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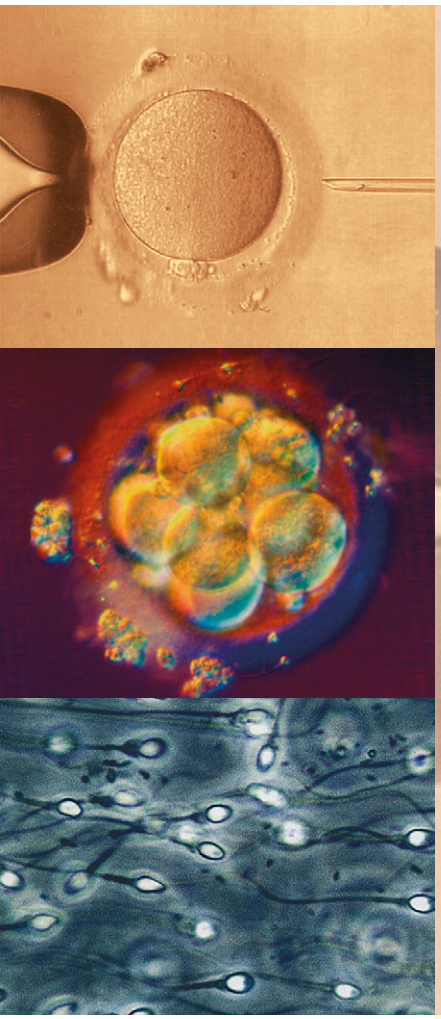

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Reproductive Phenotypes of Mouse Models Illuminate Human Infertility

C. Adelfalk[1, 2], E. A. Ahmed[3], H. Scherthan[1, 3]

Infertility represents a significant health problem in industrialized nations because reproductive activity is increasingly delayed and couples face a risk of impaired fetal health at advanced maternal age (>35 years). Furthermore, approx. fifteen percent of couples have difficulties to conceive within a year of unprotected intercourse. Reduced reproductive success often relates to a defective meiotic process that would normally lead to formation of ova and sperm. The understanding of the mechanisms of meiosis and fertility has largely benefitted from knockout and transgenic mouse models that display a fertility phenotype. Using information from meiosis-deficient mice has impacted on the diagnosis of infertility of unknown origin of human patients. In this paper we discuss insights gained in the etiology of infertility by looking at murine genetic models with a reproductive phenotype due to disruptions in genes acting during meiotic prophase. We focus on genes that are important for recombinational DNA repair, meiotic chromosome structure and reproductive aging and will compare these phenotypes to human conditions with reproductive impairment. **J Reproduktionsmed Endokrinol 2011; 8 (6): 376–83.**

Key words: genetics, infertility, meiosis, mouse models, recombination, human syndromes

Introduction

Infertility is increasingly recognized as a major health problem. Despite millions of individuals taking contraceptive measures approximately 15% of couples who wish to reproduce face difficulties to conceive within one year of unprotected intercourse [1]. Reproductive success depends on the faithful function of both female and male reproductive systems which may fail upon environmental exposures, anatomic defects, endocrinopathies, immunological problems or gametogenesis arrest. Defects in hormonal control and sexual differentiation pathways as well as in spermiogenic differentiation are well-known factors that underlie infertility in mammals of both sexes (for review see [2, 3]).

There are genetic syndromes such as e. g. Kallmann syndrome, cystic fibrosis or Turner's syndrome that are associated with infertility. But the basic mechanisms of about a quarter of all clinical infertility cases remain poorly understood, with many of the unrecognized pathologies being of genetic nature. Clinically, karyotype and mutation analysis for a few genes, for instance the cystic fibrosis transmembrane conductance regulator gene [4] and Y chromosome deletion analysis [5] are among the most common genetic tests offered to individuals seeking advice in infertility clinics.

Insights into the aetiology of infertility are obtained by an ever speeding rate of the generation of genetically modified animal models. Up to now, about 500 genetic mouse models with a reproductive phenotype have been generated. The knowledge accumulated through such model studies increasingly sheds light on idiopathic infertility met in the clinic (for review see [3, 6, 7]).

The subfertility of couples with advanced age has recently attracted interest [8, 9] and new molecular knowledge on the underlying defects has been obtained through generation of mammalian genetic models that underpin the importance of proper function of meiotic chromosome biology and checkpoint control. Here, we will focus on insights in the genetics of infertility gained through targeted disruption of murine genes involved in meiotic chromosome structure and homologous recombination (Tab. 1) during prophase I to the first meiotic division.

Mammalian Gametogenesis

In the mouse and other animals meiosis occurs in specialized organs (gonads) that form during fetal development and differentiate under hormonal control into ovaries and testes and eventually produce ova or sperm. In the female, meiosis commences and proceeds during early fetal development, but grinds to a halt prior to the first meiotic division. This arrest, depending on the species, lasts from months to even years [65]. In the male, meiosis starts at the onset of puberty in a first, rather synchronous wave and subsequently prospers throughout life [66, 67]. Gametogenesis is under the control of complex regulatory circuits involving a variety of developmental pathways such as hormone signalling, chromatin and cell cycle control and differential DNA repair pathways. Up to date there are more than 500 knockout or transgenic mouse mutants known to affect gametogenesis (reviewed by [3, 68–70] (http://jaxmice.jax.org/models/reproductive_biology.html; seen October 25, 2011).

Gene defects that interfere with reproductive success are known from different fields involving diverse aspects of cellular functions [3]. The production of germ cells starts with the division of a stem cell giving rise to a committed stem cell (spermatogonia/oogonia), the mitotic progeny of which enters the prophase to the first of two meiotic divisions that ultimately give rise to haploid sperm or eggs. In preparation for the first meiotic division (meiosis I) maternal and paternal (homologous) chromosomes have to pair and recombine. Subsequently, regulated exchanges between homologous chromosomes together with specialized cohesion between sister chromatids and

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From the [1]MPI für Molekulare Genetik, Berlin, the [2]Gyn-Gen-Lehel, Labor für Reproduktionsgenetik, München and the [3]Institut für Radiobiologie der Bundeswehr in Verb. mit der Universität Ulm, München

Correspondence: Prof. Dr. Harry Scherthan, PhD, MPI für Molekulare Genetik, D-14195 Berlin, Ihnestraße 73 und Institut für Radiologie der Bundeswehr in Verbindung mit der Universität Ulm, D-80937 München, Neuherbergstraße 11; e-mail: scherth@web.de

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Table 1: Fertility phenotypes of genetic mouse models and corresponding human conditions

		Mouse Fertility		Type of meiotic arrest/ apoptosis stage		Fertility phenotype in the human			
Mutated gene (mouse)	**Major function in meiosis**	**Male**	**Female**	**Male**	**Female**	**Human syndrome**	**Male**	**Female**	**References**
Ataxia telangiectasia mutated (*Atm*)	recombination chromosome dynamics	infertile	infertile	zygonema	no primary oocytes	Ataxia telangiectasia (A-T)	defective spermato-genesis or oligospermia	only few primordial follicles	[10–14]
Bloom's syndrome (*Blm*)[a]	recombination	reduced sperm number	nd	metaphase I	nd	Bloom's syndrome	sterile	subfertile	[15]
Breast cancer 1 (*Brca1*)	repair	infertile	fertile	pachynema	not applicable	Breast cancer	fertile	fertile	[16–18]
DMC1 dosage sup-pressor of mck1 homolog (*Dmc1*)	recombination	infertile	infertile	zygonema	pachynema	premature ovarian failure	–	early inferti-lity	[19–21]
Fanconi anemia complementation group A (*Fanca*)	recombination	subfertile	subfertile	reduced numbers of primordial germ cells	degenerating oocytes	Fanconi anemia	subfertile	subfertile	[22, 23]
Fanconi anemia complementation group C (*Fancc*)	(meiotic germ cell proliferation)	subfertile	subfertile	reduced proliferation of primordial germ cells	reduced proliferation of primordial germ cells	Fanconi anemia	subfertile	subfertile	[24–26]
Fanconi anemia complementation group D1/Breast cancer 2 (*Fancd1[Brca2]*)[b]	recombination	infertile	infertile	zygonema	follicle degeneration	Fanconi anemia, breast and ovarian cancer, azoospermia, severe oligozoospermia	variable up to infertile	subfertile	[27, 28]
Fanconi anemia complementation group D2 (*Fancd2*)	recombination (?)	subfertile	subfertile	reduced number of spermato-gonia, apo-ptosis in pachynema	reduced follicles in adults	Fanconi anemia	subfertile	subfertile	[29]
Fanconi anemia complementation group G (*Fancg*)	nd	subfertile	subfertile	spermato-zoa dege-neration	follicle degenera-tion	Fanconi anemia	subfertile	subfertile	[30, 31]
Histone H2A family, member X (*H2afx*)	repair, XY inactivation	infertile	hypofertile	pachynema	reduced litter sizes	no mutations found	fertile	?	[32–34]
Lamin A (*Lmna*)	nuclear envelope	infertile	fertile	pachynema	not applicable	Emery-Dreifuss muscu-lar dystrophy, dilated cardiomyopathy, familial partial lipodystrophy, Hutchinson-Gilford progeria	fertile	fertile	[35]
Meiotic recombination homolog A (*Mre11*)[c]	recombination	subfertile	subfertile	zygonema delay	zygonema delay	A-T like disease (ATLD)	nd	nd	[36, 37]
MutL homolog 1 (*Mlh1*)	recombination	infertile	infertile	metaphase I	very few follicles	hereditary colo-rectal cancer	fertile	fertile	[38–40]
MutL homolog 3 (*Mlh3*)	recombination	infertile	infertile	metaphase I	metaphase I	spermatogenic arrest	infertile	nd	[41–43]
MutS homolog 4 (*Msh4*)	recombination	infertile	infertile	zygonema	zygonema	nd	nd	nd	[44]
MutS homolog 5 (*Msh5*)	recombination	infertile	infertile	zygonema	zygonema	premature ovarian failure, azoospermia, severe oligospermia	infertile	early infer-tility	[21, 43, 45]
Nibrin (*Nbs1*)	recombination	fertile	infertile	not applicable	none	Nijmegen breakage syndrome	fertile	impaired oogenesis	[46]
Poly (ADP-ribose) polymerase family, member 2 (*Parp2*)	XY inactivation recombination	hypofertile	fertile	increased apoptosis at pachynema, metaphase I and of sperma-tids	not applicable	nd	nd	nd	[47]
Rec8 homolog C (*Rec8*)	cohesion	infertile	infertile	zygonema	zygonema	no mutations found	fertile	nd	[48–50]
Structural maintenance of chromosomes 1β (*Smc1β*)	cohesion, synapsis	infertile	infertile	pachynema	metaphase II	nd	nd	nd	[51]
SPO11 homolog (*Spo11*)	recombination	infertile	infertile	zygonema	oocytes de-generate the first few days postpartum	azoospermia	infertile	nd	[52–55]
Sad1 and UNC84 domain containing 1 (*Sun1*)	telomere attachment	infertile	fertile	zygonema/ pachynema	zygonema/ pachynema	nd	nd	nd	[56]
Synaptonemal complex central element 1 (*Syce1*)	synapsis	infertile	infertile	pachynema	very few oocytes	nd	nd	nd	[57]
Synaptonemal complex central element 2 (*Syce2*)	synapsis	infertile	infertile	pachynema	pachynema?	nd	nd	nd	[57]
Synaptonemal complex protein 1 (*Sycp1*)	synapsis	infertile	infertile	pachynema	oocytes loss during em-bryogenesis	nd	nd	nd	[58]
Synaptonemal complex protein 2 (*Sycp2*)	synapsis	infertile	subfertile	zygonema	interrupted synapsis	nd	nd	nd	[59]
Synaptonemal complex protein 3 (*Sycp3*)	synapsis	infertile	subfertile	zygonema	resorption of embryos (aneuploidies)	azoospermia	infertile	recurrent pregnancy loss, sterility	[7, 60, 63]
Testis expressed gene 12 (*Tex12*)	synapsis	infertile	infertile	pachynema	oocytes de-generate the first few days postpartum	nd	nd	nd	[64]

a: conditional knockout mouse; b: transgene knockout mouse; c: hypomorph; nd: no data/not known

sister centromeres allow for homologue segregation in the first meiotic division and sister chromatid segregation in the second meiotic division (for review see [71, 72]).

Chromosome Dynamics During Mammalian Meiosis

An error-free meiotic process is essential to produce functional germ cells. In the male mammal, meiosis starts with the entry into the prophase to the first meiotic division (prophase I), after B spermatogonia have completed a prolonged premeiotic S-phase. Prophase I commences with preleptonema when chromosomes start to condense and to assemble a meiosis-specific cohesin complex along tightly connected sister chromatids. Chromosome ends (telomeres) now migrate and attach to the nuclear envelope during leptonema. During the leptotene substage, thin axial cores (a.k.a. axial elements) develop along elongating chromosomes [73, 74]. Chromosomes move with their telomeres to pair during zygonema when the formation of the synaptonemal complex (SC), a proteinaceous zipper-like ribbon that connects the chromosomal axial elements, is initiated (for review see: [75, 76]). During this time there is a fleeting clustering of telomeres near the centrosome (bouquet stage), which likely contributes to homologue pairing [77]. Telomere clustering dissolves with growing synaptic pairing between homologous chromosomes that are fully synapsed at pachytene stage (Fig. 1A, C). At diplonema the nuclear membrane is dissolved and the SC breaks down so that homologous chromosomes eventually remain connected only at the sites of recombination (chiasmata) during metaphase I. The resulting secondary spermatocytes progress without an S phase to metaphase II and complete meiosis after the subsequent second division. This leads to the formation of haploid round spermatids that subsequently differentiate into mature spermatozoa (see, e.g., [80]).

In the human female fetus, diplotene oocytes undergo an extended dictyate arrest. Oocytes grow to acquire maturational and developmental competence that relies from preantral stage onwards. The resumption of maturation occurs downstream of the GnRH-induced LH surge at puberty, which initiates follicle formation and the entrance in metaphase I. The first meiotic division is completed at ovulation as signified by the extrusion of the first polar body. Then the ovulated oocyte undergoes a second arrest that is released by fertilization. The ensuing metaphase II and cytokinesis leads to formation of the second polar body [81, 82].

Meiotic Recombination and Repair are Essential for Fertility

Recombination between maternal and paternal chromosomes is essential for a successful meiotic process to occur in the germ cells. It is not only important to generate new genetic combinations, but is also necessary to pair and connect the homologous chromosomes after SC breakdown and up to metaphase I to avoid their missegregation. Chiasmata (sites of reciprocal recombination) provide the connections between homologues until their segregation at the metaphase I/anaphase transition. The number and position of recombination events is tightly regulated such that the requirement for at least one crossover/homologue pair is fulfilled and each chromosome pair receives at least one chiasma. In mammals, chiasmata are usually found within chromosome arm(s) [83–85].

Recombination is initiated in leptonema by DNA double strand breaks (DSBs) that are introduced by the meiosis-specific transesterase SPO11 [52, 53, 86, 87]. Meiotic DSBs are repaired through the homologous recombination pathway and proteins associated with DNA damage signaling and DNA repair form cytologically visible foci at the DSB sites, which is e.g. the case for the ubiquitous recombinase RAD51 and its meiosis-specific paralog DMC1 and the DSB marker phospho-histone H2AX [52, 53, 86–88]. Mice deficient of SPO11 or DMC1 are sterile and display synapsis failure. Spermatocytes in these animals arrest in a zygotene-like stage, while oocytes undergo apoptosis at pachynema in *Dmc1*$^{-/-}$ females and at dictyate in *Spo11*$^{-/-}$ females [19, 20, 52, 53].

Recently, the human *SPO11* gene has been linked to azoospermia with two azoospermic patients displaying heterozygous missense mutations in exon 1 and exon 9, respectively [54]. A Chinese study disclosed a heterozygous mutation in exon 7 of *SPO11* in 8 males with idiopathic infertility [55]. Thus, heterozygous mutations in *SPO11* have dominant effects and can lead to infertility in humans. For *DMC1* a homozygous mutation was identified that occurred in individuals with premature ovarian failure [21].

Bloom's syndrome (BS) involves defective DNA repair and is caused by mutations in the *BLM* gene, coding for a RecQ helicase. During meiotic recombinogenic DNA repair *BLM* and the single strand binding protein RPA become abundant when RAD51/DMC1 foci start to decline as prophase I progresses [88]. Male patients are sterile and females have reduced fertility, while all patients are immunodeficient, sensitive to UV radiation and cancer predisposed. A conditional mutant mouse model of *Blm* displays meiotic chromosome pairing defects, an increased recombination rate and apoptosis of spermatocytes at metaphase I [15].

The MRN complex (MRE11, RAD50 and NBS1) is binding to and processing DSBs. Mice with an N-terminal truncation of the NBS1 protein display normal spermatogenesis, while females are infertile due to degeneration of ovaries and a lack of oocytes and follicles in adult animals. This reflects the situation in human Nijmegen breakage syndrome (NBS) patients, where impaired oogenesis also has been observed [46]. Hypomorphic *Mre11* and *Nbs1* mutant mice are both subfertile [89, 90]. Spermatocytes and oocytes are delayed in zygonema and display defects in synapsis [36].

In response to DSBs the histone H2 variant H2AX is phosphorylated by ATM and other DSB responsive kinases (DNA-PKcs, ATR) at its C-terminus (then called γ-H2AX; [91]). Mice mutant for *Atm* display infertility, synapsis defects (Fig. 1B) and altered telomere behaviour in prophase I [10, 78, 92]. In pachytene and diplotene spermatocytes γ-H2AX marks the sex body containing the X and Y chromosomes that only synapse at the small pseudoautosomal region [93], while γ-H2AX contributes to the inactivation of the sex chromosomes

during male prophase I [32]. *H2ax*-deficient mouse spermatocytes display normal deposition of early markers for recombinogenic DNA repair (RAD51/DMC1) and homologues undergo synaptic paring, but there is prolonged meiotic telomere clustering (bouquet formation) and *H2ax*$^{-/-}$ spermatocytes arrest in pachytene stage, leading to male infertility [33, 94].

Meiotic sex chromosome inactivation in males is also compromised in mice deficient for the tumor suppressor BRCA1 [16] and fails in knockout mice for the fast DNA repair enzyme PARP2. *Parp2*$^{-/-}$ mice also display MI missegregation and defective spermatid chromatin remodelling [47]. Like for the *H2ax*$^{-/-}$ mice only male meiosis is affected in mutants of *Brca1* and *Parp2*. However, while *H2ax*- and *Brca1*-mutant spermatocytes arrest in pachynema [32, 33], *Parp2*$^{-/-}$ mice are subfertile due to increased apoptosis at pachytene and MI stages and defective spermatid elongation [47, 95].

The *BRCA1* tumour suppressor gene product is involved in DSB processing in meiosis. BRCA1 expression declines in aged mouse oocytes and RNAi-mediated reduction of this protein in oocytes from young animals results in perturbed spindle formation and chromosome congression failure, leading to aneuploidy [96, 97]. Thus, a decrease of BRCA1 expression with age may be a factor contributing to an increase of aneuploides with advanced maternal age. In the human, BRCA1 seems to be of importance for fertility, since *BRCA1* mutations in women have been observed to be associate with primary ovarian insufficiency [17]. However, more data are needed before this observation can be settled.

Fanconi anemia (FA) is an inherited disease due to compound heterozygosity characterized by reduced fertility or sterility, congenital anomalies, growth retardation, aplastic anemia and an increased risk of leukemia and squamous cell carcinomas. FA patients carry mutations in FANC genes whose proteins are part of the FA DNA repair pathway. Defects in the FA pathway leads to genomic instability and compromised repair of DNA crosslinks and replication error-induced DSBs. To date, five mouse models of FANC proteins have been created (*FancA, FancC, FancD1(Brca2), FancD2* and *FancG* knockout mice) and in all there are fertility defects like hypogonadism, impaired gametogenesis and reduced fertility or sterility (Tab. 1), thus mirroring the human situation (for review see [98]). *FancA*$^{-/-}$ and *FancD2*$^{-/-}$ mouse spermatocytes display an increased frequency of mispaired meiotic chromosomes suggesting a role for the FANC proteins in DNA repair during meiotic recombination [22, 29]. *FancD1*$^{-/-}$ *(Brca2*$^{-/-}$*)* spermatocytes arrest at zygonema with abnormal recombination, as there are fewer RAD51 and DMC1 foci than in the wild type [27]. In the human the polymorphism p.N372H in *BRCA2* may be associated with azoospermia or severe oligozoospermia, as the H allele frequency is significantly increased in men with such diagnoses [28].

Mismatch repair (MMR) contributes to maintenance of genomic integrity and for correcting DNA replication errors in somatic cells while it participates in crossing over in meiosis. A meiosis-specific mismatch protein, MSH4, heterodimerises with MSH5 [45, 99] and appears at recombination sites in zygonema [100]. At mid-pachynema MSH4 interacts with MLH1 and MLH3 [101]. The MLH1 and MLH3 proteins are associated with late recombination nodules that are known to correlate with crossover sites [88, 101]. Both genders of *Mlh1*$^{-/-}$ and *Mlh3*$^{-/-}$ mice are sterile [38, 41]. Males of both genotypes arrest in the first metaphase. *Mlh1*$^{-/-}$ oocytes fail to complete the second cell division [38], whereas a small proportion of abnormal *Mlh3*$^{-/-}$ oocytes extrude both the first and second polar body [41].

Mice deficient of MSH4 and MSH5, respectively, have also been engineered and are sterile in both sexes due to pairing defects and arrest in zygonema [44, 45]. A recent search for MSH4 mutations in patients displaying maturation arrest of spermatogenesis, however, failed to reveal mutations [7], but decreased relative MMR gene transcript levels (*MLH1, MLH3, MSH4, MSH5*) were noted in men with spermatogenic failure [102]. A combination of a missense mutation and an intronic variant in the *MLH3* gene was detected in male patients with primary meiotic arrest and has been suggested to predispose to spermatogenic arrest [42]. Interestingly, men with this missense mutation (C2531T) in *MLH3* or the polymorphism C85T in the *MSH5* gene have an elevated risk of infertility and both polymorphisms may act synergistically [43]. Finally, a heterozygous missense mutation in the *MSH5* gene was detected in two women with premature ovarian failure [21]. Altogether, these data underline the importance of MMR for human fertility.

While there are many more gene products known to contribute to DSB processing and recombinational repair, it is clear that perturbations in this complex process have dire consequences for fertility, as represented by reproductive failure in most knockout animals for recombination proteins (Table 1; also see Refs [3, 68, 103]).

Meiotic Chromosome Structure and Fertility

Another central process for execution of the meiotic process is the establishment of a meiosis-specific chromosome structure and the maintenance of cohesion that tightly holds sister chromatids and homologous chromosomes together during prophase I. This is accomplished by cohesin and SC proteins. At the onset of meiosis there is assembly of proteinaceous axial elements along sister chromatids, which include cohesin complex molecules that hold sister chromatids together, and meiosis-specific proteins like e.g. SYCP3 and SYCP2. Axial elements are then connected by synaptonemal complex proteins like SYCP1 and the like (see below). SC formation solidifies homolog pairing, facilitates meiotic recombination and crossover formation giving rise to chiasmata that allow for homologue segregation at metaphase I [72, 104].

The cohesin complex consists of ubiquitous components, i.e. 2 SMC subunits, SMC1α and SMC3. In gametogenesis the meiosis-specific SMC1β cohesin appears and also forms a heterodimer with SMC3, while SMC1α expression is diminished. The heterodimer has a V-like structure that is closed to a ring by a kleisin, SSC1/RAD21 or the meiosis-specific REC8. Further components of the cohesin complex are SA1, SA2 or the meiosis-specific STAG3 that bind to the kleisin subunit of the complex [105]. Besides REC8- and SSC1/RAD21-con-

taining complexes there are also RAD21L cohesin complexes at mutually exclusive sites [106]. Through its ring-like structure the cohesin complexes hold sister chromatids together and form the axial elements of meiotic chromosomes, the resolution of which depends on polo-like kinase I and the protease separase [106, 107]. Prior to the onset of anaphase separase is inhibited by securin that itself is degraded after ubiquitination by the anaphase promoting complex [108]. In the metaphase to anaphase transition of meiosis I cohesin is lost from sister chromatids when the phosphorylated REC8 cohesin subunit along the chromosome arms is cleaved by separase. Centromeric cohesion is protected by Shugoshin in association with protein phosphatase 2A up to the metaphase/anaphase II transition. Then, loss of centromere cohesion at the metaphase anaphase transition allows sister chromatids to separate in metaphase II [109, 110].

SMC1β and REC8 cohesin-deficient mice have been generated and are sterile in both sexes [48, 49, 51]. REC8-deficient mice display apoptotic germ cells at a zygotene-like stage. Other cohesin subunits bind to the chromosomes that are shorter in length compared to wild-type, but homologous chromosomes do not synapse. Early recombination foci do form, but late nodules are absent [48, 49]. The phenotype of the Smc1β-deficient mice, similarly involves hyper-condensed prophase I chromosomes (Fig. 1D) and often synapsis defects. Spermatocytes arrest at mid-pachynema, whereas oocytes can reach metaphase II [51]. While *Smc1β*$^{-/-}$ spermatocytes initiate but never complete recombination, oocytes display less chiasmata at MI [51]. In aging *Smc1β*$^{-/-}$ oocytes chiasmata distribution is skewed towards the distal chromosome end leading to increasing numbers of univalents and single sister chromatids in older metaphase oocytes [111]. Oocyte chromosomes of senescence accelerated (SAM) mice display a decline of *Smc1β*, REC8 and STAG3 proteins, which results in increased single chromatids, misalignment on the metaphase spindle and segregation failure [112, 113]. In accordance with the theory that the absence of cohesin turnover leads to the attenuation of cohesion with age, oocytes from aged mice display less and mostly distally located chiasmata and an increase of univalents [111]. This theory is further bolstered by failure of endogenous REC8 reloading in engineered mice that express the REC8 protein with an artificial cleavage site [114]. Likewise results with *Smc1β*$^{-/-}$ mice that express a mutant form of the protein only after prophase I display normal oocytes, indicating that cohesin only required in first meiotic prophase as oocytes from these mice appear normal [115].

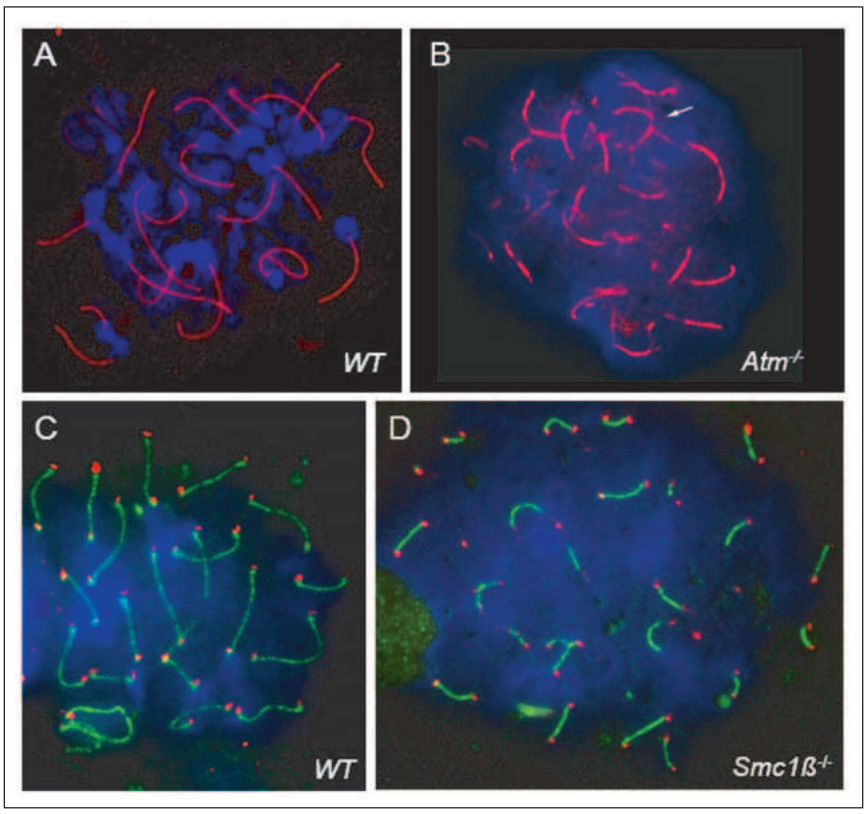

Figure 1. (A): Pachytene chromosome axes (SCs) of a wild-type mouse revealed by SYCP3 immunostaining **(B):** Atm$^{-/-}$ zygotene-like spermatocyte which displays pairing errors (arrow). In this condition SC formation is never complete. For details see [78]. **(C):** Wild-type spermatocyte stained for the cohesin subunit STAG3 (green, SCs) and fluorescence in situ hybridization of telomeres (red). Wild-type chromosome axes (SCs) are long and capped by a distinct telomere signal. **(D):** In the Smc1β$^{-/-}$ spermatocyte, chromosome axes and SCs are hyper-condensed and significantly shorter than in the wild type. For details see [79]. Magnification 630× in the original.

Cohesin appears to be a crucial component player of female meiotic prophase chromosomes from which it is lost with age. Cohesin loss can lead to premature chromosome and sister chromatid segregation and thus aneuploid oocytes. If this scenario extends to humans as well, this might be one explanation for the higher frequency of aneuploidy in pregnancies and newborns of mothers with advanced age. So far, only mRNA measurements of cohesin have been performed in human oocytes of different age, but failed to reveal a correlation [116]. Since experiments in mice showed that the mRNA levels in young and old oocytes remained the same but the chromosome-associated protein diminished [117], it seems that it is chromosome-bound cohesin that is important for oocyte health.

The Importance of the Synaptonemal Complex to Fertility

Cohesin cores run along meiotic chromosomes (see above) and lay the basis for generation of a protein zipper, the synaptonemal complex (SC; Fig. 1) that connects two homologous chromosomes by transverse filaments (TFs) which reach between the lateral elements (LEs) along each homologue. Between the LEs a central element (CE) can be discerned. The SC protein SYCP1 is a TF protein whose N-terminal end is connected in the central element by SYCE1, SYCE2 and TEX12 [57, 118, 119], while the C-terminal end of SYCP1 binds to each of the opposing LEs that contain the LE proteins SYCP2 and SYCP3 [59]. Mice mutant for CE or LE proteins are sterile in the male sex owing to synapsis failure

and spermatocyte death during a zygotene-like stage [59, 120–125], while SYCP2 and SYCP3-deficient females are subfertile with ~50% reduced litter sizes [59, 60]. For the *Sycp3*$^{-/-}$ mutant it has been shown that there is a maternal age-dependent intrauterine embryo death, which possibly relates to reduced chiasmata numbers and presence of univalents in MI oocytes that can lead to aneuploidy in oocytes and consequently zygotes after fertilization [60].

Several studies revealed *SYCP3* mutations in infertile men. A heterozygous mutation in *SYCP3* has been found to be associated with a lack of postmeiotic cells and azoospermia [7, 61]. In women mutations in *SYCP3* have been associated with recurrent pregnancy loss because of aneuploidies [62]. This condition mirrors the findings in the *Sycp3*$^{-/-}$ mice described above. Furthermore, a homozygous mutation that does not cause an amino acid substitution has been found in two infertile patients, and this SNP frequency is significantly higher in infertile women than in control patients [63]. Thus, this variant may be associated with an increased risk for infertility. Further investigations of more meiotic genes have the potential to disclose a deeper insight in the role of meiotic proteins in human infertility.

The Importance of the Nuclear Envelope in Meiotic Differentiation

Finally, the process of meiotic chromosome pairing and telomere mobility requires an intact nuclear envelope [126]. Spermatocytes that lack the meiosis-specific Lamin C2 at the inner nuclear membrane (*Lmna*$^{-/-}$ mice) [127] display a failure of meiotic sex chromosome pairing and a dramatic increase in apoptosis during the late pachytene stage leading to a breakdown of spermatogenesis [35]. However, female *Lmna*$^{-/-}$ gametogenesis and fertility remain unaffected. During early prophase I telomeres attach to the nuclear envelope [77] through an interaction with the transmembrane protein SUN1. When this process fails, as in *Sun1*$^{-/-}$ mice, infertility ensues in both sexes due to pairing failure and defective recombination [56] underlining the importance of a normal nuclear envelope and telomere behaviour for the meiotic process.

Conclusions

Infertility in man is largely of unknown origin. Hence, knowledge about meiotic mouse models can guide the search for genes that play a role for idiopathic infertility in the human situation. In relation to the long list of mouse mutants displaying spermatogenic and oogenic failure (Tab. 1) [3], so far only a few infertility cases and syndromes have been noted where the underlying genetic defect could be disclosed. Using the compiled knowledge in model organisms has the potential to extend diagnostics for human patients and hence may provide new insights in the aetiology of infertility.

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Conflict of Interest

The authors declare no conflict of interest.

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