Schwörer et al. focused on changes in H3K4me3 to explain the transcriptional and subsequent translational difference in **Hoxa9** between activated adult and aged stem cells, but other possibilities cannot be ruled out. RNA sequencing by the authors indicated that **Hoxa9** transcripts are expressed in both adult and aged activated stem cells. However, H3K4me3 is not present at the **Hoxa9** region in activated adult stem cells. Perhaps, then, a different epigenetic mechanism enables **Hoxa9** transcription in adult stem cells, but protein activity is repressed. Alternatively, maybe a subset of activated adult stem cells is in a permissive state, allowing low-level **Hoxa9** gene expression.

It remains unclear why chromatin unwinds in aged stem cells following injury. It is possible that changes in the activity of anti- and pro-ageing factors over a lifetime of wear and tear drive a maladaptive epigenetic response to injury. Alternatively, the chromatin might open as an injury-response mechanism to facilitate DNA repair.

This impressive study demonstrates how abnormal stress-induced epigenetic activation can alter stem-cell function during ageing. The work could have broad medical implications if **Hoxa9** is confirmed to be an intermediary between the epigenetic response to injury and developmental signalling pathways during regeneration in elderly humans. Understanding the upstream events that cause epigenetic de-repression of **Hoxa9** might then be beneficial for strategies to prevent — or even reverse — age-associated declines in muscle regeneration.

**Figure 1 | A changing epigenetic landscape during ageing.** Molecular modifications to histone proteins, around which DNA is wrapped as chromatin, determine whether chromatin is loosely packaged — a state permissive for gene transcription — or closed in a repressive state. a, In quiescent young-adult-muscle stem cells, chromatin has high levels of activating modifications (for example, H3K4me3) and low levels of repressive marks (H3K27me3), leading to a permissive state. Following injury, when stem cells are activated, chromatin accumulates H3K27me3 and becomes repressive.

b, Schwörer et al. analysed histone modifications and **Hoxa9** gene expression in aged-mouse muscle stem cells. Aged quiescent stem cells acquire more repressive marks than their young-adult counterparts, presumably repressing **Hoxa9** transcription. Injury results in a global increase of another active marking (acetylation, Ac) and a decline in repressive marks, opening chromatin. There is also an increased recruitment of a Mll1–Wdr5 protein complex to the **Hoxa9** region, which promotes expression of **Hoxa9** and downstream developmental signalling pathways, contributing to the loss of muscle stem-cell function.

### An eye on retinal recovery

**Retinal-cell transplants restore vision in mouse models of retinal degeneration.** It emerges that the transplant leads to an exchange of material between donor and host cells — not to donor-cell integration into the retina, as had been presumed.

**Michael A. Dyer**

The degeneration of the light-sensing photoreceptor neurons in the retina at the back of the eye is a cause of blindness in millions of people worldwide. One possible therapeutic approach to treating advanced photoreceptor degeneration would be to transplant healthy photoreceptor precursors into the damaged eye, in the hope that they would integrate into the retina and restore vision. Such a strategy was shown to be promising in mouse models, raising the possibility of clinical trials in the near future. But three studies in *Nature Communications* report that the transplanted cells rarely integrate into the retina as previously believed — instead, they transfer some of their contents to recipient photoreceptors. This finding is a setback for efforts to replace lost photoreceptors, but might point to fresh approaches to rejuvenating aged or diseased photoreceptors and decelerating retinal degeneration.

In 2006, a group of researchers transplanted photoreceptor precursors that were indelibly marked with green fluorescent protein (GFP) into the subretinal region underlying the retinas of adult mice. Several weeks later, the team found GFP-expressing mature photoreceptors in the retina, and concluded that the immature photoreceptors had migrated into the site and differentiated.

In a subsequent study, the same research team showed that transplantation of photoreceptor precursors could partially restore vision in mouse models of retinal degeneration. The researchers concluded that the transplanted photoreceptor precursor cells...
had functionally integrated into the neural circuitry. Transplantation studies using GFP-expressing bone-marrow cells had previously revealed that donor cells could fuse with neurons, giving rise to cells with two nuclei, but the research team ruled out this possibility in the retina, showing that GFP-expressing cells in the recipient contained only a single nucleus.

Unlike the stem cells that can rejuvenate adult muscle and blood, the human retina has no stem cell that can regenerate photoreceptors. However, advances in stem-cell programming have enabled the production of a renewable pool of photoreceptor precursors. These advances, together with the retinal-transplant research, set the stage for a personalized stem-cell therapy for retinal degeneration. In theory, a patient’s blood or skin cells could be reprogrammed into stem cells that give rise to photoreceptor precursors for transplantation into the eye. There, they would integrate into the retina and partially restore vision.

Unfortunately, the possibility that precursors transfer molecular or genetic information to recipient photoreceptors, rather than integrating, had not been fully excluded. Material transfer would not be beneficial in advanced neurodegeneration, in which few of the patient’s original photoreceptor cells remain. Singh et al., Santos-Ferreira et al. and Pearson et al. tested this possibility directly.

The three groups transplanted GFP-expressing photoreceptor precursors taken from mice up to one week old into the subretinal space of a recipient mouse retina that was labelled with the red fluorescent protein dsRED. If donor cells integrated as previously proposed, GFP-expressing cells would be surrounded by dsRED-expressing retinal cells. However, the investigators discovered that most of the GFP-expressing photoreceptors in the retina after transplantation also expressed dsRED. A series of complementary experiments ruled out the possibility of either integration or full nuclear fusion. Instead, donor cells had transferred factors (DNA, RNA or protein) that confer GFP expression to the cytoplasm of photoreceptors in the recipient retina (Fig. 1).

The 2006 experiments showed that GFP persisted in the recipient retina for up to a year, indicating that the transferred material is stable (although it remains to be seen whether this reflects the continuous active transfer of material or persistence after a single transfer event). Furthermore, the three current studies showed that the enzyme Cre recombinase can be transferred from donor to recipient photoreceptors, indicating that transfer is not restricted to fluorescent proteins. In addition, the restoration of vision in genetically engineered mouse models of retinal degeneration suggests that the genetic defects that cause degeneration can be at least partially rescued in a subset of recipient photoreceptors. Together, these data point to a potential new approach to preserve photoreceptors in an injured or diseased retina — engineering cells or cellular products to efficiently transport factors required to preserve photoreceptors into the retina.

One aspect of transfer that must be carefully validated and optimized in advance of human trials is the developmental-stage specificity of material transfer from donor photoreceptor precursors. Singh et al. found that such precursors taken from mice between one and seven days old transfer GFP into the recipient retina more efficiently than do more highly differentiated donors. It remains to be seen whether this specificity reflects a unique aspect of the cellular physiology of photoreceptors at this age, when they are partway through differentiating into mature cells, or a nonspecific by-product of the process by which the cells were prepared for transplantation. Pearson et al. found that GFP-expressing retinal progenitor cells in the embryo rarely transfer material to recipient photoreceptors, suggesting that only photoreceptors, and not all retinal lineages, can transfer material in this way.

Like many important advances, these three papers lead to more questions than answers. First and foremost, what are the underlying molecular and cellular mechanisms for material transfer? Perhaps transfer occurs through membrane-derived microvesicles or through protein complexes that form junctions between the cells. What is the cellular material being transferred from the donor to the recipient — DNA, RNA or proteins? Pearson and colleagues found that subretinal injection of purified GFP protein failed to produce labelled recipient photoreceptors, suggesting that proteins are not the transferred material. However, it is possible that transfer is mediated by a larger protein complex, absent in the purified sample.

Although the findings of these studies might dampen enthusiasm for replacing photoreceptors lost during retinal degeneration in advanced cases, they also open up an exciting area of retinal research. Pursuing this avenue will advance our understanding of photoreceptors and might eventually lead to the design of methods to preserve retinal function in people with early-stage disease.

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