in the fluid into patterns. In the temporal domain, the pressure that acts on a particle will vary during a single oscillation. The particle will vibrate, but the fluctuations will be too rapid to lead to movement. However, if there is also spatial variation in the pressure field, the momentum of the fluid will impart a force on the particle that is, on average, non-zero. Over many oscillation cycles, this acoustic-radiation force will cause the particle to move.

By combining this temporal effect with shaping of the pressure field in the spatial domain, acoustic-radiation forces can cause particles to migrate to predetermined locations. This allows such particles to be manipulated[5], sorted[6] or patterned[7]. For example, a standing wave — created when a sound wave reflects back and forth in a chamber — is characterized by nodes (points of minimum amplitude) and antinodes (points of maximum amplitude). Particles will cluster at either the nodes or the antinodes of the pressure field[5], the exact final locations being dependent on the particles' properties[6]. Such fields can be produced using a single transducer (a device for converting electrical energy into the mechanical deformation of matter that causes sound, just as a speaker does at audible frequencies). However, with additional complexity come more possibilities.

If two sets of transducers are placed perpendicular to each another, their sound waves will interfere to create a pressure field that consists of a grid of nodes and antinodes[7]. By altering the relative phase of the sound waves from each set of transducers, the nodes and antinodes will shift, taking the trapped particles with them. This allows the trajectory of the particles to be controlled[8].

Going further, arrays of transducers, in which each member has a different phase[9], can produce acoustic holograms for complex particle manipulation (Fig. 1a). Such phased arrays are most prevalent in medical ultrasonic imaging, in which sound waves in the form of an 'acoustic beam' are directed across an object and then analysed to build up a scan image. When pebbles are dropped into a pond in a row, the ripples created by each pebble will interfere to form a wave pattern. By changing the time at which each pebble is dropped, the shape of this wave pattern can be controlled. In a similar way, by applying a different time (or phase) delay to each member of an array of independent, spatially distributed transducers, the shape of the acoustic beam can be designed, enabling intricate particle patterning and trajectory control[9].

In conventional systems, there is thus a strong correlation between the complexity of the instrumentation and that of the pressure field. In stark contrast to this, the elegance of Melde and colleagues' approach lies in the fact that it can be used to create an extremely detailed acoustic hologram by means of a simple experimental set-up. In an array, signals that have different phases are applied to each transducer, but here, the same phase distribution can be produced using only one transducer (Fig. 1b). The transducer is coupled to a 3D-printed monolithic element, which is a finely contoured solid plastic block. In this set-up, a sound wave will emanate from the transducer and pass through the element into the fluid; the time taken for this to occur is determined by the element's thickness. Therefore, if the element has a varying thickness, the time at which different parts of the sound waves enter the fluid will also vary, as will their phases. In addition to the simplicity of this technique, the level of control over the beam's shape is enhanced because it is not limited by the resolution due to the transducer's size, but rather by the resolution of the 3D printer, which is about 100 times higher.

The authors create an extremely detailed acoustic hologram by means of a simple experimental set-up.

In previous work, particle trajectory was controlled by changing the phase of the transducers, but here the phase is hard-wired into the system, so that objects move along a pre-programmed path. Clearly, this demands prior knowledge of the required trajectory, but, in return, it offers a huge reduction in complexity. To demonstrate the patterning potential of their technique, Melde and colleagues arrange particles into the outline of a dove in flight (see Figure 1 of the paper[4]). They also demonstrate trajectory control by continuously moving particles around a circular path and using particles to draw shapes (see Figure 3 of the paper[4]). It is therefore easy to see how this might be used to govern the motion of cells in a Petri dish or through different chemical environments in a microfluidic network. The authors' method of producing acoustic holograms also has applications in a multitude of fields that require the production of complex acoustic beams, such as extremely high-resolution imaging and selective heating. ■

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DEVELOPMENTAL BIOLOGY

Panoramic views of the early epigenome

Four studies detail changes in how DNA is wrapped around histone proteins and in molecular modifications to histones that occur after fertilization. The results shed light on the early regulation of gene expression. SEE LETTERS P.548, P.553 & P.558

JUAN M. VAQUERIZAS
& MARIA-ELENA TORRES-PADILLA

The beginning of life, marked by the fertilization of an egg by a sperm, has been a major focus of research for decades. When the differentiated cells give rise to an embryo, there is a dramatic reprogramming of the epigenome — the collection of molecular modifications to DNA and associated histone proteins that alter gene expression without changing DNA sequence. But details of the genomic regions affected by epigenetic reprogramming have been lacking. Four papers in *Nature* (three in this issue[1–3] and one published in June[4]) now reveal striking and unexpected features of this process in the developing oocyte (the unfertilized egg) and the early mouse embryo.

Gene expression changes drastically during the generation of oocytes and sperm in mammals, and halts completely by the time these cells are fully mature. In mice, expression resumes shortly after fertilization, with a minor wave of gene activation (dubbed zygotic genome activation; ZGA). A second, major wave of ZGA occurs at the late two-cell stage, marking deployment of the developmental gene-expression program. Four divisions later, a cell population called the inner cell mass develops. These cells will form the embryo proper, and can be extracted to derive embryonic stem (ES) cells *in vitro*. The epigenomic state of ES cells has been thoroughly

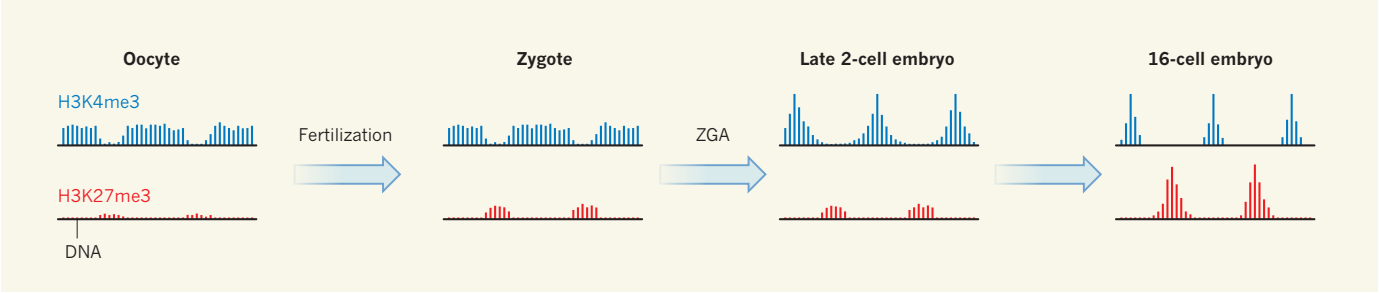

Figure 1 | Measuring methylation during early development. Four studies[1–4] analyse regions of the mouse genome that are associated with histone proteins that have been modified at amino-acid residues lysine 4 or lysine 27 by the addition of methyl groups (modifications called H3K4me3 or H3K27me3, respectively). In this simple schematic, the heights of vertical lines represent the level of modification associated with sequential regions of DNA. There is no gene transcription in mature, unfertilized eggs (oocytes), and H3K4me3 is distributed in broad regions across the genome, which is atypical for this modification. These domains are mostly maintained following fertilization (at the zygote stage) until the late two-cell stage, when a process called major zygotic genome activation (ZGA) leads to a wave of gene expression. From then on, the broad signature is replaced by narrow H3K4me3 regions associated with gene activation at sites at which transcription is initiated. By contrast, H3K27me3, which is associated with gene repression, is lowest in the oocyte and at early stages, and becomes increasingly abundant as development proceeds, showing a mutually exclusive distribution with narrow H3K4me3 regions until the 16-cell stage.

investigated, but that of earlier developmental stages has remained elusive, mostly owing to the minimal amount of material available for study.

The four current studies analysed the regions of the genome with which three histone modifications are associated in sperm and oocytes and in early mouse embryos. The authors adapted techniques to allow the analysis of just a few cells. First, Liu *et al.*[1] (page 558), Dahl *et al.*[2] (page 548) and Zhang *et al.*[3] (page 553) studied modification of the amino-acid residue lysine 4 (K4) on histone H3 by three methyl groups (a modification referred to as H3K4me3). Second, Dahl *et al.* and Wu *et al.*[4] examined modification of lysine 27 (K27) by an acetyl group (H3K27ac). Third, Liu *et al.* and Wu *et al.* analysed trimethylation of K27 (H3K27me3). The studies differed in the number of cells analysed and how the DNA and associated proteins (collectively called chromatin) were treated before analysis, but the groups all reached similar conclusions.

In ES cells and mature cell types, H3K4me3 is primarily clustered around small DNA regions at which gene transcription begins, and is associated with gene activity. One of the most striking findings of the current papers is that, in oocytes, H3K4me3 is enriched at low levels across large genomic regions, spanning more than 10 kilobases, and is mostly distant from transcription start sites. This pattern of 'non-canonical' H3K4me3 persists in the fertilized oocyte and in embryos at the early two-cell stage (Fig. 1).

Dahl *et al.* and Zhang *et al.* delineate two groups of genes associated with non-canonical H3K4me3 in the mature oocyte[2,3]. First, non-canonical H3K4me3 is found close to genes that are expressed during oocyte growth — in agreement with previous work[5] suggesting that dynamic remodelling of H3K4 methylation occurs as the oocyte matures, and is coupled to changes in gene expression and in DNA methylation, which represses transcription. Second, the modification is found associated with genes expressed during major ZGA. Therefore, this atypical modification seems to provide an epigenetic memory of the transcriptional state of the oocyte that is inherited by the developing embryo.

More unexpected findings are also reported. First, Zhang and colleagues observed non-canonical H3K4me3 in regions enriched in certain repetitive sequences, some of which are highly active during early embryonic development[3]. H3K4me3 had previously been reported[6] to associate with only one such repetitive element in embryos, LINE-1. This is of particular interest because Wu *et al.* find[4] that large domains of DNA are accessible to transcription-factor binding before major ZGA. This accessibility is associated with the transcription of specific families of repetitive elements and nearby genes, highlighting the regulatory potential of repetitive elements.

Second, Zhang *et al.* found that removing methyl groups from H3K4me3 in oocytes resulted in increased — albeit aberrant — transcriptional activation[3], and Dahl *et al.* reached similar conclusions using a complementary approach[2]. This surprising finding implies that non-canonical H3K4me3 can have a role in transcriptional silencing. It remains to be determined whether this effect is direct, or whether the presence of H3K4me3 somehow sends signals that lead to alterations in the levels of other histone modifications, regulating silencing indirectly.

The papers reveal that the histone demethylase enzyme KDM5B is crucial in limiting the genomic distribution of H3K4me3 during oocyte maturation and ZGA. And Liu *et al.* show[1] that, in the developing embryo, H3K4me3 domains become broader following the loss of KDM5B. Thus, keeping the levels of H3K4me3 in check seems to be essential for correctly establishing and deploying early-embryonic gene-expression programs.

Zhang *et al.* and Wu *et al.* also examine differences in the histone modifications inherited by the embryo from the father and the mother[3,4]. They find that parental differences in H3K4me3 distribution are retained in the two sets of chromosomes in the early embryo, supporting the idea that some epigenetic information is inherited.

Turning to other histone modifications, Liu and colleagues[1] compared changes in H3K27me3, which is associated with gene repression, with those of the activation-associated H3K4me3. In contrast to the other studies, the group focused on analysing these modifications only in regions close to ZGA genes that harbour the typical, 'canonical', high-level H3K4me3 signal around transcription start sites. They found that levels of canonical H3K4me3 increased from the late two-cell stage onward. This differs from the non-canonical H3K4me3 sites, where levels drop off after the two-cell stage.

Liu *et al.* found that the number of regions that contain canonical H3K4me3 but not H3K27me3 increased sharply at the late two-cell stage. By contrast, the number of H3K27me3-only regions increased gradually (Fig. 1). This probably reflects different dynamics, and hence different mechanisms, in establishing these two epigenetic marks. H3K4me3 and H3K27me3 are mutually exclusive up to the 16-cell stage, possibly because of the low levels of H3K27me3. By contrast, ES cells contain many domains marked by both such histone modifications. Thus, bivalent domains of modification are established at later stages of development. By having both 'active' and 'repressive' modifications, bivalent domains are thought to be crucial for the efficient expression of lineage-specific developmental programs as cells start to differentiate into mature lineages.

Finally, Dahl *et al.* found stage-specific H3K27ac domains[2], which are presumed to activate the expression of nearby genes. H3K27ac domains tended to be near genes associated with ZGA, and the authors used the domains to identify transcription factors that potentially bind to these nearby genes to

regulate early, stage-specific developmental programs. Although this will certainly constitute a powerful resource, some of the factors identified differ from those documented in a paper published in June[7]. Further work will be required to determine the specific details of the mechanisms by which these transcription factors drive development.

Overall, the studies demonstrate a drastic epigenetic remodelling process in oocytes and sperm, and at early stages of embryonic development. This hints at mechanisms by which histone modifications are passed between two generations, playing a vital part in the activation of the newly formed genome. Further work will be necessary to characterize the precise molecular mechanisms that govern these transitions. ■

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This article was published online on 14 September 2016.

EXOPLANETS

Migration of giants

The origin of hot Jupiters, large gaseous planets in close orbits around stars, is unknown. Observations suggest that such planets are abundant in stellar clusters, and can result from encounters with other celestial bodies.

AMAURY TRIAUD

Hot Jupiters are a rare and peculiar class of exoplanet that have masses comparable to that of Jupiter and short orbital periods of typically four to five days[1]. The first hot Jupiter was discovered[2] in 1995, and, since then, astronomers have debated the physical processes that are responsible for their production. Because hot Jupiters are the most extreme outcome of planet formation, discovering their origin will considerably refine our understanding of how planets are assembled and how their orbits evolve. Writing in *Astronomy & Astrophysics*, Brucalassi *et al.*[3] find that hot Jupiters are five to ten times more abundant in stellar clusters than elsewhere in the Milky Way, and the authors provide evidence for a scenario that explains the production of such planets.

Hot Jupiters are extreme in every way. Imagine objects that have radii ranging between half and twice that of Jupiter, and atmospheric temperatures of between about 1,000 and 3,000 kelvin. These temperatures imply that many hot Jupiters emit more infrared radiation than some stars[4].

The orbital proximity of hot Jupiters to their host stars also means that they experience intense gravitational (tidal) forces, which elongate the planets into a rugby-ball shape[5]. These forces synchronize the planets' rotation and orbital speeds in a similar way to the forces exerted on the Moon, such that one side of the planet (the dayside) is always facing the star. Powerful winds can reach supersonic velocities within the atmospheres of hot Jupiters[6], transporting heat from the dayside to the nightside. Finally, several of these planets have been observed to lose mass under the intense radiation that they receive from their host stars[7].

Three properties distinguish a hot-Jupiter population from all other exoplanets. First, there is an excess of objects that have orbital periods shorter than about 10 days and masses similar to that of Jupiter[1]. Second, the objects rarely have companion planets on nearby orbits[8]. Finally, nearly one-third of hot Jupiters have orbital paths that are inclined with respect to their star's equator[9], and several planets in the population rotate in the opposite direction to the star.

Several hypotheses have been put forward to explain the existence of hot Jupiters. For example, they could have formed close to their host stars, although this idea is disputed by most of the scientific literature. A more likely explanation is that they formed far from their stars and then migrated inward.

Two main scenarios could explain this migration. First, a hot Jupiter might lose angular momentum to the material of the protoplanetary disk from which it formed[10]. Second, the planet might exchange angular momentum with another celestial body (a planet, a stellar companion or a passing star), throwing the planet onto a highly eccentric orbit[11–13] (a process called dynamical migration; Fig. 1). Then, when the planet reaches periastron — the closest point on its orbit around the host star — tidal forces deform it, and friction dissipates its angular momentum as heat. The planet's orbital distance therefore shrinks, and

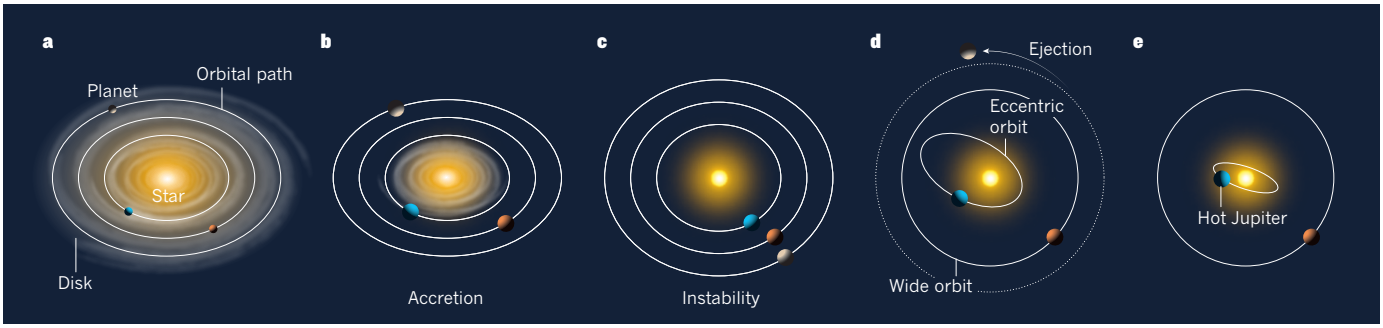

Figure 1 | Possible scenario for the dynamical migration of a hot Jupiter. Brucalassi *et al.*[3] show that a class of exoplanet called hot Jupiters can form because of interactions with other celestial bodies. **a**, Two or more planets form within a protoplanetary disk — the dust and gas surrounding a newborn star — far from the star. **b**, The disk material accretes onto the star, but also onto the planets, whose masses become similar to that of Jupiter. **c**, At some point, a dynamical instability occurs, either as an inherent, unstable planetary configuration (shown) or as a result of a passing celestial body such as a star (not shown). **d**, One of the planets is launched on a highly eccentric orbit, whereas the others either adopt wide orbits or are ejected. **e**, When the eccentrically orbiting planet passes close to the star, tidal forces cause its orbit to shrink and become more circular. The result is a large planet that has a short orbital period: a hot Jupiter.