magnetization-induced shape changes[6] (which involves only the constants λ_{100} and λ_{111}) fails to describe such changes in the new alloys.

Second, the researchers' samples are quite difficult to magnetize, as seen from the modest slope of the plots of magnetization against applied magnetic field (Fig. 1c). Intriguingly, they are equally hard to magnetize in all directions of the crystal lattice, even though shape changes owing to magnetostriction are highly direction dependent. Third, and perhaps most interestingly, the materials are nearly hysteresis free.

Chopra and Wuttig explain these unexpected behaviours by proposing a concept called autarky: the independent action of magnetic domains[5]. These domains adopt the shape of a classic rectangular Landau pattern (see Fig. 3c of the paper[1]) decorated by tiny zigzags, and are formed from several subregions. The domains undergo local, rather large shape changes during magnetization, but no domain seems to influence its neighbours. This behaviour is no doubt aided by the fact that the magnetization of each domain can point in any direction — that is, the magnetic force associated with a domain does not favour any particular direction.

To put it another way, in the absence of an applied field, it is as if each subregion within a rectangle is a piece of a jigsaw puzzle, but each piece is substantially distorted from its ordinary, regular shape. Nevertheless, the puzzle stays perfectly flat and rectangular rather than buckling up out of its plane, with each distorted piece fitting perfectly with its neighbours.

Given that further development of energy technology hinges largely on making exceptionally soft and exceptionally hard magnets, and that we understand so little about magnetic hysteresis, Chopra and Wuttig's finding is not only a dramatic fundamental discovery, but it could also be a touchstone on the way to a predictive theory of magnetic hysteresis. As a first step, it will be essential to find out in detail the changes of strain and magnetization that occur in the autarkic domains during magnetization. ■

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STEM CELLS

Equilibrium established

Pluripotent cells can produce all cell types in the body. It emerges that this state of potential is endowed by cues, including inhibition of Wnt signalling, that maintain a balance between diverse cellular outcomes. SEE ARTICLE P.316

KYLE M. LOH & BING LIM

Achieving dualism — a state in which two opposing forces coexist in balance — is central to Taoist philosophy, and, it has now emerged, to stem cells too. Stem cells reside at a nexus of opportunity, harbouring the potential to form myriad tissues, from blood to bone to brain. Balancing these diverse potentials is key to endowing and maintaining stem-cell identity[1]. On page 316 of this issue, Wu *et al.*[2] show that neutralizing one cellular signalling pathway, Wnt, helps stem cells to achieve such balance.

Stem cells that can form all bodily tissue types are said to be pluripotent[3]. Pluripotency is not a singular state, but is a property of at least two related developmental cell types. The first pluripotent cells to arise in mouse embryos have broad cellular potential and are dubbed naive[4]. Soon after naive cells form, they become primed for differentiation[4], as many extracellular signals, including Fgf and Wnt proteins, direct them to become one of various specialized cell types. Specifically, primed pluripotent cells can become either ectoderm (the progenitor to skin and brain tissue) or mesendoderm (the progenitor to blood, bone, intestines and other organs)[3] (Fig. 1a).

Because primed pluripotent cells are poised to undergo imminent differentiation, they exist in a precarious position[1]. If taken from an embryo and cultivated in a Petri dish, primed cells often spontaneously lose pluripotency, and develop into differentiated cell types[5]. This is partly attributable to the action of Wnt and Fgf proteins, which both induce mesendoderm differentiation and block ectoderm formation (Fig. 1a)[6,7].

Primed pluripotent cells produce Wnt, and might thereby intrinsically prompt their own differentiation[5,8,9]. Wu *et al.* thus reasoned that they could block mesendoderm differentiation in this cell type by blocking Wnt[5,10,11] and simultaneously restrict ectoderm formation by supplying Fgf (Fig. 1b). By stabilizing a seesaw of opposing lineage forces, an uncommitted pluripotent state might be realized at the fulcrum. The authors found that such treatment broadly 'stabilized' primed pluripotent cells, whether of human, macaque, chimpanzee or mouse provenance.

To investigate whether primed pluripotent cells stabilized in this manner retain the potential to develop into ectodermal and

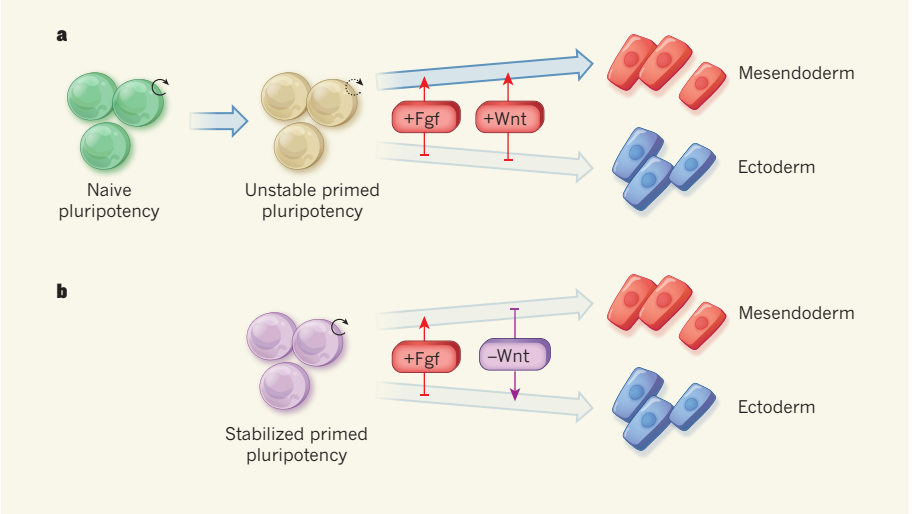

Figure 1 | Stabilizing the stem-cell seesaw. a, During normal development, naive pluripotent cells, which have the potential to give rise to all bodily cell types, mature into unstable primed pluripotent cells. These primed cells differentiate into more-specialized cell types (mesendoderm or ectoderm) in response to various signalling pathways. Fgf signalling and Wnt signalling both block ectoderm formation while promoting mesendoderm formation. **b,** Wu *et al.*[2] demonstrate that primed pluripotent cells are perched on a precarious seesaw between mesendoderm and ectoderm fates. By providing Fgf signals and simultaneously inhibiting Wnt signals, primed pluripotent cells can be stabilized.

mesendodermal cells, Wu *et al.* grafted stabilized human pluripotent stem cells onto 7.5-day-old post-implantation mouse epiblasts placed in a Petri dish (epiblasts are isolated, non-intact embryonic tissue fragments that lack supporting tissues and are therefore not viable). Strikingly, the stabilized human pluripotent cells successfully integrated into these mouse epiblasts, and the engrafted cells seemed to resume their natural developmental programme, differentiating into cells that expressed human ectoderm- and mesendoderm-specific genes in the confines of the epiblast. Although the full repertoire of the developmental genes expressed awaits a more extensive analysis, these findings imply that stabilized pluripotent cells are still capable of differentiation once released from stabilizing conditions.

Do the stabilized pluripotent cells correspond to any natural cellular state on the timeline of *in vivo* development? The classification of pluripotent cells as either naive or primed is probably an artificial dichotomy, and, indeed, gene expression in the Wnt-inhibitor-grown cells differs from that of either naive or primed pluripotent cells. Does this mean that such stabilized cells are genuinely a different class of pluripotent cell, or do they simply represent a more stabilized type of primed pluripotency, owing to a rebalancing of competing lineage forces? Perhaps 'stabilized' primed pluripotency is short-lived *in vivo* because of the speed of embryonic development, complicating efforts to assign *in vivo* counterparts to these cells. Some evidence[10] argues that the stabilized cells correspond to an intermediate between naive and primed pluripotency.

A final possibility is that Wu and colleagues' cells exist orthogonally to the natural developmental timeline — that is, they are an artificial, non-developmental cell type. Maybe the priming of these cells has not been rewritten by Wnt inhibition at all. Instead, a change in adhesion properties could enable the stabilized human cells to engraft into the isolated mouse epiblast *in vitro*. Perhaps reflecting some degree of artificiality, the stabilized cells engraft only into the posterior of such epiblasts, whereas conventional primed cells from mice can engraft into all regions. This bias remains unexplained.

Finally, we propose that the idea of lineage balance[1] might not be specific to pluripotent stem cells, but might also extend to more-specialized ones, such as gut[12] or blood[13] stem cells. If stem cells represent a state in which opposing lineage potentials coexist, then negotiating a balance in competing lineage forces might prove decisive in stabilizing and thus capturing diverse types of stem cell. ■

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MOLECULAR BIOLOGY

Splicing does the two-step

An intricate recursive RNA splicing mechanism that removes especially long introns (non-coding sequences) from genes has been found to be evolutionarily conserved and more prevalent than previously thought. SEE LETTERS P.371 & P.376

HEIDI COOK-ANDERSEN & MILES F. WILKINSON

One of the biggest surprises in molecular biology was the discovery in 1977 that coding information in genes is interrupted by non-coding sequences known as introns. Much has since been learned about how introns are recognized and spliced out of precursor RNA to yield mature messenger RNA in which the remaining sequences — the exons — are stitched together. A lingering challenge has been to work out the way in which long introns are correctly recognized and spliced out, because they have a greater potential for splicing errors than do short introns.

One intriguing solution to this problem arrived 17 years ago, with the discovery that a long intron in the *Ultrabithorax* gene in the fruit fly *Drosophila melanogaster* is removed in a progressive, stepwise fashion, thereby reducing the size of the chunks that need to be defined for splicing[1]. However, subsequent studies identified only a handful of fly genes that undergo this 'recursive' splicing[2,3], and no examples were demonstrated in other species[4], casting doubt on the generality of the process. Two papers in this issue report that recursive splicing is actually quite widespread in fly genes[5] and that it is also used by genes expressed in the human brain[5,6].

Recursive splicing depends on juxtaposed 3′ and 5′ splice-site sequences, called recursive splice sites, in the middle of long introns (Fig. 1a). Duff *et al.*[5] (page 376) set out to identify recursive splice sites in *D. melanogaster* using deep-sequencing methods. Their screen yielded 197 functional recursive splice sites, many of which were highly conserved across several *Drosophila* strains. The authors identified a total of 115 fly genes that undergo recursive splicing, greatly expanding the range of this mechanism.

By evaluating the spliced-out intron segments (lariats), Duff *et al.* obtained evidence that recursive splicing is a sequential and largely obligate process for genes that have recursive splice sites. They also found that recursive 3′ splice sites are typically richer in the long tracts of pyrimidines (the nucleotide bases cytosine and uracil) required for splicing than are non-recursive 3′ splice sites. This raises the possibility that their splicing depends more than that of typical introns on the polypyrimidine-tract-binding protein U2AF. Indeed, the authors found that recursive splicing is strikingly more sensitive to U2AF depletion than is canonical splicing. The physiological significance of this intriguing discovery remains to be determined.

Sibley *et al.*[6] (page 371) addressed the long-standing question of whether recursive splicing is evolutionarily conserved. Using two complementary approaches, they identified nine genes that undergo recursive splicing in the human brain. In contrast to sites in *Drosophila*, in which the majority of recursive introns are completely spliced out[1–3,5], all recursive splice sites identified in humans harboured an 'RS exon' that seems to be pivotal for removing the long intron and can be retained in some circumstances (Fig. 1b).

The authors identified two roles for the RS exon in recursive splicing in humans. First, it facilitates recognition of the recursive splicing site, presumably through the process of exon definition. This is a complex mechanism that defines splice sites on either side of an exon through recruitment of splicing-promoting