develop. They show that the fates of cells in the germinal zone of the rhombic lip are specified both spatially and temporally. Spatial specification comes from molecular domains distributed along the dorsal–ventral[5,6,9] and rostral–caudal axes[3,4,10] (such as those in the spinal neural tube), and temporal specification is established through sequential egress from those domains[1] (Fig. 1).

The specification of progenitors before their dispersal from the germinal zone has a logic to it from a functional perspective. The collection of brain nuclei defined by these coordinated molecular activities, although spatially separated in the adult brain, together constitute components of the proprioceptive system. This is the sensory system that allows the positions of the limbs to be detected in the absence of visual cues. So this dispersed network of functionally cooperative brain structures can trace its origins back to the same continuous strip of germinal tissue.

These studies, particularly the work of Landsberg and colleagues[5], unveil a precise, molecularly defined organization within the rhombic-lip germinal zone. This organization is in keeping with the model already established for the spinal neural tube, where neural sub-domains are characterized by the expression of specific transcription factors, established in response to graded intercellular signals, now extended to include the germinal zones of the brain.

The work relied on powerful genetic techniques for fate mapping developed in the past few years[1,2]. Although accurate fate maps are crucial to our understanding of development, generating them has usually required unfettered access to the developing embryo, prohibiting *in vivo* mammalian fate mapping, and has been limited by the inability to molecularly define the cell population that was labelled initially. Also, because of the difficulty in garnering such data, the development of fate maps in mutant tissues has been unfeasible, so investigators could only speculate about how specific genetic modifications might alter the migratory routes and ultimate fate of specific cell types. As exemplified by the current studies, the new genetic approaches in mice allow cell fates to be correlated precisely with gene-expression domains in both normal and mutant embryos. It is clear that the ever-increasing pace of mammalian genetics will continue to refine our view of the molecules that regulate cellular fate throughout the embryo. ■

Richard V. Pearse II and Clifford J. Tabin are in the Department of Genetics, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, Massachusetts 02115, USA.
e-mail: tabin@genetics.med.harvard.edu

1. Zinyk, D. L., Mercer, E. H., Harris, E., Anderson, D. J. & Joyner, A. L. *Curr. Biol.* **8**, 665–668 (1998).
2. Branda, C. S. & Dymecki, S. M. *Dev. Cell* **6**, 7–28 (2004).
3. Machold, R. & Fishell, G. *Neuron* **48**, 17–24 (2005).
4. Wang, V. Y. *et al. Neuron* **48**, 31–43 (2005).
5. Landsberg, R. L. *et al. Neuron* **48**, 933–947 (2005).
6. Jessell, T. M. *Nature Rev. Genet.* **1**, 20–29 (2000).
7. Lin, J. C. & Cepko, C. L. *J. Neurosci.* **21**, 159–168 (2001).
8. Cumle, D. S., Cheng, X., Hsu, C. M. & Monuki, E. S. *Development* **132**, 3549–3559 (2005).
9. Hoshino, M. *et al. Neuron* **47**, 201–213 (2005).
10. Sgaier, S. K. *et al. Neuron* **45**, 27–40 (2005).

MATERIALS SCIENCE

A new order for metallic glasses

Alain Reza Yavari

Like normal glass, metallic glasses lack long-range order. But experiments and simulations show that, on the nanoscale, clusters of atoms interconnect in these materials to form highly structured 'superclusters'.

Metallic glasses are peculiar metallic materials, usually alloys, that lack the long-range order of normal, crystalline metals. The attractive interactions, and differences in size, of atoms of different types in metallic glasses do, however, lead to a short-range order characterized by clusters of 'solute' atoms of one type surrounded by atoms of a more numerous species, the solvent. This much has been known for a long time. But just how these atomic clusters connect to fill space nearly as densely as crystalline solids with the same atomic composition has remained a mystery.

Some 45 years on from the discovery of the first metallic glasses[1], Sheng and colleagues (page 419 of this issue)[2] provide an essential missing piece of the puzzle, determining the three-dimensional structure of several metallic glasses that contain two different types of atoms. In these 'binary' glasses, they find nanoscale medium-range order, often consisting of closely packed icosahedral (20-faced) assemblies of some 13 neighbouring atomic clusters each centred on a solute atom.

The lack of long-range order in metallic glasses is signalled by the absence of sharp Bragg peaks — features characteristic of a periodically structured material — in the angular distribution of diffracted beams (X-rays, electrons and neutrons) used to probe them. These missing peaks led early researchers to consider atomic packing in metallic glasses to be similar to John Bernal's 'dense random packing' of hard spheres in liquids[3]. In this picture, the larger solvent atoms are densely, randomly packed[4], and the solute atoms are jammed into cavities left available to them by the geometry of this packing. Such models were later abandoned — in part because metallic glasses such as copper–zirconium ($Cu_{60}Zr_{40}$) were discovered whose solvent atoms were smaller than their solute atoms — in favour of packings of atom clusters in fixed ratios[5] with short-range order similar to that of crystalline compounds of the same atomic composition. These 'stereochemical' models could reproduce the experimental diffraction patterns and the corresponding distributions (known as radial distribution functions) of nearest and next-to-nearest neighbour atomic shells. But metallic glasses also exhibit order over 1–1.5 nanometres (for comparison, a typical metallic atom has a diameter of around 0.3 nm), and, until recently, no tangible description of how clusters of atoms interconnect to generate this medium-range order was available.

This situation changed with the proposal[6] a couple of years ago of dense packings of overlapping atomic clusters as the fundamental scheme for metallic glasses. In this model, an arbitrary 'face-centred-cubic' (fcc) lattice of clusters is chosen to achieve high density. (The fcc lattice is the densest possible cubic packing, and consists of elements placed at each vertex, and in the middle of each face, of a cubic structure.) But to maintain long-range disorder — to keep the material glassy — a strain factor has to be introduced to limit the coherence of such a lattice to the 1–1.5-nm scale. This model has been successful in predicting the compositions of most glass-forming alloys, and alloys with lower melting points than any of their constituents, known as eutectics[7].

Sheng *et al.*[2] set out to solve the three-dimensional structure of metallic glasses without resorting to a predetermined structural model. Instead, they use reverse Monte Carlo[8] simulations based on experimental X-ray diffraction and absorption data, as well as *ab initio* simulations of molecular dynamics[9], to determine the structure of a variety of binary nickel-based and zirconium-based metallic glasses with different ratios of atomic size and different levels of solute concentration. (Figure 1d on page 420 provides an example of the structure of a nickel–phosphorus glass, $Ni_{80}P_{20}$, ascertained through the reverse Monte Carlo method.) The radial distribution functions calculated using both simulation methods agree remarkably well with those measured directly using diffraction, and the mass (or atomic) densities they yield are within 1–2% of the experimentally measured values.

Knowing the three-dimensional positioning of the atoms of the glass allows the short- to medium-range details of its structure to be investigated. The number of nearest neighbours in an atomic cluster (the 'coordination

number[7]) can be determined using a technique known as Voronoi tessellation[10], which involves the division of the glass's structure into regions centred on individual solute atoms. The basic units of the short-range order that emerges are various polyhedra[11] of around 9 to 13 atoms, with a solute atom in the middle. The precise form of these polyhedral clusters is controlled by the ratio of the effective sizes of solute and solvent atoms, and so changes according to the elemental constituents of the glass. Sheng and colleagues also find a moderate variation in coordination numbers (that is, a range of different, quasi-equivalent clusters) in the same material. This flexibility allows for a more efficient packing of 'soft' atoms without requiring an fcc structure.

Once the three-dimensional positions of the clusters have been mapped out, their topological packing can be determined by a technique known as common neighbour analysis[12]. In three of the metallic glasses investigated by Sheng and colleagues[2] — $Ni_{81}P_{19}$, nickel–boron ($Ni_{81}B_{19}$) and zirconium–platinum ($Zr_{64}Pt_{36}$) — the clusters pack with appreciable icosahedral medium-range order, regardless of the short-range order within the clusters. Each solute-centred cluster shares its solvent atoms with about 12 neighbouring clusters, forming 'super-icosahedra' of 70–80 atoms that are about 1.5 nm wide, or fragments of such structures. As does the fcc-packing model[6], this icosahedral packing of clusters generates cavities similar to those in the random dense packing model[1], into which additional solute species of different sizes may be introduced[13]. This allows bulk metallic glasses to form[14,15].

Sheng and colleagues' *ab initio* calculations indicate that, as the solute content of the metallic glass is increased and solute–solute nearest neighbours become numerically unavoidable, the connection between solute atoms becomes string-like. When the solute strings percolate, as in nickel–niobium glass ($Ni_{65}Nb_{35}$), the solute–solute connection begins to resemble a network, and a spectrum of atomic packing schemes that varies with solute radius and concentration is generated.

The modelling techniques used by the authors do have some inherent limitations. *Ab initio* molecular dynamics simulations can still, for example, only be performed on limited time and length scales because of present limits on computational power. The short time-window also means that the cooling ('quench') rates currently used in simulations are more than 10^{12} K s^{-1}, far above laboratory quench rates of 10^{1}–10^{6} K s^{-1}, restricting the ability of the atoms to sample all possible configurations as they cool.

Nevertheless, the work of Sheng *et al.*[2] will serve to establish a firmer picture of the structure of metallic glasses. This information is fundamental to further applications involving these materials, which are already used commercially because of their exceptional magnetic and mechanical properties. More extensive exploitation of their mechanical properties — in particular their elastic response up to 2% strain — depends on better understanding of their plastic deformation. This deformation, usually leading to failure of the material beyond the 2% elastic limit, is heterogeneous at ambient temperature[16], and occurs in highly localized thin shear bands associated with tiny areas of collective atomic mobility ('shear transformation zones'[17]) that can percolate across the cross-section of the glass. Contrary to the hardening observed in crystalline materials under strain, heterogeneous deformation in metallic glasses has the opposite effect owing to the destruction of medium-range order. Sheng and colleagues' investigations on exactly this scale could thus provide further insight into the effects of deformation, and ways to improve the mechanical properties of metallic glasses. ■

Alain Reza Yavari is at the Laboratoire de Thermodynamique et Physico-Chimie Métallurgiques, Institut National Polytechnique de Grenoble, BP 75, 38402 St-Martin-d'Hères Campus, France, and at the Centre Nationale de la Recherche Scientifique (CNRS) and European Synchrotron Radiation Facilities, Grenoble, France.
e-mail: yavari@ltpcm.inpg.fr

1. Klement, W., Willens, R. H. & Duwez, P. *Nature* **187**, 869–871 (1960).
2. Sheng, H. W., Luo, W. K., Alamgir, F. M., Bai, J. M. & Ma, E. *Nature* **439**, 419–425 (2006).
3. Bernal, J. D. *Nature* **185**, 68–70 (1960).
4. Polk, D. E. *Acta Metall.* **20**, 485–489 (1972).
5. Gaskell, P. H. *Nature* **276**, 484–485 (1978).
6. Miracle, D. B. *Nature Mater.* **3**, 697–702 (2004).
7. Yavari, A. R. *Nature Mater.* **4**, 1–2 (2005).
8. McGreevy, R. L. *J. Phys. Condens. Matter* **13**, R877–R913 (2001).
9. Payne, M. C., Teter, M. P., Allan, D. C., Arias, T. A. & Joannopoulos, J. D. *Rev. Mod. Phys.* **64**, 1045–1097 (1992).
10. Finney, J. L. *Nature* **266**, 309–314 (1977).
11. Nelson, D. R. *Phys. Rev. B* **28**, 5515–5535 (1983).
12. Clarke, A. S. & Jónsson, H. *Phys. Rev. E* **47**, 3975–3984 (1993).
13. Greer, A. L. *Science* **267**, 1947–1953 (1995).
14. Inoue, A. *Acta Mater.* **48**, 279–285 (2000).
15. Johnson, W. L. *Mater. Res. Bull.* **24**, 42–56 (1999).
16. Spaepen, F. *Acta Metall.* **25**, 407–412 (1977).
17. Argon, A. *Acta Metall.* **27**, 47–53 (1979).

DNA REPAIR

Tails of histones lost

André Nussenzweig and Tanya Paull

A double-stranded break in DNA can profoundly destabilize a cell's genome. But how does the cell recognize the damage and halt division until it can be fixed? The answer lies in the proteins that package and unravel DNA.

DNA damage induces cell-cycle checkpoints that transiently arrest progression through the cell-division cycle. This delay gives the DNA-repair machinery sufficient time to fix genomic damage before the cell cycle resumes. Two studies, one by Tsukuda *et al.*[1] published at the end of last year and one by Keogh *et al.* in this issue (page 497)[2], demonstrate that modifications to the DNA packaging around the break site help to coordinate DNA repair with cell-cycle checkpoints.

Double-strand breaks in chromosomal DNA are repaired either through direct end-joining or through a process known as recombination in which the broken ends are spliced to the corresponding undamaged DNA on a sister chromosome, and the break is filled in using the undamaged DNA as a template. DNA breaks that are not rapidly rejoined are chewed back by exonuclease enzymes so that a length of single-stranded DNA hangs out from the remaining DNA. These single-stranded intermediates perform at least two crucial functions: the exposed single strands are bound by Rad51 proteins that initiate the search for a complementary template from which to repair them, and they act as a signal to arrest the cell cycle. Resumption of the cell cycle following checkpoint arrest is generally concurrent with repair, suggesting that the elimination of single-stranded intermediates may also control exit from the checkpoint.

In the nucleus, DNA is wrapped about histone proteins to create nucleosomes, and then it is further twisted up into higher levels of packaging. This tight packing probably creates a structural barrier to molecules that recognize and respond to DNA damage. This problem seems to be solved by proteins that control the organization of the chromatin (that is, DNA and its associated proteins). Complexes of such chromatin-remodelling proteins have been found near double-strand breaks; for example, the INO80, SWR1 and NuA4 complexes in budding yeast bind within two kilobases of a break, and are needed for the DNA to be repaired[1–5]. It is proposed that the chromatin-remodelling complexes might unravel the packaging, allowing repair enzymes access to the DNA.

Tsukuda *et al.*[1] show that double-strand breaks do indeed cause a loss of nucleosomes from sequences within a few thousand base pairs of the break, with kinetics that coincide with those of the loading of Rad51 on to single-stranded DNA. The loss of nucleosomes was catalysed by INO80 and facilitated