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'Open minded' cells: how cells can change fate

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It has long intrigued researchers why some but not all organisms can regenerate missing body parts. Plants are remarkable in that they can regenerate the entire organism from a small piece of tissue, or even a single cell. Epigenetic mechanisms that control chromatin organization are now known to regulate the cellular plasticity and reprogramming necessary for regeneration. Interestingly, although animals and plants have evolved different strategies and mechanisms to control developmental processes, they have maintained many similarities in the way they regulate chromatin organization. Given that plants can rapidly switch fate, we propose that an understanding of the mechanisms regulating this process in plant cells could provide a new perspective on cellular dedifferentiation in animals.

Regeneration: the significance of undifferentiated and differentiated cells

The capacity to regenerate missing body parts, organs or tissues in animals and plants relies on the ability to maintain or generate groups of stem cells. Stem cells are undifferentiated cells that can both renew themselves and differentiate; their generative potential depends on the type of organism and tissue. In mammalian nervous system, muscle and epithelia, the generative potential of stem cells is restricted to a limited number of cell types, and in the bone marrow, stem cells seem to be able to colonize damaged sites in different tissues and give rise to a broad spectrum of cell types [1–3]. In a very few cases, stem cells are totipotent and can give rise to every cell type in an organism; the entire organism can therefore be regenerated from a single cell. Known totipotent cells are the zygotes and planaria blastema cells [4].

When a population of stem cells is not maintained, differentiated cells can sometimes be induced to switch their fate and acquire a new one, a phenomenon known as transdifferentiation. Injury or changes in external stimuli or in positional information can induce transdifferentiation, a process that is common in amphibians, in which entire organs or organ parts can be regenerated. For example, in axolotls, neural cells can transdifferentiate into muscle and cartilage during tail regeneration [5] and in the newt, eye epithelial cells can transdifferentiate into lens cells (Figure 1a) [6,7]. In mammals, examples of transdifferentiation are seen in the liver [8] and in the Schwann cells of the peripheral nervous system [9] and, recently, mouse auditory epithelial support cells were shown to transdifferentiate into sensory hair cells [10].

Plants not only maintain pools of stem cells, known as meristematic cells, from which new shoots and roots are produced throughout the life of the plant, but can also induce differentiated cells to acquire new fates and generate new organs. An entire plant can be regenerated *in vitro* from a single somatic cell [11], and the ability of many plant species to generate embryos from cells other than the zygote shows that plant cells can retain their totipotency. These asexual embryos, termed somatic embryos, recapitulate the sequence of zygotic embryonic stages and their origins can be diverse – from somatic cells, unfertilized egg or maternal tissue, from pollen grains or from undifferentiated masses of cells derived from explants cultured *in vitro* [12]. The full zygotic potential retained by somatic plant cells can also be observed in some species, in which entire plantlets, with shoots and roots, are generated from the margins of the leaf [13] (Figure 1b). Here, we discuss the abilities of animal and plant cells to change their fate and propose how plant cells can maintain their totipotency.

How cells change their mind: nuclear reorganization, cellular memory and cell division

During development, cell type-specific gene expression programs are established and are then maintained through subsequent cell division cycles. At the beginning of the 20th century, one of the important questions was whether cells undergo stable changes during the course of differentiation and whether these changes are associated with the loss of genetic material. Nuclear transfer studies in the 1950s demonstrated that cells do indeed maintain their genetic information during differentiation and that they can reprogram this information and acquire new identity. In fact, in pioneering experiments it was shown that differentiated somatic nuclei introduced into enucleated *Xenopus* oocytes re-entered the cell cycle and gave rise to normal embryos similar to those generated from fertilized eggs [14]. Subsequent studies on heterokaryons – binucleate cells derived from the fusion of two different cell types – showed that changes in cell type-specific gene expression patterns occur in the absence of DNA synthesis and replication and involve a phase of 'genome resetting' during which patterns of gene expression are reorganized [15,16]. Recent results show that treatment of heterokaryons with the histone deacetylase

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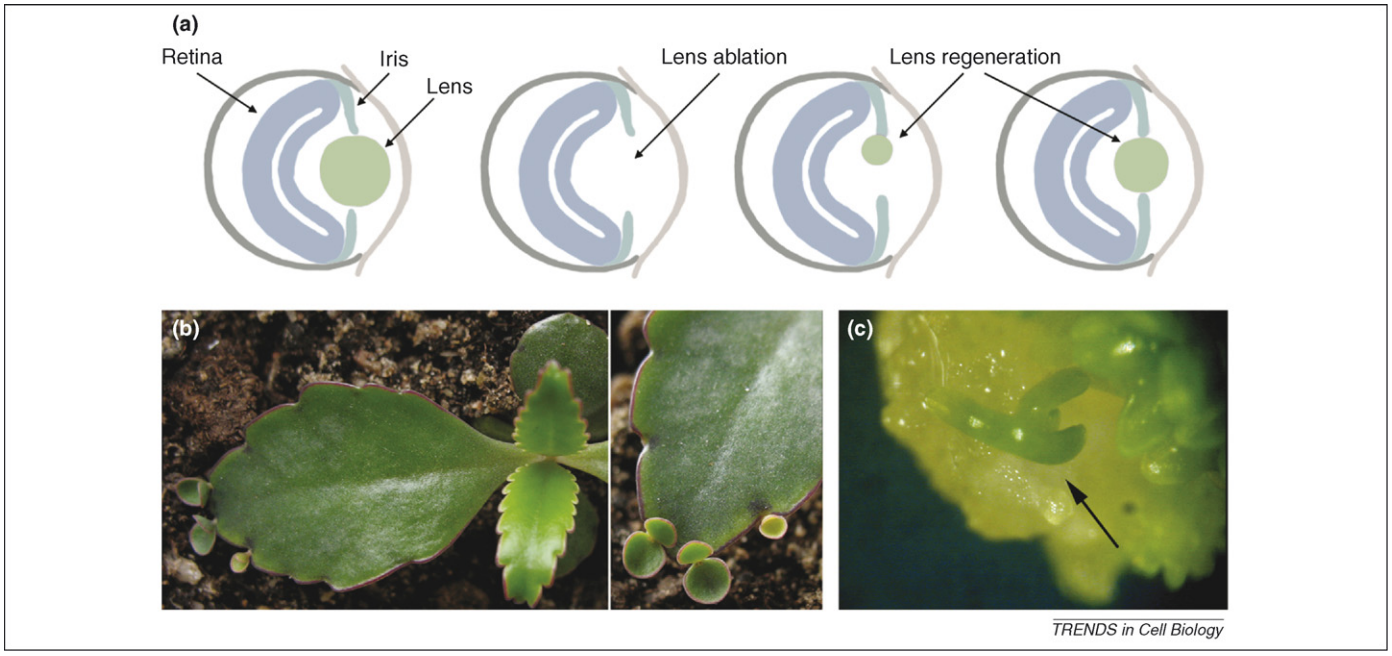

Figure 1. Examples of regeneration. **(a)** Schematic representation of eye lens regeneration. In adult newts, the regeneration of the lens after damage or removal is characterized by the transdifferentiation of differentiated epidermal cells from the dorsal iris into lens cells. **(b)** The small plants formed from Kalanchoe leaves provide a fascinating example of totipotency: when leaves are still attached to the plant, small groups of cells located in the sinuses of the leaf margins proliferate and give rise to entire small plants with shoots and roots. The plantlets spontaneously detach and fall on soil, where they continue to grow and expand. **(c)** In the *clf swn* double mutant of *Arabidopsis*, which lacks the activity of two components of the plant PRC2 complex, tissue proliferation (the mass of cells with pale yellow or green colour) and formation of somatic embryos (arrow) are observed. Therefore, polycomb genes are required to maintain the differentiated states and, in their absence, plant cells can display their totipotency and give rise to embryos derived from somatic cells. Part (c) is courtesy of Justin Goodrich.

inhibitor trichostatin A impairs the reprogramming process, and gene expression programmes of the two cell types co-exist. Thus, reprogramming in heterokaryons is suggested to occur in two distinct phases: first extinction of one cell type-specific expression program and then activation of the other cell type-specific program [16]. Reprogramming is accompanied by nuclear enlargement and large-scale chromatin reorganization in heterokaryons and in nuclear transfer experiments [17–19]. Similar chromatin changes have been observed in plant protoplasts, which are differentiated cells from which the cell wall has been removed. In protoplasts the loss of differentiated state is accompanied by changes in the distribution and organization of heterochromatin, localized chromatin decondensation and disruption of the nucleolus [20].

Post-translational histone modifications, such as methylation, acetylation, ubiquitination, phosphorylation, ribosylation, histone variants and DNA methylation, contribute to the establishment and maintenance of chromatin states associated with defined gene expression programmes. As yet we do not know in detail how genome resetting and reprogramming is achieved, but an increasing number of chromatin remodelling factors and complexes required for the removal of epigenetic markings during these processes are being identified [21–23]; we cannot discuss most of them in this article. However, to understand the basis of cellular plasticity it is necessary to understand not only how chromatin remodelling is achieved, but also what controls chromatin remodelling and therefore what promotes or prevents it.

Although reprogramming has been observed during *in vivo* and *in vitro* heterokaryon formation [16,17], cell fate switch is commonly regarded as being associated with the re-entry of the cell into the cell cycle. Recent studies in *Drosophila* have begun to unravel the molecular basis of transdifferentation and have provided new insights into the link between cell fate switch, cellular memory and cell division. Transdifferentation has been studied in *Drosophila* imaginal discs – larval structures in which cells are already committed to a fate destined to give rise to defined body parts in the adult. After mechanical fragmentation of the imaginal discs, some cells committed to a leg fate can switch to a wing fate [24]. This fate switch takes place in response to the inductive signal of the c-Jun N-terminal kinase (JNK) signalling pathway, which is required for wounding healing and down-regulates Polycomb group (PcG) proteins [25,26]. Polycomb (PcG) proteins are a group of highly conserved regulatory factors responsible for the maintenance of transcriptionally silenced states through multiple rounds of cell division [27]. Two distinct PcG complexes have been identified in animals, Polycomb repressive complex (PRC)1 and PRC2. The current model is that PRC2 complexes are involved in depositing epigenetic marks that are subsequently recognized by PRC1. PRC1 is then responsible for locking in repressive chromatin states that maintain long-term cellular memory (Figure 2) [27].

In *Drosophila* there is direct evidence that changes in the cell cycle are involved in the acquisition of cellular plasticity. Leg to wing transdifferentiation is observed in cells that undergo proliferation and form a mass of undifferentiated cells, but these cells have a distinctly longer S phase than stem cells and committed cells [28]. Transdifferentiating cells might need to spend extra time in S phase to reset the epigenetic marks characteristic of the previous commitment [28]. Moreover, the down-regulation of PcG

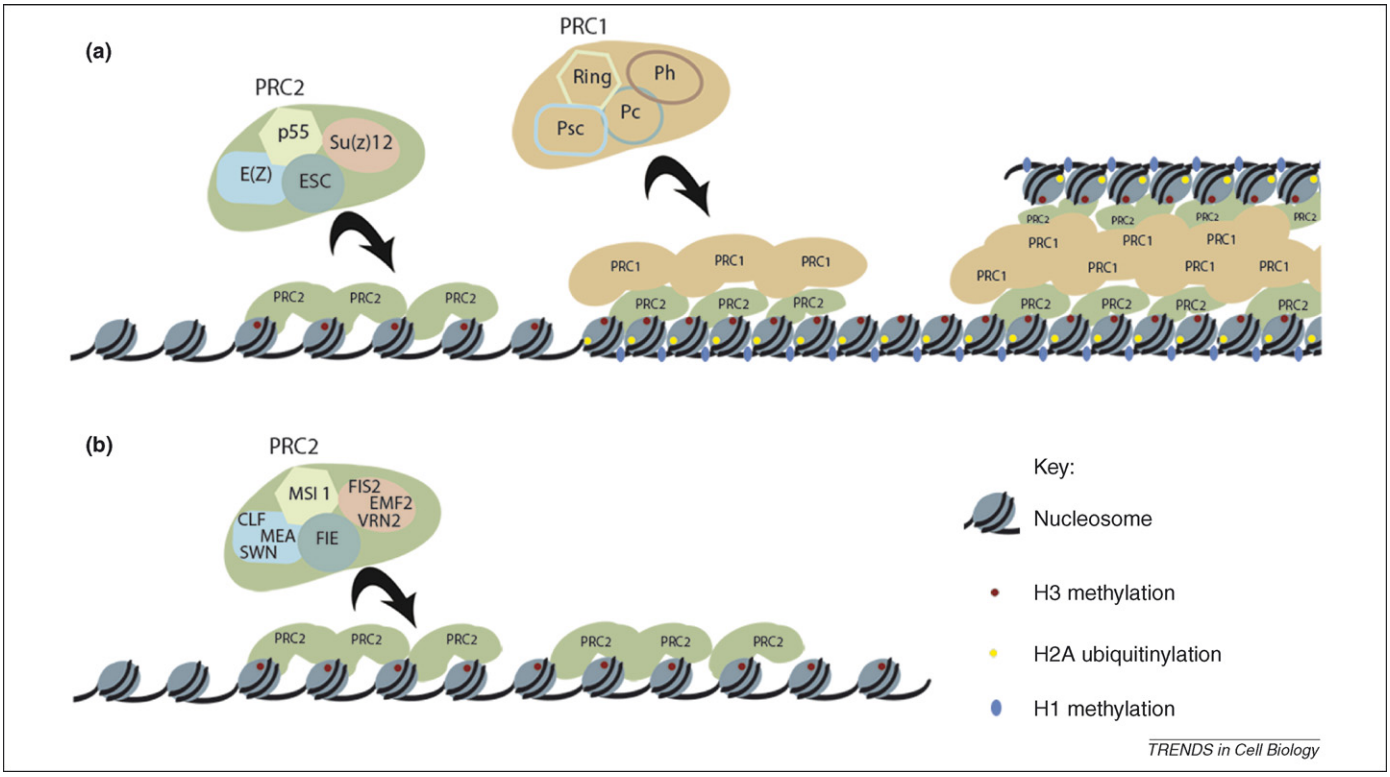

Figure 2. Schematic representation of the composition and role of PRC1 and PRC2 in inhibiting gene expression and chromatin organization. In **(a)** animals and **(b)** plants, PRC2 is responsible for the methylation of histone H3 at the residues Lys27 and Lys9, which are post-transcriptional modifications associated with repressive states of transcription (denoted by red dots on nucleosome histone cores). The core components of animal PRC2 are E(Z), Su(z)12, p55 and ESC, which are conserved between animals and plants. (*Drosophila* homologues have been used to represent the animal components.) Plant PRC2 components have been duplicated: CLF, SWN and MEA are homologous to E(Z); FIS2, EMF2, VRN2 to Su(z)12, MSI 1 to p55 and FIE to ESC. In animals it is not known whether PRC2 is able to silence its targets on its own, but plant PRC2 can do so. In addition to PRC2, animals possess PRC1, whose core components are Pc, Ph, Psc and Ring. PRC1 has been implicated in several different functions that, either together or individually, are responsible for the establishment and maintenance of long-term memory. PRC1 has been shown *in vitro* to cause compaction of chromatin (represented by the close proximity of nucleosomes to one another). *In vivo*, it inhibits ATP-dependent chromatin remodelling and transcription by interacting directly with the transcriptional machinery (not shown), and it is responsible for the ubiquitination of histone H2A Lys119 (yellow dots on the nucleosome histone cores) and methylation of histone H1 Lys26 (blue ellipses between nucleosomes). In addition, PRC1 promotes inter-chromosomal association and the clustering of PcG bodies (nuclear structures containing large concentrations of PcG) has been observed. Genes structurally or functionally homologous to PRC1 components have not yet been found in plants. CLF, Curly Leaf; ESC, Extra Sex Combs; EMF2, Embryonic Flower 2; E(Z), Enhancer of Zeste; FIE, Fertilisation Independent Endosperm; FIS2, Fertilisation Independent Seed 2; MEA, Medea; MSI 1, Multicopy Suppressor of Ira 1; Pc, Polycomb; Ph, Polyhomeotic; Psc, Posterior Sex Combs; Su(z)12, Suppressor of Zeste-12; Swn, Swinger; VRN2, Vernalisation 2.

proteins observed in transdifferentiating cells might be linked not only to changes in chromatin organization, but also to cell cycle re-entry, because PcG proteins have been found to interact with cyclin A, which is involved in the progression through S and M phase in *Drosophila* [29]. S phase might be the best time to reset the genome efficiently and rapidly because at this stage, when DNA is duplicated, chromatin is in an open conformation and structural proteins can be rapidly reorganized. However, from the experimental data it is not yet clear whether differentiated cells regain their pluripotency before division or whether division alone is necessary and sufficient to reset the previous cellular commitment. In newt, upon damage or removal of the lens, epithelial cells from the dorsal iris can dedifferentiate, proliferate and redifferentiate into lens cells and recent data indicate that dedifferentiation can take place in the absence of proliferation [7]. Therefore, from this work and also the work on heterokaryons and plant protoplasts, it could be suggested that a phase of dedifferentiation occurs before cell division and is required for cell cycle re-entry. It would be interesting to know the role of PcG proteins during reprogramming in heterokaryons, in which no replication and cell division occur.

How plant cells can switch fate

Plant totipotency remains a mystery, although there is indirect evidence that PcG proteins are also involved in cell fate switch. PRC2 is conserved between animals and plants (Figure 2). In plants, as in mammals, several genes encoding members of the PRC2 complex have been duplicated, thus conferring a high versatility of complex composition that can be associated with temporal and tissue specificity of activity [30]. In *Arabidopsis*, mutations affecting genes encoding members of PRC2 cause reorganization of heterochromatin domains and affect several developmental processes [31]. The double mutant *curly leaf swinger* (*clf swn*) is interesting. Among other defects, it forms masses of undifferentiated cells on the plantlet tissues that then give rise to somatic embryos (Figure 1c) [32]. CLF and SWN act redundantly and are homologues of *Drosophila* Enhancer of Zeste E(Z), a PRC2 component [32]. By analogy with the mechanism of transdifferentation in *Drosophila*, we might hypothesize from the phenotype of the *clf swn* mutant that a down-regulation of PcG proteins is involved in resetting gene expression programmes before or during the formation of somatic embryos.

Changes in cell fate can be observed *in vivo* in the root epidermis of *Arabidopsis*, in which the fate of the two

epidermal cell types – hair-forming and non-hair-forming cells – is under strict control of positional information emanating from the underlying tissue layer (Figure 3) [33]. Changes in positional information are accompanied by fate switch and rapid changes in chromatin accessibility of a large genomic region of ~40 kb spanning the *GL2* locus, which promotes one of the two alternative epidermal cell fates [34]. Such large-scale chromatin reorganization upon fate switch suggests the presence of a chromatin complex occupying the genomic region around the *GL2* locus and involved in maintaining epidermal cell identity. As a hypothetical working model, we suggest that the *GL2* region is silenced by the presence of PcG proteins or a similar protein complex. This would be consistent with the size of Polycomb chromatin binding sites, which have been shown to range from 10 kb to 145 kb in the *Drosophila* genome [35]. Therefore the down-regulation of PcG proteins or their removal could reduce the silencing of the target genes and increase cellular plasticity by facilitating the accessibility of new transcription factors to developmental regulators and easing the switch to new epigenetic states.

The fate switch described earlier in the root epidermis occurs in cells that have spontaneously undergone a change of 90° in the division plane. This division causes cells to become exposed to new positional information and the division itself could be necessary for cell fate switch. One possibility is that plant cells rapidly respond to changes in external stimuli, such as positional information, because they reset and establish *de novo* their gene expression programmes at every cell division. This might suggest that plant cells do not use or require a cellular memory mechanism and just respond to positional information. However, it has been shown that plants do use cellular memory mechanisms mediated by PcG proteins in several processes, such as leaf and flower development, tissue imprinting in the seed and vernalization – a period of cold exposure required by many plants to flower in the right season [36]. It would be interesting to know whether all plant cells or just some cell types use cellular memory mechanisms and exactly when and how they are set into place.

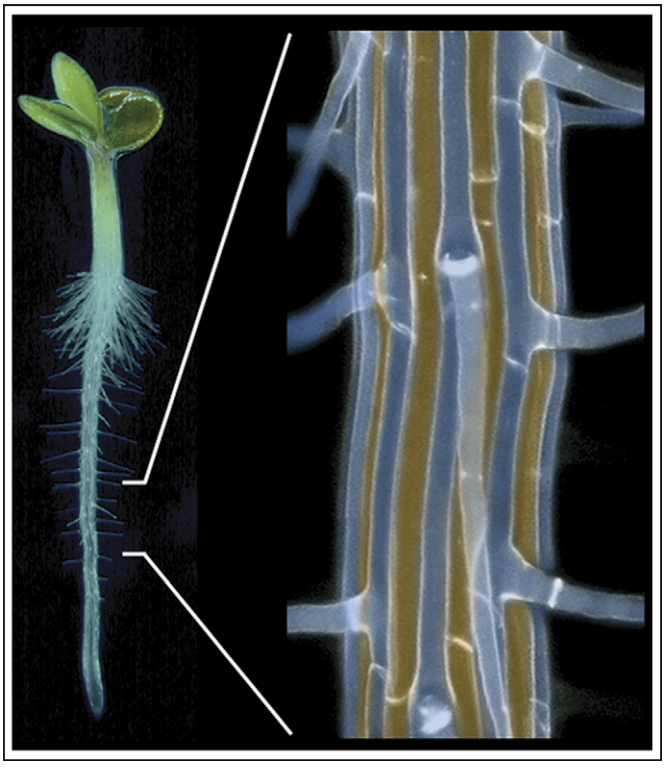

Figure 3. In *Arabidopsis* young seedlings (left, with a close-up on the right), the root epidermis is composed of two cell types organized into alternating files of hair (pseudo-coloured blue) and non-hair cells (pseudo-coloured brown). Extracellular signals control the fate of epidermal cells and when these change, cells switch fate.

Experimental results from somatic embryogenesis further support the idea that plants maintain their fate using a cellular memory mechanism and not just by positional information. Gene expression profile studies carried out on soybean suggested that cells that give rise to somatic embryos undergo a phase of dedifferentiation of about two weeks during which cell proliferation takes place [37]. This work shows a link between reprogramming and re-entry into the cell cycle, as in animal cells. However, laser ablation studies have shown that cells can switch fate without undergoing division when exposed to new positional information [38,39]. In this case cell division is not necessary for reprogramming to occur. Therefore, as in animals, cellular plasticity occurs in plants both with and without cell division; plant cells seem to be more responsive to their microenvironment than animal cells.

Why, then, can plant cells switch fate so readily in response to extracellular signals, and what prevents most animal cells from doing so? One possibility is that plant cells maintain a degree of 'commitment' but can rapidly integrate external stimuli with the intrinsic mechanisms controlling patterns of gene expression, and that this integration depends on maintaining a dynamic chromatin state. Interestingly, animal stem cells seem to display a more dynamic chromatin state than differentiated cells, because structural chromatin proteins like histones are exchanged more rapidly in stem cells than in differentiated cells, which could favour rapid changes in gene expression programmes [40]. Furthermore, the promoter regions of genes required to control cell type-specific commitment are marked by mixed sets of histone modifications. These include modifications that are normally associated with gene silencing and modifications associated with expression in differentiated cells, thus creating a set of preselected cell-type specific genes that are kept in a silenced state in stem cells [41]. PcG proteins are necessary to maintain the pluripotent animal stem cell state. In fact, embryonic stem cells lacking EMBRYONIC ECTODERM DEVELOPMENT (EED), a PRC2 component homologue required for the methylation of histone H3 Lys27, an epigenetic mark associated with transcriptional repression, express several neural-specific genes [41–43]. These strategies could enable stem cells to maintain their undifferentiated state but also, under the appropriate inductive signals, to undergo differentiation by rapidly inducing the expression of particular patterns of cell type-specific genes.

In plants, although PRC2 homologues are present and are functionally conserved, no functional or structural PRC1 homologues have so far been found [36]. Therefore, plants might be able to maintain a degree of cellular

memory established by PRC2 but, in the absence of PRC1, might not be able to lock this state and preserve long-term silencing by this mechanism, as animals do.

Concluding remarks

Overall, differentiated plant cells might be more similar to pluripotent animal stem cells in their ability to continuously perceive extracellular signals and in maintaining a chromatin organization that allows a fast response to the signals. This strategy could be important because plants, unlike animals, grow throughout their life and are sessile organisms and so, to guarantee their survival, have an over-riding need to integrate their growth and development continuously with their surrounding environment and its sudden changes. Overexpression of transcription factors required for stem cell identity in differentiated cells is sufficient for their reprogramming and confers cellular pluripotency to both plant and animal cells [44,45]. In plants these experiments resulted in the generation *in vivo* of shoots from roots; in animals *in vitro* reprogrammed cells underwent differentiation upon transplantation, but failed to give rise to fully developed foetuses. This suggests that additional or different epigenetic checks are in place in animal cells compared with plant cells. The ability to compare the mechanisms regulating cellular plasticity between plants and animals might provide insights into why fate switch and regeneration are rare events in animals. Such understanding could help to find new strategies to improve animal regenerative capacity.

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References

1 Alison, M.R. *et al.* (2006) Stem cell plasticity and tumour formation. *Eur. J. Cancer* 42, 1247–1256
2 Raff, M. (2003) Adult stem cell plasticity: fact or artifact? *Annu. Rev. Cell Dev. Biol.* 19, 1–22
3 Wagers, A.J. and Weissman, I.L. (2004) Plasticity of adult stem cells. *Cell* 116, 639–648
4 Salo, E. (2006) The power of regeneration and the stem-cell kingdom: freshwater planarians (Platyhelminthes). *Bioessays* 28, 546–559
5 Echeverri, K. and Tanaka, E.M. (2002) Ectoderm to mesoderm lineage switching during axolotl tail regeneration. *Science* 298, 1993–1996
6 Grogg, M.W. *et al.* (2005) BMP inhibition-driven regulation of six-3 underlies induction of newt lens regeneration. *Nature* 438, 858–862
7 Madhavan, M. *et al.* (2006) The role of Pax-6 in lens regeneration. *Proc. Natl. Acad. Sci. U. S. A.* 103, 14848–14853
8 Taub, R. (2004) Liver regeneration: from myth to mechanism. *Nat. Rev. Mol. Cell Biol.* 5, 836–847
9 Harrisingh, M.C. *et al.* (2004) The Ras/Raf/ERK signalling pathway drives Schwann cell dedifferentiation. *EMBO J.* 23, 3061–3071
10 White, P.M. *et al.* (2006) Mammalian cochlear supporting cells can divide and trans-differentiate into hair cells. *Nature* 441, 984–987
11 Vasil, V. and Hildebrandt, A.C. (1965) Differentiation of tobacco plants from single isolated cells in microcultures. *Science* 150, 889–892
12 Zimmerman, J.L. (1993) Somatic embryogenesis: a model for early development in higher plants. *Plant Cell* 5, 1411–1423
13 Kerstetter, R.A. and Hake, S. (1997) Shoot meristem formation in vegetative development. *Plant Cell* 9, 1001–1010
14 Briggs, R. and King, T.J. (1952) Transplantation of living nuclei from blastula cells into enucleated frogs' eggs. *Proc. Natl. Acad. Sci. U. S. A.* 38, 455–463
15 Blau, H.M. and Blakely, B.T. (1999) Plasticity of cell fate: insights from heterokaryons. *Semin. Cell Dev. Biol.* 10, 267–272
16 Terranova, R. *et al.* (2006) Acquisition and extinction of gene expression programs are separable events in heterokaryon reprogramming. *J. Cell Sci.* 119, 2065–2072
17 Weimann, J.M. *et al.* (2003) Stable reprogrammed heterokaryons form spontaneously in Purkinje neurons after bone marrow transplant. *Nat. Cell Biol.* 5, 959–966
18 Byrne, J.A. *et al.* (2003) Nuclei of adult mammalian somatic cells are directly reprogrammed to oct-4 stem cell gene expression by amphibian oocytes. *Curr. Biol.* 13, 1206–1213
19 Gonda, K. *et al.* (2003) Reversible disassembly of somatic nucleoli by the germ cell proteins FRGY2a and FRGY2b. *Nat. Cell Biol.* 5, 205–210
20 Grafi, G. (2004) How cells dedifferentiate: a lesson from plants. *Dev. Biol.* 268, 1–6
21 Bultman, S.J. *et al.* (2006) Maternal BRG1 regulates zygotic genome activation in the mouse. *Genes Dev.* 20, 1744–1754
22 Hsieh, J. and Gage, F.H. (2005) Chromatin remodeling in neural development and plasticity. *Curr. Opin. Cell Biol.* 17, 664–671
23 Cairns, B.R. (2005) Chromatin remodeling complexes: strength in diversity, precision through specialization. *Curr. Opin. Genet. Dev.* 15, 185–190
24 Maves, L. and Schubiger, G. (2003) Transdetermination in *Drosophila* imaginal discs: a model for understanding pluripotency and selector gene maintenance. *Curr. Opin. Genet. Dev.* 13, 472–479
25 Klebes, A. *et al.* (2005) Regulation of cellular plasticity in *Drosophila* imaginal disc cells by the Polycomb group, trithorax group and lama genes. *Development* 132, 3753–3765
26 Lee, N. *et al.* (2005) Suppression of Polycomb group proteins by JNK signalling induces transdetermination in *Drosophila* imaginal discs. *Nature* 438, 234–237
27 Ringrose, L. and Paro, R. (2004) Epigenetic regulation of cellular memory by the Polycomb and Trithorax group proteins. *Annu. Rev. Genet.* 38, 413–443
28 Sustar, A. and Schubiger, G. (2005) A transient cell cycle shift in *Drosophila* imaginal disc cells precedes multipotency. *Cell* 120, 383–393
29 Martinez, A.M. *et al.* (2006) Polycomb group-dependent Cyclin A repression in *Drosophila*. *Genes Dev.* 20, 501–513
30 Guitton, A.E. and Berger, F. (2005) Control of reproduction by Polycomb Group complexes in animals and plants. *Int. J. Dev. Biol.* 49, 707–716
31 Schubert, D. *et al.* (2005) Epigenetic control of plant development by Polycomb-group proteins. *Curr. Opin. Plant Biol.* 8, 553–561
32 Chanvivattana, Y. *et al.* (2004) Interaction of Polycomb-group proteins controlling flowering in *Arabidopsis*. *Development* 131, 5263–5276
33 Ueda, M. *et al.* (2005) Stepwise understanding of root development. *Curr. Opin. Plant Biol.* 8, 71–76
34 Costa, S. and Shaw, P. (2006) Chromatin organization and cell fate switch respond to positional information in *Arabidopsis*. *Nature* 439, 493–496
35 Tolhuis, B. *et al.* (2006) Genome-wide profiling of PRC1 and PRC2 Polycomb chromatin binding in *Drosophila melanogaster*. *Nat. Genet.* 38, 694–699
36 Goodrich, J. and Tweedie, S. (2002) Remembrance of things past: chromatin remodeling in plant development. *Annu. Rev. Cell Dev. Biol.* 18, 707–746
37 Thibaud-Nissen, F. *et al.* (2003) Clustering of microarray data reveals transcript patterns associated with somatic embryogenesis in soybean. *Plant Physiol.* 132, 118–136
38 van den Berg, C. *et al.* (1995) Cell fate in the *Arabidopsis* root meristem determined by directional signalling. *Nature* 378, 62–65
39 Berger, F. *et al.* (1998) Positional information in root epidermis is defined during embryogenesis and acts in domains with strict boundaries. *Curr. Biol.* 8, 421–430
40 Meshorer, E. *et al.* (2006) Hyperdynamic plasticity of chromatin proteins in pluripotent embryonic stem cells. *Dev. Cell* 10, 105–116

41 Azuara, V. *et al.* (2006) Chromatin signatures of pluripotent cell lines. *Nat. Cell Biol.* 8, 532–538
42 Boyer, L.A. *et al.* (2006) Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature* 441, 349–353
43 Lee, T.I. *et al.* (2006) Control of developmental regulators by Polycomb in human embryonic stem cells. *Cell* 125, 301–313
44 Gallois, J.L. *et al.* (2004) WUSCHEL induces shoot stem cell activity and developmental plasticity in the root meristem. *Genes Dev.* 18, 375–380
45 Takahashi, K. and Yamanaka, S. (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126, 663–676