Exploring meiotic division in Cargèse

Meeting on Meiotic Divisions and Checkpoints

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The EMBO workshop on 'Meiotic Divisions and Checkpoints' was organized by C. Jessus, M.H. Verlhac, T. Hunt and A. Nebreda and took place in Cargèse, France, between 16 and 20 March 2005.

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and transverse filaments (Fig 1; Page & Hawley, 2004). The lateral elements comprises cohesins (Rec8/C(2)M/SYN1, STAG3/Rec11, SMC1-b and SMC3), the structural proteins SCP2 and SCP3, and the HORMA-domain proteins Hop1/HIM3/Asy1 and Red1; the transverse filaments are formed by the proteins Zip1, SCP1, C(3)G and SYP1. Once the synaptonemal complex is assembled, crossover recombination events take place between homologous partners. Crossovers form temporary connections or chiasmata that hold homologues together and allow their correct attachment to the meiosis I spindle. However, in most vertebrate oocytes, spindle I formation and germinal vesicle breakdown (GVBD) is preceded by an arrest at prophase I. This arrest is maintained until progesterone stimulates re-entry into the meiotic cycle by inducing the polyadenylation and translation of several dormant mRNAs that encode proteins such as Mos or cyclin B. Translation of Mos and cyclin B activates the maturation-promoting factor (MPF) and thereby induces spindle formation and GVBD. Homologous chromosomes then attach to the spindle and when aligned correctly along the metaphase plate, they segregate—a process that in some species is regulated, at least in part, by the ubiquitin-dependent degradation of different substrates by the anaphase-promoting complex (APC; Tunquist & Maller, 2003). Subsequently, oocytes go through meiosis II and arrest at metaphase II owing to the cytostatic factor (CSF) until fertilization, which finally induces exit from metaphase II and cytokinesis. The correct completion of all these meiotic events is assured by various checkpoints, such as the DNA-damage checkpoint at pachytene stage and the spindle checkpoint at metaphase–anaphase transitions.

In the opening lecture of this meeting, T. Hunt (Herts, UK) began by honouring Andre Picard, one of the pioneers of the study of meiotic division in starfish, who died in November 2004. Hunt then introduced some of the key mechanisms that regulate meiotic and mitotic cell cycles, such as the control of MPF activity by cell-division-cycle protein 25 (Cdc25), Wee1, CDK-activating kinase (CAK) and the APC, the activity of CSF, the role of the different cyclins and the regulation of cyclin B/Cdc2 and cyclin A/Cdc2 by the spindle checkpoint. Finally, he highlighted some unanswered questions, including the identity of the calmodulin kinase II substrate on metaphase II exit, the elucidation of the mechanisms that regulate APC activity, the identification of the phospho-protein pattern that is present during meiosis and mitosis, and the role of the

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Introduction

Meiosis is a special type of cell division through which haploid gametes are generated from diploid parent cells. This is accomplished by a first division that induces homologous chromosome segregation followed by a second mitosis-like division that promotes sister chromatid separation. During the prophase of meiosis I, three basic events take place: pairing of homologous chromosomes, synapsis and recombination. Pairing or alignment of homologous chromosomes allows chromosome stabilization by the formation of the synaptonemal complex, whereas synapsis facilitates the subsequent recombination events. The synaptonemal complex is a proteinaceous structure formed by lateral elements

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Fig 1 | Model of the synaptonemal complex structure. The synaptonemal complex (SC) is a proteinaceous structure formed by a lateral element (LE), central element (CE) and transverse filaments. The LE comprises cohesins (Rec8/C(2)M/SYN1, STAG3/Rec11, SMC1- β and SMC3), the structural proteins SCP2 and SCP3 and the HORMA-domain proteins Hop1/HIM3/Asy1. The transverse filaments are formed by the proteins Zip1/SCP1/C(3)G/SYP1. (Adapted with permission from Page & Hawley (2004) *Annual Review of Cell and Developmental Biology* 20 ©2004 by Annual Reviews www.annualreviews.org).

spindle poles versus the kinetochores in the segregation of homologous chromosomes and sister chromatids.

In this summary of the meeting, we focus on new data reported about the mechanisms that control meiosis. The article is divided into six parts that reflect the phases of meiotic division wherein important new findings have been elucidated. These include pairing of homologous chromosomes, prophase I arrest, spindle formation, homologous chromosome segregation, CSF arrest and meiotic checkpoints.

Pairing of homologous chromosomes

One of the first features observed in early prophase is the extensive reorganization of the chromosomes in the nucleus, which results in telomeres clustering at the nuclear envelope. This organization, known as a 'bouquet', has been proposed to facilitate the subsequent pairing of homologous chromosomes (Zickler & Kleckner, 1998). M. Shimanuki (O. Niwa's group, Okinawa, Japan) introduced a model for the mechanism of bouquet formation in *Schizosaccharomyces pombe*. In this model, the complexes that connect telomeres to cytoplasmic microtubules through the nuclear envelope first form at multiple sites on the nuclear envelope. Telomeres are then pulled towards the spindle pole body (SPB) in concert with microtubule nucleation. In accordance with this model, Shimanuki showed the colocalization of cytoplasmic microtubules, dynein, telomeres and the transmembrane component of the SPB, Sad1, at several sites of the nuclear envelope before bouquet formation. Moreover, he showed that, in two mutants in which the telomere–Sad1 complex was disrupted, the telomeres did not move towards the SPB and therefore abnormal chromosome segregation was induced.

Some proteins of the axial elements of the synaptonemal complex are also required to control chromosome pairing. Using *Caenorhabditis elegans*, A. Villeneuve (Stanford, CA, USA)

determined the roles of one of these proteins, high incidence of males-3 (HIM-3), in the establishment of initial contacts between homologues and in the coordination of these events with the subsequent assembly of the synaptonemal complex. She showed that *him-3* mutants fail to establish homologue pairing and that this is associated with a reduced amount of the HIM-3 protein on chromosome cores and with a subsequently reduced staining of one of the proteins of the transverse filaments of the synaptonemal complex, synaptonemal protein-1 (SYP-1). However, SYP-1 was also present in a significant proportion of non-paired chromosomes, which indicates that in *him-3* mutants, synapsis occurs between non-homologous chromosomes. Villeneuve also showed that the *him-3* mutant can initiate and resolve sites of recombination, which indicates that neither the HIM-3 protein nor homologue pairing is a prerequisite for the initiation of recombination and that this mutant uses sister chromatids as a repair template.

Prophase I arrest

Most vertebrate oocytes are arrested at the prophase of meiosis I and progesterone stimulates re-entry into meiotic division by inducing oocyte maturation. Oocyte maturation has been mainly studied in *Xenopus laevis*. In this species, progesterone induces the polyadenylation and translation of several dormant mRNAs that encode proteins such as Mos or cyclin B. Cytoplasmic polyadenylation requires two 3' untranslated region (UTR) elements and a cytoplasmic polyadenylation element (CPE), the latter being bound by the CPE-binding protein (CPEB). CPEB also binds to Maskin, a protein that interacts with the translation initiation factor eIF4E. This disrupts the eIF4E–eIF4G complex and inhibits mRNA translation. A previous model put forward by J. Richter (Worcester, MA, USA) proposed that progesterone stimulation induces the activation of CPEB through its phosphorylation by Aurora A. This activation could cause the recruitment of the cleavage and polyadenylation specific factor (CPSF) and result in the attraction of poly(A) polymerase to the end of the mRNA and polyadenylation. In this meeting, Richter presented new data that considerably modify this model (Richter & Sonenberg, 2005). By using immunodepletion/rescue and polyadenylation assays in *Xenopus* egg extracts, he described the presence of two new factors that are essential for polyadenylation: Symplekin and an unusual poly(A) polymerase, xGLD2. In the newly proposed model, the CPEB–CPSF–Symplekin–xGLD2 complex is stable, and stimulation with progesterone induces the phosphorylation of CPEB by Aurora A. This causes a conformational change in CPEB, which increases its affinity for CPSF and activates xGLD2. However, no role for Maskin was proposed. Intriguingly, C. Prigent (Rennes, France) showed that Maskin is phosphorylated *in vitro* by Aurora A and that the inhibition of this phosphorylation by the microinjection of an Aurora A-specific inhibitor in *Xenopus* oocytes accelerates maturation induced by progesterone, as well as the massive production of proteins such as cyclin B1 and Cdc6, the translation of which is regulated by Maskin. Therefore, the involvement of Maskin and Aurora A in the control of cytoplasmic polyadenylation in oocytes still needs to be clarified. The function of the poly(A) polymerase GLD2 in the elongation and stabilization of maternal mRNAs was also reported in *Drosophila*. By using *Gld2* mutant females, P. Benoit (M. Simonelig's group, Montpellier, France) showed that this protein is required for poly(A) tail elongation as well as stabilization of the maternal

mRNAs *oskar*, *nanos* and *bicoid*. Moreover, she reported that, in this mutant, eggs did not develop owing to a metaphase–anaphase arrest of the first meiotic division. Thus, GLD2 seems to be the poly(A) polymerase implicated in mRNA cytoplasmic polyadenylation induced by progesterone during oocyte maturation.

Besides the study of the mechanisms that control mRNA polyadenylation in response to progesterone, the search for the specific proteins that are subsequently synthesized and that induce the activation of MPF and meiotic resumption has been an important goal for many years. O. Haccard (C. Jessus's group, Paris, France) addressed this topic by studying the effect of a block of either the *Mos*/Mapk/p90rsk or the cyclin B synthesis pathways on the activation of MPF. He showed that the separate inhibition of either *Mos*/Mapk/p90rsk by the microinjection of *Mos* morpholinos or by the meiosis-specific Ser/Thr protein kinase MEK inhibitor U0126, or of cyclin B neo-synthesis by microinjection of cyclin B antisense oligonucleotides did not prevent oocyte maturation. By contrast, the concomitant block of both pathways completely prevented meiotic resumption in response to progesterone. Haccard proposed that the activation of one of these two pathways is sufficient to induce oocyte maturation.

However, there is also another newly synthesized protein, RINGO, that is required to induce oocyte maturation. The function of this protein was described by A. Nebreda (Madrid, Spain). His group has previously shown that depletion of RINGO in prophase I impairs oocyte maturation and that its overexpression can induce meiotic resumption in the absence of progesterone, probably through the activation of Cdk. Here, he presented data showing that RINGO levels are controlled by ubiquitylation/degradation and that RINGO degradation after metaphase I is required to prevent the occurrence of DNA replication during meiosis. He also showed results suggesting that partial proteolysis might be another mechanism that regulates RINGO function in oocytes. Hence, the identification of newly synthesized proteins that are required for cyclin B/Cdk1 activation as well as the exact regulatory mechanisms of this pathway still need to be unravelled.

Spindle formation

One of the most striking differences between the meiotic and mitotic spindles is the absence of centrosomes in the spindle poles of the former. H. Ohkura (Edinburgh, UK) addressed this topic by analysing acentrosomal spindle formation in female *Drosophila* mutants. He described three mutants that are affected in various aspects of spindle formation. The first, named *Mini spindles* (*Msp*s), has tripolar spindles and is mutated in a gene that encodes the MSPS protein, a mitogen-activated protein. The second, named *Remnants* (*Rem*), carries a mutation in a gene that encodes a homologue of the Cks/Suc1 protein. *Rem* mutants show chromosome misalignment and spindle malformation as well as a mislocalization of the MSPS protein and the transforming acidic coiled-coil protein (D-TACC) at the metaphase plate. In the third mutant, named *Triplet*, each spindle is formed from three chromosomes. The mutated gene in *Triplet* encodes nucleosomal histone kinase 1 (NHK1). Ohkura proposed different roles for each of these three proteins: MSPS could be required to stabilize the poles; *Triplet* (NHK1) could regulate spindle unification; and *Rem* (Cks) could control spindle organization and chromosome alignment in acentrosomal spindles.

Homologous chromosome segregation

The control of homologous chromosome segregation was discussed at the meeting by several speakers. This process depends not only on the mechanisms that directly control metaphase–anaphase transition, but also on the correct development of preceding processes such as chromosome condensation, chromosome pairing, synapsis and recombination.

T. Orr-Weaver (Cambridge, MA, USA) emphasized the role of chromosome condensation in the segregation of homologues. She showed that *Drosophila* mutated in the gene that encodes the condensin DCap-G recombine normally but present an abnormal metaphase I arrest with decondensed chromosomes. W. Earnshaw (Edinburgh, UK) reported further on the role of chromosome structure in chromosome segregation by pointing out that in male *Drosophila* meiotic division, mutants of the passenger protein inner centromere protein (INCENP) present defects in meiotic chromosome condensation and alignment, central spindle assembly, chromosome segregation and cytokinesis. Finally, he showed that these mutants are impaired in the maintenance of bivalent integrity and chromatid cohesion, a phenotype that might be associated with the requirement of INCENP for the stable localization of the kinetochore protein Mei-S332 (Shugoshin) in the centromeres of meiotic chromosomes.

The implication of the synaptonemal complex in the segregation of homologous chromosomes was another of the topics covered by T. Orr-Weaver. She presented results showing that in the *Drosophila* *Nmr4* mutant, C(3)G, a component of the transverse filaments of the synaptonemal complex, dissociates incorrectly from the chromosomes and that this induces a phenotype in which chromosomes are dispersed on the oocyte instead of being grouped in the karyomer. C. Höög (Stockholm, Sweden) also showed that the lack of the synaptonemal complex protein Scp3 in mice promotes aneuploidy in oocytes because of a failure to establish chiasmata between homologous chromosomes. In *Scp3*^{−/−} mice, Scp2 localizes to nuclear foci rather than to filaments in pachytene oocytes and cohesins dissociate abnormally from the chromosome during the diplotene stage.

One of the mechanisms that promotes chromosome segregation at the metaphase–anaphase I transition is the ubiquitin-dependent degradation of different substrates by the APC during this phase of the meiotic division. The implication of the APC in this process seems to be species-specific, as it has been shown to be involved in the separation of homologues in yeast, worm and mouse (Salah & Nasmyth, 2000; Terret *et al*, 2003) but not in frogs (Peter *et al*, 2001; Taieb *et al*, 2001). Two talks addressed the role of the APC in the transition from metaphase I to anaphase I by describing the mutants of two APC regulators. First, Orr-Weaver reported results showing that *Drosophila* females mutated in the *Cortex* gene are sterile and present a defect in meiosis I segregation. *Cortex* encodes a distant member of the Cdc20 family and could be a female meiotic-specific activator of the APC. Second, T. Oelschlaegel (W. Zachariae's group, Dresden, Germany) introduced Mnd2, a new *Saccharomyces cerevisiae* APC inhibitor that is required in S phase and meiotic prophase to prevent APC-dependent proteolysis of the securin Pds1. Mutations in Mnd2 promote aneuploidy because of the premature degradation of Rec8 and an early activation of separase. Mnd2 is required during meiotic prophase to induce cohesin loading, synaptonemal complex formation and to prevent premature separation of sister chromatids through the specific inhibition of the APC–Ama1 complex.

Fig 2 | Model for the generation and maintenance of cytotostatic factor activity. Cytostatic factor (CSF) activity could result from the combined action of four pathways. First, the Mos/MEK/MAPK/p90^{rk}-dependent pathway regulates the Mad1/Mad2/Bub1 spindle checkpoint proteins. Second, the cyclin E/Cdk2-dependent pathway controls the Mps1 spindle checkpoint protein. The third is dependent on Emi1, which in turn is regulated through phosphorylation by Plx1 and through isomerization by Pin1. The fourth depends on the Erp1/Emi2 protein, which, similarly to Emi1, is controlled through phosphorylation by Plx1. A putative synergic activity or interaction of Emi1 and Erp1 cannot be excluded.

Finally, J. Liu (Ottawa, Canada) introduced a new role for the small G protein Cdc42 in the regulation of the transition from metaphase I to anaphase I in *Xenopus laevis* and mouse oocytes by showing that Cdc42 inhibition by microinjection of a dominant-negative mutant form blocked anaphase I initiation.

Cytostatic factor arrest

The identity of the CSF—the biological factor responsible for metaphase II arrest in vertebrate oocytes—provided the topic for one of the most lively debates of the meeting. Clear, controversial results about the participation of the APC inhibitor Emi1 in CSF arrest were presented by different speakers (Fig 2). The role of Emi1 in CSF arrest was first described by Reimann and colleagues (Reimann & Jackson, 2002). This result was subsequently questioned by Ohsumi and co-workers (Ohsumi *et al*, 2004), who did not detect the Emi1 protein during oocyte maturation or in the first division of embryonic cells. P. Jackson (Stanford, CA, USA) presented data showing that four different antibodies developed against Emi1 recognize a band at the expected molecular weight of endogenous Emi1 in extracts derived from cells in metaphase II arrest and that these antibodies immunoprecipitate *in vitro*-translated Emi1 protein. However, he also showed that they could recognize the Emi1-related protein (Erp1/Emi2). Erp1/Emi2 has been recently identified in *Xenopus* oocytes as a powerful APC inhibitor that is also required for maintaining metaphase II arrest (Schmidt *et al*, 2005; Tung *et al*, 2005). Therefore, Jackson did not exclude the possibility that exit from CSF arrest induced by Emi1 immunodepletion could be the result of the indirect depletion of Erp1/Emi2. T. Lorca (Montpellier, France) also presented data that showed the presence of Emi1 in *Xenopus*

oocytes. By using a different anti-Emi1 antibody, he detected the protein at constant levels in maturing oocytes and, in agreement with the results of Jackson, he observed exit from metaphase II after Emi1 depletion from CSF egg extracts. In accordance with Ohsumi and colleagues (Ohsumi *et al*, 2004), he also showed that ectopically expressed Emi1 is degraded rapidly in these oocytes. However, he demonstrated that endogenous Emi1 protein is protected from degradation by the peptidyl-prolyl isomerase Pin1 in the physiological situation in which its degradation pathway is constitutively active. The presence of Emi1 in maturing oocytes was also discussed by J. Maller (Denver, CO, USA), who showed western blot data indicating that Emi1 is present in stage VI oocytes but not in metaphase I- or metaphase II-arrested oocytes. Further studies are required to establish the role of Emi1 in CSF arrest.

The role of other proteins in CSF arrest was also discussed by Maller. He showed data indicating that two different pathways could also participate in this arrest in *Xenopus* oocytes. The first pathway depends on cyclin E/Cdk1 and the spindle checkpoint protein Mps1, and the second on Mos/Mapk/p90^{rk} and the Mad1, Mad2 and Bub1 spindle checkpoint proteins. The role of Mos/Mapk/p90^{rk} in CSF arrest in mouse and starfish eggs was also raised by M.H. Verlhac (Paris, France) and T. Kishimoto (Yokohama, Japan). Verlhac showed that, unlike in *Xenopus*, the injection of RNA that encodes constitutively active mutant Rsk1 and Rsk2 in mouse two-cell embryos does not induce cell-cycle arrest. Moreover, these two mutant forms do not restore metaphase II arrest when microinjected into *mos*^{-/-} oocytes. Finally, oocytes from triple *Rsk1/2/3* knockout mice undergo meiotic maturation and arrest properly at metaphase II. These data indicate that Rsk is not implicated in metaphase arrest in mouse oocytes. Kishimoto showed that Mos/Mapk/p90^{rk} is necessary and sufficient to arrest starfish oocytes at G1 in which mini chromosome maintenance (Mcm) proteins but not Cdc45 are already loaded onto the chromatin. Therefore, he concluded that this pathway might induce G1 arrest in these oocytes by preventing DNA replication through inhibition of the loading of Cdc45 onto chromatin.

In summary, CSF activity could result from the combined action of four pathways: the Mos/MEK/MAPK/p90^{rk}-dependent pathway that regulates the spindle checkpoint proteins Mad1/Mad2/Bub1, the cyclin E/Cdk2-dependent pathway that controls Mps1, the Emi1-dependent pathway and the Erp1/Emi2-dependent pathway (Fig 2).

Finally, two speakers focused on the mechanisms that regulate the first embryonic cell division. J. Ferrel (Stanford, CA, USA) raised the important role of the feedback mechanisms that are required to generate the Cdc2 and APC oscillations that are essential for correct cell-cycle division. By using cycling *Xenopus* egg extracts, he showed that a modification of the feedback loop that controls Cdc2 activation induced by either the addition of Cdc2 activation factor or by Wee1 OP11 mutants, clearly modifies Cdc2 oscillations, compromises subsequent activation of cyclin B destruction and interferes with mitotic exit and DNA replication. B. Maro (Paris, France) presented data on the initiation of polarity in mouse oocytes during meiotic maturation. He showed video microscopy images of two-cell mouse embryos showing that these cells do not change orientation until cleavage. In late metaphase and anaphase, the spindle poles are anchored to the cortex and the forming daughter cells then change their relative positions only at the time of cleavage. These results indicate that the cleavage planes are randomly orientated in mouse two-cell embryos.

Meiotic checkpoints

The successful completion of these meiotic events is monitored by various checkpoints, such as the DNA-damage checkpoint at pachytene stage and the spindle checkpoint at metaphase–anaphase transitions.

Meiotic recombination causes severe DNA damage that must be repaired before the segregation of chromosomes at meiosis I. The pachytene checkpoint ensures that this is the case (Roeder & Bailis, 2000). In yeast, this checkpoint prevents entry into meiosis I when DNA damage has not been repaired by preventing the activation of CDK through the activation of Wee1 and the inhibition of cyclin transcription. Once the damage has been repaired, protein phosphatase 1 (PP1) induces recovery from checkpoint arrest. A. Hochwagen (A. Amon's group, Cambridge, MA, USA) revealed that the proline isomerase Fpr3 binds and inhibits PP1, which prevents recovery of checkpoint arrest before DNA repair has taken place. A. Gartner (Dundee, UK) presented a new mechanism in *C. elegans* that induces germ-cell death in response to DNA damage through a cep1/p53-dependent pathway. He showed that only late pachytene cells die in response to this checkpoint signal. In the *op236* mutant, which corresponds to a point mutation in the translational repressor germline development-1 (GLD-1), late pachytene cells show an increase in apoptosis that correlates with cep1/p53 upregulation. Gartner demonstrated that GLD-1 binds directly to the 3' UTR of cep1/p53 mRNA and inhibits its translation. Therefore, the presence of GLD-1 in the transition and early pachytene zones, but not in late pachytene cells, prevents translation of the cep1/p53 protein and renders cells refractory to apoptosis in the presence of DNA damage.

Two presentations addressed the roles of various components of the spindle checkpoint in the regulation of the transition from metaphase I to anaphase I. By injecting Mad2 and BubR1 morpholinos into mouse oocytes, M. Herbert (Newcastle-upon-Tyne, UK) revealed that both these proteins have an important function in controlling the duration of meiosis I. Indeed, she showed that meiosis I was shorter in morpholino-injected oocytes compared with controls, which was mirrored by an accelerated onset of the proteolysis of cyclin B and securin. Finally, W. Gilliland (S. Hawley's group, Kansas City, MO, USA) also reported a role for the spindle checkpoint protein Mps1 in meiosis I by showing that the *ald(1)* Mps1 mutant in *Drosophila* represents a clear defect in chromosome segregation, and that this defect is more severe in achiasmate homologues.

Conclusions

This was an excellent meeting with a relaxed and friendly atmosphere, despite the presence of growing controversies in several topics. This ambience was probably largely due to Cargèse, the heavenly location where the meeting took place.

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Many thanks to the meeting organizers and particularly to C. Jessus and M.H. Verlhac for their tireless efforts. We apologize to all the speakers whose work has been omitted due to space limitations, and we look forward to hearing more about advances in understanding the meiotic cell cycle at the next EMBO Workshop on Meiotic Divisions and Checkpoints. A.C. and T.L. are supported by the Ligue Nationale Contre le Cancer.

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