It is important to note that the *Opn5*-mutant animals did not express the gene at any point in their lives – including during crucial developmental periods when the neural circuitry and identities of neurons are established. It is not yet known whether this led to unexpected developmental changes that might underlie the animals' insensitivity to violet light. Going forward, the same analysis should be performed in animals in which *Opn5* is deleted only during adulthood, after normal neurological development has finished.

To prove that violet light could penetrate the skull and reach the POA neurons, Zhang *et al.* implanted a miniature, wavelength-sensitive radiometer probe into the brain. They found that violet light could indeed penetrate deep enough to activate OPN5-expressing POA neurons. Finally, they compared the response to cold of animals exposed to a full spectrum of light and of animals exposed to light that lacked violet wavelengths. The 'full-spectrum' animals showed greater reductions in BAT and body temperature in response to cold than did the 'minus-violet' animals. This experiment indicates a physiologically relevant role for OPN5-expressing POA neurons – repressing heat production in BAT in response to violet light.

Whether violet light directly stimulates OPN5 neurons remains to be proved. Zhang *et al.* used neuroimaging techniques to show that light activates the neurons in tissue slices, but proof will involve applying these techniques *in vivo*.

OPN5 has been identified in the hypothalamus (the brain region in which the POA is located) in monkeys[2]. However, we do not yet know whether ambient light will reach this deep brain region. Such a demonstration would be a key step in determining the applicability of these results to humans.

As with many exciting and unanticipated findings, Zhang and colleagues' study opens the door to larger questions of biological relevance. Humans today have unprecedented control over ambient light, temperature and nutrient supply, and are consequently much less susceptible to natural environmental metabolic challenges than were our ancestors. Eating only during daylight hours has been shown to markedly improve insulin sensitivity in people with prediabetes[5] – a change that might lower the risk of developing full-blown diabetes. It is tempting to speculate that limiting violet light might activate BAT, and thereby augment the metabolic benefits of daytime-restricted eating. Similarly, drugs called β-agonists activate BAT, lower blood glucose levels and increase resting metabolic rate and insulin sensitivity in people[6–9], and Zhang and co-workers demonstrated that animals reared without violet light show increased responses to these drugs. Limiting violet light might therefore extend the beneficial metabolic effects of β-agonists.

Remarkably, mouse and human BAT expresses a red-light-sensitive protein, OPN3 (ref. 9). Red-light stimulation of OPN3 increases glucose uptake and heat production in BAT, both *in vitro* and in mice. Thus, different spectra of environmental light might act both in the brain and in brown-fat cells to alter BAT heat production in ways that can help the body to control glucose levels.

Finally, a population of neurons has recently been found in the mouse POA that controls torpor – a state characterized by low body temperature and a markedly reduced metabolic rate, typically induced by harsh environmental challenges such as cold and lack of food[10]. It remains an open question whether this neuronal circuit is also sensitive to violet light. But Zhang and colleagues' findings raise the possibility that environmental light might orchestrate a host of coordinated brain responses that together determine the highs and lows of metabolism.

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Developmental biology

Keratin as an aide-memoire

Mateusz Trylinski & Buzz Baum

Filaments of keratin – stable protein polymers best known for their function in hair and nails – provide a memory of cell polarity at a crucial stage in early mouse development. **See p.404**

The processes by which a single cell – the fertilized egg – gives rise to all the different cell types that make up an adult organism remain some of life's great mysteries. We know that it takes time for cells in an embryo to settle on a fate, because a single embryo that splits during early development can give rise to twins, triplets and more. But how are cell-fate decisions made, and how do cells coordinate their choices with their peers? Researchers have suggested numerous mechanisms that influence the paths taken by cells in early mammalian embryos. On page 404, Lim *et al.*[1] describe a surprising role for a protein polymer, keratin, in the first of these decision-making processes.

"Keratins provide a physical memory of polarity that is relatively independent of cell-division events."

Two of the main challenges of early development are to increase the number of cells through repeated rounds of cell division, and to ensure that these cells assume distinct forms and functions at the right time and place to generate functional tissues and organs. The two processes can be coupled through 'asymmetric' cell divisions. These are divisions that give rise to two sibling cells with distinct identities, either as a result of the asymmetric segregation of material, or in response to local differences in the extracellular environment that the cells encounter after division.

It is during the 8- to 16-cell transition that cells in early mammalian embryos first become asymmetrically organized – with subsets of proteins becoming concentrated at opposite cell poles, a feature called apical–basal polarity. Cell identity remains plastic at this stage, but daughter cells that end up at the periphery (termed the trophectoderm) of the 16-cell embryo give rise to the placenta, whereas daughter cells that end up inside the embryo contribute to the fetus.

The observation of apical–basal polarity at the 8- to 16-cell transition led to the proposal that the future identity of these cells is determined by the asymmetric inheritance of the outward-facing apical domain[2], which is rich in

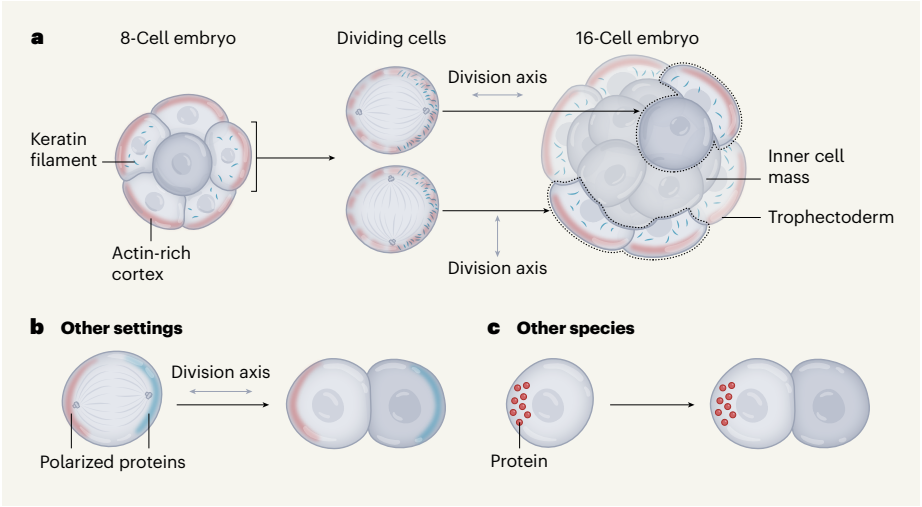

Figure 1 | Keratin in early embryos. a, In 8-cell mouse embryos (not all cells shown), keratin filaments are expressed stochastically in a subset of cells, before associating with a 'cortex' on one side of the cell (called the apical side). The cortex is rich in the protein actin. Lim and colleagues[1] show that, as these cells divide, the cortex disassembles but keratin filaments remain apically localized. The identity of daughter cells is determined by the position of keratin relative to the axis along which division occurs. Daughter cells that lack keratin end up inside the embryo and go on to form the inner cell mass. Daughter cells that inherit the mother's apical region also inherit keratin, which helps to re-establish the cortex at the apical pole. These cells contribute to the trophectoderm, from which the placenta arises. **b**, In most other settings studied, asymmetric division involves coordination between multiple polarized cues (such as polarized proteins) and a specific division axis. **c**, In other species, such as flies, asymmetric inheritance of protein aggregates provides a memory of the mother cell's state.

actin (a component of the cell's 'skeleton') and polarity proteins[3]. But, using fast live imaging, the group that performed the current study showed previously[3] that the apical domain is transiently lost during mitotic cell division, before re-forming in the daughter cells on the embryo's periphery. This puzzling observation suggested the existence of other factors that act as a memory of polarity during divisions. Following up hints from the old literature on mouse embryos[4], Lim and colleagues have now homed in on keratin, a type of intermediate filament protein.

Imaging keratin, the team observed a few short keratin polymers in a subset of cells in the 8-cell embryo. As these filaments grew during the part of the cell cycle between divisions, called interphase, they became preferentially associated with the apical, actin-rich cortex — a layer of proteins just inside the cell membrane. When the apical domain became disassembled during mitosis, these keratin filaments remained in place (Fig. 1a).

Although this might seem unexpected, other intermediate filaments have been shown to remain associated with the cortex during mitosis[5,6]. Lim *et al.* found that apical retention of these polymers depends on their slow diffusion, which is limited by their large molecular weight and the cytoplasmic actin meshwork in which they are embedded. As a result, keratin filaments are inherited by daughter cells that retain an outward face. So, once positioned at one end of the cell, these relatively inert stable polymers act as a physical memory of polarity.

The authors went on to show that, as cells of the new 16-cell embryo exit mitosis, inherited keratin filaments accelerate the repolarization of the apical cell cortex, which biases the cell towards becoming trophectoderm (through signalling pathways that involve Yap and Hippo proteins[7]). In turn, this bias is associated with high levels of keratin expression. So, over a period of hours, positive feedback in the system reinforces the accumulation of keratin in peripheral cells, and inhibits its expression in cells at the embryo's centre. By the 32-cell stage, when cell fate is more firmly established, the embryo itself is clearly polarized, with an outer, keratin-rich supporting cell layer, and inner cells that lack keratin.

Given its well-established role in stiffening epithelial cells[8], in an embryonic context keratin might both prevent outer cells from becoming internalized by apical constriction and help to give the trophectoderm its near-perfect spherical shape. Conversely, keeping keratin levels low in cells in the centre might help them retain the flexibility in shape that they require to generate a multilayered embryo.

By using keratin filaments to stably mark the peripheral cortex, mammalian embryos (in which patterns of cell division differ widely between individuals) can ensure that cells fated to become trophectoderm are always formed in the outer layer of the cell cluster, irrespective of the orientation of divisions. Keratins play a part as asymmetrically inherited fate determinants only in these relatively rare 'inside-out' divisions. The early mammalian embryo therefore differs from most other systems in which asymmetric division has been studied (Fig. 1b). In those cases, in order to impose a reproducible division asymmetry, the mitotic apparatus itself is oriented so that daughter cells inherit different complements of cortically localized cell-fate determinants[9].

In the coming years, it will be important to reconcile Lim and colleagues' data with suggestions of roles for the unequal segregation of messenger RNA encoding the Cdx2 protein[10] (one function of which is in forming the trophectoderm), or for differential contractility of the actomyosin protein complex[11], in the symmetry-breaking events that occur at this stage in mouse embryos. The fate of dividing cells that do not express keratin at the 8-cell stage also remains to be studied.

Taking a broader perspective, this work shows how the cellular function of a protein such as keratin can emerge from its physical characteristics. In early mouse embryos, keratins provide a physical memory of polarity that is relatively independent of cell-division events. In other organisms, from bacteria to multicellular animals, other proteins that polymerize or form aggregates have also been found to provide a physical memory of cell state during asymmetric divisions[12] (Fig. 1c). So Lim and co-workers' study provides another intriguing example of nature exploiting the material properties of a protein.

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