random packing of spherical atoms[8] (Fig. 1b), and the motifs are clusters of atoms that define the vertices of various polyhedra (such as the polyhedra defined in ref. 9). The principle of dense random packing has been elaborated to include the chemical propensity of some elements to bond preferentially to other elements[10]. Experiments have confirmed various aspects of these descriptions of metallic-glass structure[11], but only computer simulations have been able to determine the unique position and element for every atom (see ref. 12, for example). Unfortunately, simulations can model the motions of atoms only at short timescales, and therefore can't really account for the very slow motions of atoms that occur in glasses and glass-forming liquids — thus limiting their ability to predict the atomic structure of glasses.

Yang and colleagues' results (Fig. 1c) are a major step towards experimental confirmation of current models of metallic-glass structure. The authors' structural analysis provides support for a model in which solute atoms (those that occur in small quantities in the glass) are found at the centres of clusters of solvent atoms (which account for the majority of the atoms). The clusters act as 'super atoms' that pack together densely at length scales greater than the atomic scale to form the glass structure[13]. Yang *et al.* show that, in their glass, some of these clusters are densely packed, but others are not. The observed loose packing of some clusters might be a product of the extremely rapid cooling that was used to synthesize the studied glasses, but it could also point to important gaps in current models.

The next experimental challenges are to identify the specific element for every atom, which should be possible for glasses that have a simpler composition than that of the glass in the current study, and to improve the precision of the determined atom positions. Yang *et al.* report a random uncertainty of 21 picometres in the atomic positions (1 pm is 10^{-12} metres). That is a tiny distance, but it represents about 8% of the most common interatomic distance in the glass. Shifts in position of that scale would cause significant changes in the energy of the bonds between the atoms and in the geometries of the super-atom clusters. The uncertainty might also explain why the abundances of polyhedra observed in the current study differ from those predicted by previously reported simulations[12] — if the atoms in the simulations were all randomly shifted by up to 21 pm, the resulting polyhedra distributions could be more similar to those reported by Yang and co-workers. It remains to be seen whether the authors' characterization of the structure (the specific way in which they partitioned atoms into super-atoms, and the packing of those super-atoms) is the best theoretical description of the studied system, and whether solute-centred clusters will become the most useful general description of metallic-glass structures.

Advanced electron tomography promises to substantially advance glass science. The acquisition of complete atomic-structure data for more metallic glasses could provide insights that aid the development of methods for discovering new glass-forming alloys, and could improve our understanding of unusual materials such as polyamorphous[14] and structurally anisotropic[15] glasses. It could also open the way to techniques for characterizing structural defects in glasses; such characterization is currently restricted to defects that have a spectroscopic signature. Technologies such as superconducting quantum bits (used in quantum computers) and the LIGO gravitational-wave observatory are limited by glass defects known as two-level systems[16,17], which can be detected only by their effects, not by their structure. Having the ability to identify defect structures could be a first step towards engineering better materials for various applications. In the meantime, Yang *et al.* have achieved something that glass scientists have dreamt of for at least 90 years[6] — measuring the positions of all the atoms in a glass.

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Molecular biology

A new phase in meiotic cell division

Kevin D. Corbett

The exchange of DNA between pairs of chromosomes is key to sexual reproduction. It emerges that one step in this process — the introduction of DNA breaks by the enzyme Spo11 — relies on condensation of proteins into liquid-like droplets. **See p.144**

Our cells carry two copies of each chromosome, known as homologous chromosomes or homologues, with one inherited from each parent. Sexual reproduction requires the formation of germ cells that have only one copy of each chromosome; the fusion of two germ cells during fertilization restores the original chromosome number in the next generation. Germ cells are formed by a specialized cell division called meiosis, an early step of which involves the segregation of homologues into separate daughter cells. Errors in meiotic chromosome segregation can produce germ cells that have too many or too few chromosomes — a condition called aneuploidy that underlies disorders such as Down's syndrome and is a major cause of miscarriage. On page 144 Claeys Bouuaert *et al.*[1] highlight a key role for a process called liquid–liquid phase separation in the molecular events underlying this crucial biological pathway.

Accurate chromosome segregation in meiosis requires that each chromosome first identify and physically link to its homologous partner. These steps depend on a DNA-repair pathway called homologous recombination, which begins with programmed DNA breakage at a few randomly chosen sites along each chromosome. The broken DNA ends seek out similar sequences on other chromosomes, eventually identifying their homologous partner and establishing physical links called crossovers. Crossovers also enable the exchange of genetic information between homologous chromosomes, ensuring genetic variation between parents and offspring.

The molecular mechanisms that control homologous recombination in meiosis have been studied for more than two decades, since the identification of a set of ten proteins in the

budding yeast *Saccharomyces cerevisiae* that are required for the formation of DNA breaks during meiosis[2]. Four of these proteins make up the Spo11 core complex[3,4], which breaks DNA. Three others form the MRX complex, which mediates post-breakage processing steps[2]. The roles of the remaining three proteins — Rec114, Mei4 and Mer2, together called the RMM complex — have remained mostly mysterious.

RMM-complex proteins physically associate with one another and localize to meiotic chromosomes before most other proteins, suggesting that they are responsible for recruiting the Spo11 core complex to DNA break sites[5]. Claeys Bouuaert *et al.* shed further light on this localization process. The authors purified the *S. cerevisiae* RMM complex for the first time, revealing that Rec114 and Mei4 form a subcomplex that associates with Mer2. The authors then showed that the purified RMM proteins can condense on DNA into liquid-like droplets containing hundreds of copies of each protein.

The tendency of some proteins to condense into liquid-like droplets is known as liquid–liquid phase separation (LLPS), and underlies myriad cellular processes, including genome organization, RNA processing, and diverse signalling pathways[6]. LLPS has already been reported to have a key role in meiosis, driving assembly of the synaptonemal complex, which holds together homologous chromosomes and aids the final steps of recombination and crossover formation[7]. Claeys Bouuaert *et al.* found that purified RMM forms liquid-like condensates on DNA at low-nanomolar concentrations, strongly suggesting that the observed LLPS is key to their biological functions. Bolstering this conclusion, the authors showed that a mutation in Mer2 that prevents it from forming condensates *in vitro* also compromises Spo11-mediated DNA breakage in cells.

In a separate study[4] published this year, Claeys Bouuaert and colleagues' research group reported the first purification and biochemical characterization of the Spo11 core complex — a major step forwards in understanding the molecular mechanisms of meiotic DNA breakage. Taking advantage of this purified complex in the current work, the group showed that RMM condensates recruit the Spo11 core complex to DNA. A mutation in Rec114 that disrupts its binding to the Spo11 core complex also compromises DNA breakage in meiotic cells, indicating that the RMM complex recruits the Spo11 core complex to DNA break sites.

Taken together, these data reveal the RMM complex as a key mediator of meiotic recombination, self-assembling through LLPS to recruit the Spo11 core complex to DNA break sites across the genome (Fig. 1). The high evolutionary conservation of RMM proteins strongly suggests that this mechanism is preserved in most sexually reproducing organisms.

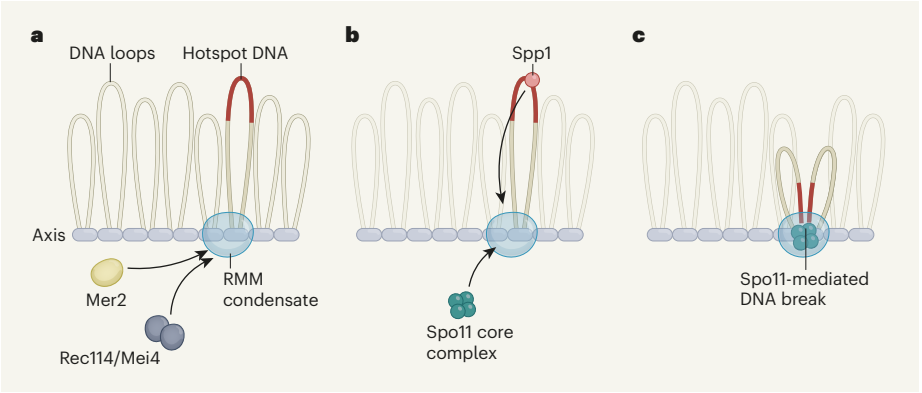

Figure 1 | Unpacking the role of RMM proteins in meiotic cell division. A specialized type of cell division called meiosis produces the germ cells involved in sexual reproduction. **a**, In early stages of the process, chromosomes become organized as arrays of DNA loops around a protein-rich structure called the chromosome axis. Claeys Bouuaert *et al.*[1] report that a protein subcomplex comprising Rec114 and Mei4, along with the protein Mer2, condense into liquid-like droplets (RMM condensates) through a process called liquid–liquid phase separation. **b**, RMM condensates probably recruit DNA regions called hotspots through an interaction with the protein Spp1, and also recruit the Spo11 core complex. **c**, Spo11 catalyses DNA-break formation — a key step in meiosis.

The results also raise several questions. First, how might phase separation regulate the number and distribution of meiotic DNA breaks across the genome? Claeys Bouuaert *et al.* suggest that the condensation of RMM proteins at specific sites along the chromosome might deplete RMM subunits in the surrounding solution, inhibiting the formation of further condensates and thereby limiting the overall number of DNA breaks catalysed in any given cell.

"Liquid–liquid phase separation underlies myriad cellular processes."

Because DNA breaks form mainly at particular 'hotspots' along each chromosome, another question is how RMM cooperates with other meiotic chromosome-associated proteins that help to dictate hotspot locations. These proteins include Hop1, which is part of a protein-rich structure called the chromosome axis that forms in early meiosis. Hop1 helps to organize chromosomes as arrays of DNA loops, and probably recruits RMM to the axis by binding to Mer2 (ref. 8). Chromosome-associated proteins of interest also include Spp1, which recognizes molecular modifications on histone proteins bound to hotspot DNA, and might recruit these sequences to RMM condensates for breakage[8–10].

Finally, it remains unknown whether RMM condensates regulate later steps of meiotic recombination after DNA breakage. For instance, the liquid-like nature of RMM condensates might enable them to specifically recruit or exclude particular DNA-repair factors.

Claeys Bouuaert and colleagues' work marks the start of an exciting 'phase' of research into the fundamental mechanisms of meiotic recombination. Taken together with steady progress in our understanding of meiotic chromosome architecture and dynamics, the stage is set for further advances, including the *in vitro* reconstitution of meiotic DNA-break formation and inter-homologue recombination.

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