombination levels. That is, Lynn et al. (2002) reported a simple linear relationship between the length of the SC and the number of MLH1 foci in human males and in mouse males and females; from this, they suggested that a physical structure (the SC) "measures" genetic distance in mammalian species. Other groups have now confirmed the relationship between SC length and recombination levels in humans (Tease and Hulten 2004; Sun et al. 2005a), although the basis for the association remains unclear. Possibly, chromatin loop sizes are responsible for the total SC length, i.e., smaller loop sizes generate longer SCs, which in turn provide more room for DSBs to occur along the SC length (Kleckner et al. 2003). A constant SC length may also be considered as a factor behind this covariation wherein the length remains unaffected despite mutations on DSB machinery and/or SC formation. From an evolutionary point of view, it may also be possible that hot spots are being replaced by cold spots (negative selection), resulting in restrictions in recombination (Myers et al. 2005; Pineda-Krch and Redfield 2005).

In contrast to the human male, relatively little MLH1 data are yet available on the human female, partly because of the difficulties inherent in ascertaining the appropriate material (i.e., ovaries from female fetuses). Nevertheless, the initial observations were intriguing with both expected and unexpected results. Included among the expected outcomes: as in the male, MLH1 foci display positive interference (Vallente, Cheng, and Hassold, unpublished observations) and consistent with linkage analysis, MLH1 foci are preferentially interstitially located. However, there also were two surprises. First, the MLH1-based estimates of genome-wide genetic length are significantly lower than those based on genetic linkage analyses. Indeed, in the largest study (Lenzi et al. 2005), the estimated genetic length is approximately the same as that observed in human males and only 55–65% that of genetic linkage analyses of human females. These MLH1-based data almost certainly do not represent the real situation in fertilized female oocytes because genetic linkage analyses indicate that females have approximately 1.6 the amount of recombination as males (Kong et al. 2002). Nevertheless, it is still possible that these data reflect the situation in the fetal ovary, e.g., selection may preferentially cull out oocytes with low levels of recombination so that the oocytes that are eventually ovulated are those with the highest levels of recombination. Clearly, additional analyses of fetal ovaries will be useful in confirming or refuting this idea and, more importantly, in determining the range of recombination values in individual human fetal oocytes. Secondly, the

Table 1 Summary of genome-wide human genetic maps

	Male				Female			
Method of analyses	**No. of meioses**	**Mean no. chiasmata**	**Mean no. MLH1 foci**	**Genetic length (cM)***	**No. of meioses**	**Mean no. MLH1 foci**	**Genetic length (cM)***	**Reference**
Chiasmata	389	53.7	---	2,700	---	---	---	(McDermott 1973)
	55	49.6	---	2,480	---	---	---	(Laurie and Hulten 1985b)
MLH1 foci	46	---	50.9	2,545	3	95.0	4,750	(Barlow and Hulten 1998)
	1,384	---	49.1	2,455	---	---	---	(Lynn et al. 2002)
	1,231	---	45.9	2,295	---	---	---	(Gonsalves et al. 2004)
	2,182	---	49.8	2,490	---	---	---	(Hassold et al. 2004)
	102	---	50.0	2,500	49	70.3	3,515	(Tease and Hulten 2004)
	---	---	---	---	250	50.3	2,515	(Lenzi et al. 2005)
	1,100	---	48.0	2,400	---	---	---	(Sun et al. 2005b)
Genetic linkage	---	---	---	2,625	---	---	3,799	(Matise et al. 1994)
	---	---	---	2,730	---	---	4,435	(Broman et al. 1998)
	---	---	---	2,590	---	---	4,460	(Kong et al. 2002)
	---	---	---	2,642	---	---	4,414	(Matise et al. 2003)
	---	---	---	2,813	---	---	4,600	(Kong et al. 2004)
	---	---	---	2,654	---	---	4,320	(Jorgenson et al. 2005)

*Genetic map lengths may be directly estimated from the number of meiotic crossovers (chiasmata or MLH1 foci); each crossover corresponds to a genetic distance of 50 cM

timing of localization of MLH1 foci to SCs was surprising: In contrast to reports from human males and mouse males and females, MLH1 is visualized early in zygotene and even as early as leptotene in human oocytes (Vallente, Cheng, and Hassold, unpublished observations; Fig. 1a,b). Whether this reflects additional functions for MLH1 in human oocytes or variation in the processing of recombination events, is not yet clear.

The SC and human infertility

The chronology of events in oogenesis makes it difficult to link early meiotic abnormalities to female infertility but in the male, abnormalities in meiotic recombination and/or SC assembly have long been known to be associated with cases of infertility (Chaganti et al. 1980; Vidal et al. 1982; Templado et al. 1984; Navarro et al. 1986). However, these early studies were largely descriptive and not geared to examining the underlying reasons for the infertility. The recent reinvigoration in human meiotic research now provides the opportunity to revisit this question and to ask whether specific mutational processes can be identified. In general, investigators addressing this question have taken one of two approaches: either using sequencing methodology to identify mutations in known meiotic genes or using cytological methodology to identify specific meiotic arrest phenotypes. Both approaches have yielded positive results. For example, Miyamoto et al. (2003) screened for SCP3 mutations in controls and in 19 individuals diagnosed with idiopathic infertility. In the infertile group, they identified two unrelated individuals heterozygous for identical deletions that led to a premature stop codon; presumably, the resultant truncated protein acted as a dominant negative, interfering with normal AE assembly. Similarly, Christensen et al. (2005) identified heterozygous missense mutations in SPO11 in a small proportion (2 of 192) of azoospermic/oligospermic individuals, but not in controls, suggesting a causative relationship between the mutation and azoospermia.

Several groups have now taken the other approach, i.e., using immunofluorescence methodology to examine meiotic progression, SC assembly, or localization of cohesions or recombination-associated proteins in meiosis I spermatocytes of populations of infertile individuals. In an initial study, Judis et al. (2004) analyzed 13 individuals with nonobstructive azoospermia/oligospermia and identified one individual with a complete zygotene stage arrest. AE formation appeared normal, but there was no evidence of synapsis, leading the authors to suggest a defect in assembly of the transverse filament (e.g., a mutation in SCP1). Similarly, Sun et al. (2004) recently reported a variety of pairing defects and reduced MLH1 counts in a single azoospermic individual; Gonsalves et al. (2004) reported on three azoospermic individuals with partial or complete zygotene stage arrest phenotypes. Taken together, these results suggest that a proportion of azoospermic individuals is infertile because of abnormalities in pairing, synapsis, or recombination that lead to prophase arrest. In future studies, it will be important to carefully analyze the meiotic phenotypes of these individuals to ask whether they might have subtle differences in the timing of the meiotic arrests indicative of different mutational origins. Indeed, in such individuals, it may be possible to use immunofluorescence analysis as an initial screening technique before subsequent mutation detection analysis. For example, initial immunofluorescence observations may simply implicate a protein family (e.g., abnormalities in sister chromatid cohesion could be due to one of several sister chromatid cohesion proteins), while others may suggest a specific genetic lesion (e.g., failure to detect the transverse filament of the SC implies a mutation in the SCP1 locus). Thus, subsequent studies would vary depending on the initial observations: They might involve additional protein localization studies or might move immediately to mutation detection assays.

Perspective

Researchers studying human meiosis have long been envious of their colleagues who examine meiosis in lower organisms. Short breeding times, relatively easy access to the cells of interest, and the ability to generate mutations and analyze their effects on germ cell behavior, all have combined to produce extraordinary insights into the meiotic process in a variety of model organisms. Clearly, such successes will be virtually impossible to replicate in humans: Both the biology of human gametogenesis and ethical considerations necessitate different approaches to the study of human meiosis. Nevertheless, the advances from model organisms now have provided us with a set of tools to begin the work of human gametogenesis and the initial results are encouraging. The ability to directly visualize spermatogenesis and oogenesis means that we can finally characterize the normal process and, hopefully, we will ultimately be able to apply this information to treat the abnormal process, i.e., those abnormalities that lead either to infertility or to chromosomally abnormal gametes.

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