on spin manipulation and detection than do electrons, yielding new ways to explore the richness of spintronics.

To make spintronic devices based on atomic spins, spin–orbit coupling needs to be addressed. In atomic physics, the effect couples the electron's spin with its orbital angular momentum through the electrical field of the nucleus, and leads to the fine structure (small splitting) of the internal states of the atom. In condensed-matter systems, however, the coupling is between the electron's spin and its linear motion, and is caused by the electrical field of the underlying atomic lattice. Researchers have recently proposed ways to create artificial electromagnetic fields (gauge fields) to induce such spin–motion interaction in atomic systems. These fields are produced by coupling internal states of atoms with laser beams at ultra-low temperatures. In their experiment, Beeler *et al.* used one such field to engineer spin–motion interaction in an atomic system and to observe a quantum effect known as the spin Hall effect.

The spin Hall effect is similar to the conventional Hall effect, in which the positively and negatively charged particles of an electrical conductor are separated by a transverse magnetic field, producing a voltage at a right angle to the current. In the spin Hall effect, the particles go their separate ways according to whether their spin points in one of two opposing directions. By using their gauge field, which was created by means of two laser beams, Beeler *et al.* convincingly show that atoms with opposite spin states that travel at right angles to the magnetic field produced by the gauge field move in opposite directions (Fig. 1). The researchers go on to show that their data agree well with theoretical calculations, indicating that the authors have a proper understanding of the mechanism behind the spin Hall effect in their system.

But Beeler and colleagues have taken their work one step further: they realized the atomic analogue of a spin transistor. Although previously proposed[2] in 1990, the spin transistor has been made only within the past few years[4]. By using the displacement of the atoms in the gauge field as the transistor's voltage difference between the drain and source electrodes, and the strength of the two laser beams as the transistor's voltage of the gate electrode, Beeler *et al.* realized an atomic system that shows the characteristics of a typical spin transistor. The simplicity and robustness of the authors' transistor also makes it a good option for splitting atoms according to their spin in a device known as a Mach–Zehnder interferometric sensor.

Beeler and colleagues' experiment opens up many avenues in the field of ultracold atomic gases. The gauge field produced is of the 'Abelian' type; however, there are proposals to generate non-Abelian gauge fields[5]. These non-Abelian fields are more difficult to realize experimentally but allow a closer comparison with condensed matter, in which non-Abelian fields are usually responsible for the spin–motion interaction. Beeler *et al.* induce the spin Hall effect in their system by using spin–motion coupling, but in condensed matter the effect can also be induced by scattering of electrons by impurities. Although ultracold atomic gases are free of impurities, interactions between the atoms can be tuned to be made strong and yield exotic phenomena such as superfluidity.

Spin–orbit interactions can lead to topological insulators, which are insulating in their bulk but have topologically protected conducting states on their boundaries. Such states can easily be controlled and detected in ultracold atomic gases. The crossroads between ultracold atomic gases and condensed-matter physics provide fertile ground for research: the former focuses on fundamental knowledge obtained through the study of well-characterized systems under controllable conditions, whereas the latter applies such knowledge in information technologies. Many new phenomena can be expected to surface in these areas in the next few years. ■

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STEM CELLS

Regulation by alternative splicing

Stem-cell differentiation is controlled by RNA processing — as well as by gene expression and transcription. This finding is a milestone towards realizing these cells' potential for research and therapy. SEE LETTER P.241

YAIR AARONSON & ERAN MESHORER

Mammalian genomes contain some 23,000 genes. Yet the process of alternative splicing ensures that the number of proteins arising from these genes is at least ten times greater[1]. It achieves protein diversity by varying the way in which the RNA transcript of a gene is processed: each of the protein-coding sections of a transcript can be either spliced out or left in to form different mature messenger RNAs. Consequently, multiple variants of a protein (isoforms) can be produced from a single gene, in a tissue-specific or developmental-stage-specific manner. On page 241 of this issue, Han *et al.*[2] describe the role of alternative splicing in the regulation of embryonic stem cells, thereby adding another notable regulatory layer to the known mechanisms that govern stem-cell state and differentiation*.

Embryonic stem (ES) cells have two special qualities: they can undergo an unlimited number of divisions, and they are pluripotent — that is, they can differentiate into any cell type of a mature organism. These cells, therefore, have great potential for clinical use and can serve as models for studying disease. Research into how ES-cell pluripotency is regulated has mainly focused on the control of gene expression through modifications of chromatin[3] (the complex of DNA and proteins in chromosomes) and during transcription[4]. But, despite several master regulators of alternative splicing having been identified[5,6], none has been implicated in ES-cell maintenance, differentiation or transcription (Fig. 1).

To screen for alternative-splicing events associated with pluripotency, Han *et al.* studied RNA data from pluripotent cells and various differentiated cells from humans and mice. The pluripotent cells they investigated included not only ES cells but also induced pluripotent stem (iPS) cells, which are ES-like cells derived through molecular reprogramming of differentiated cells[7].

The authors identified dozens of alternative-splicing events that differed between pluripotent and differentiated cells, including a previously known[8] ES-cell-specific event in the mRNA for the pluripotency factor FOXP1. And when they measured the expression levels of many known splicing regulators, the authors found a few that differed significantly between pluripotent cells and differentiated cells. In particular, two of the regulators — MBNL1 and MBNL2 — showed very low expression in ES cells and much higher expression in differentiated cells.

How do MBNL1 and MBNL2 affect stem-

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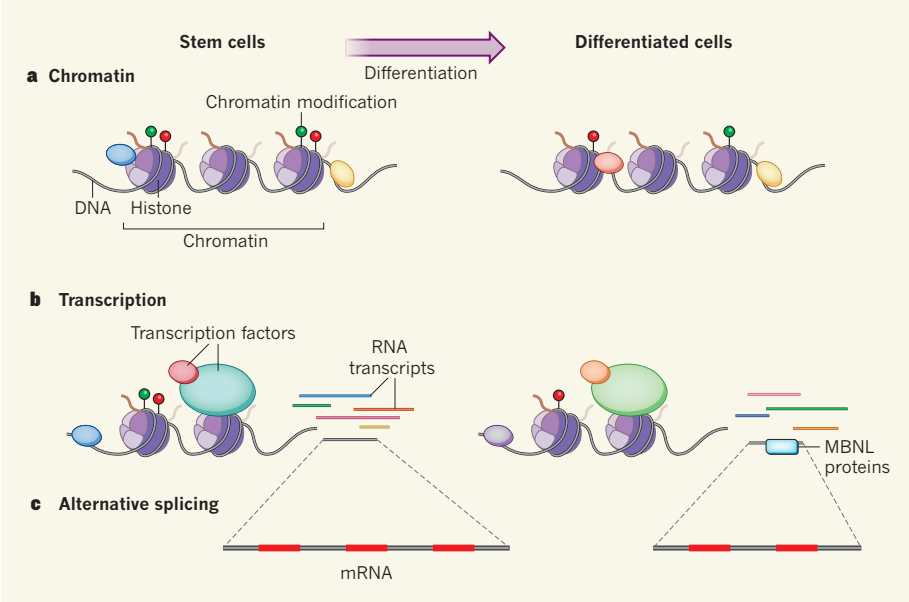

Figure 1 | Multilayer regulation of cell differentiation. **a**, The nature and amounts of chromatin-modifying and -remodelling proteins (blue and yellow) that bind to DNA and its associated histone proteins differ between stem cells and differentiated cells, affecting gene expression through regulation at the level of chromatin. **b**, At the level of transcription, specific transcription factors orchestrate the distinct transcript output of stem cells compared with differentiated cells. **c**, Han *et al.*[2] show that at the level of transcript processing, regulators of alternative splicing, such as MBNL proteins, govern the differences in mRNA, and thus protein, output between stem cells and differentiated cells.

cell identity? The researchers report that sites of alternative splicing in ES-cell transcripts are highly enriched in MBNL1- and MBNL2-binding motifs, and that these factors specifically bind to the sites in a unique pattern. So it seems that the binding patterns of these regulators control the omission or inclusion of protein-coding regions (exons) in the mature mRNA.

The cellular levels of MBNL proteins also seem to affect the differentiation state. Increased expression of these proteins in ES cells induced differentiation-specific alternative-splicing events, and decreased the levels of an ES-cell-specific isoform of FOXP1. Consistently, reducing expression of these proteins in differentiated cells led to a switch of the alternative-splicing program to an ES-cell-like pattern. And the efficiency of reprogramming of differentiated cells into iPS cells was greatly enhanced with reduced expression of MBNL1 and MBNL2 (the splicing pattern associated with 'stemness' was particularly prominent in cells that were successfully sustained through the later parts of the reprogramming process).

Han and co-workers' paper sets the stage for extensive follow-up studies. Understanding the exact mechanism of action of the MBNL proteins might help to identify upstream elements of this regulatory network. Moreover, the epigenetic state of ES cells — that is, genomic modifications that affect gene expression without changing the DNA sequence — is subject to continuous regulation, and a link between epigenetics and alternative splicing has been proposed[9,10]. Understanding how alternative splicing interacts with epigenetic and other networks that are known to regulate pluripotency would be fascinating. Furthermore, Han *et al.* identified many more sites of alternative splicing, and differential regulators of splicing in ES cells that they could not investigate in the current work. These should be studied, as they might provide additional insights into the mechanism by which alternative splicing controls pluripotency.

The authors' observations might also have a notable practical implication. Splicing regulators could potentially be harnessed to control the efficiency and outcome of cellular differentiation and reprogramming — akin to the use of transcription factors for these purposes. While we tune in for follow-up studies, Han and colleagues' findings will surely change the ways in which researchers examine and manipulate pluripotent cells. ■

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MALARIA

The vector as protector

Malaria infections are not always lethal. One reason for this may be that transmission from mosquitoes creates malaria parasites that trigger a more protective mammalian immune response. SEE LETTER P.228

ANDREW F. READ & NICOLE MIDEO

Malaria parasites can kill people, but death is not inevitable. Most infected individuals recover, some after experiencing relatively mild symptoms or none at all. What accounts for this variability? Host factors such as the expression of sickle-cell genes or acquired immunity are part of the explanation. But it is also well known that malaria parasites themselves can be more or less nasty[1,2]. In this issue, Spence *et al.*[3] (page 228) report a set of clever experiments in a mouse model of malaria infection that shows that the conditions experienced by parasites before they reach the mammalian bloodstream can determine just how virulent they are*.

Malaria parasites transmitted to people by mosquitoes migrate to the liver, where they replicate before entering the bloodstream. For convenience, and because only blood-stage parasites cause disease, most experimental studies of malaria in humans and animals bypass the mosquito and liver stages and inject parasites directly into the bloodstream. Using the malaria parasite *Plasmodium chabaudi*, which infects rodents, Spence and colleagues compared the blood-stage infections generated by this method with those initiated naturally, by mosquito bite. They found that, compared with directly injected parasites,

*This article and the paper under discussion[3] were published online on 29 May 2013.