Review

Regeneration in plants and animals: dedifferentiation, transdifferentiation, or just differentiation?

Kaoru Sugimoto, Sean P. Gordon and Elliot M. Meyerowitz

Division of Biology 156-29, California Institute of Technology, Pasadena, CA 91125, USA

The textbooks and literature of plant biology indicate that plant cells are totipotent, and that regeneration occurs via dedifferentiation, by which the cell and its descendents recapitulate earlier stages of development. However, recent work on the generation of callus, a presumed undifferentiated or dedifferentiated and disorganized cellular mass, indicates that the cells of callus are neither, and that callus forms predominantly from a pre-existing population of stem cells. Recent work in animal regeneration, for example in salamander limbs, also indicates that previous assumptions about the extent of dedifferentiation and pluripotency in animals are in need of critical reassessment. We review here some of these data, compare plant and animal regeneration, and argue that the importance of dedifferentiation and plasticity in regenerating systems is due for reevaluation.

Introduction

A student of botany learns from textbooks that living plant cells are totipotent, and that after wounding or in culture, they generate an undifferentiated cell mass termed callus, from which new shoots or roots can regenerate; that is, that the cells dedifferentiate on the path to regeneration of a new plant [1–4]. In contrast to this accepted lore, recent papers on plant regeneration indicate that plant cells regenerating injured tissues do not appear to dedifferentiate [5], that callus is an organized and differentiated tissue, and that callus is not generated from all plant cells, but predominantly from a specialized population of adult stem cells [6,7]. Whereas these new results do not necessarily indicate that plant regeneration never occurs from differentiated cells, that there is never dedifferentiation on the path to regeneration, or that callus is always differentiated, they do indicate that the current view of plant regeneration is due for critical re-analysis.

Just as in plant regeneration, it is widely accepted that dedifferentiation is a pivotal event in some animal regeneration systems, and new results on the extent to which cells dedifferentiate during regeneration contradict earlier beliefs [8–10]. Also as in plants, adult stem cells present in tissues could be a source for regenerating organs. Numerous studies of adult stem cells, and the remarkable recent advances in this field might convey the impression that it is certain that adult stem cells serve as the primary mover in regeneration. However, it is only recently that the origin of regenerating tissues, whether dedifferentiated cells or pre-existing stem cells or both, is beginning to be revealed, and only in some regenerating systems. Moreover, recent studies on direct reprogramming induced by exogenous transcription factors bring a new view of the potential plasticity of animal cells, and of the mechanisms that define cell types [11–14].

Birnbaum and Alvarado have suggested that almost all regeneration phenomena in one kingdom have a counterpart in the other, despite the diverse array of regeneration mechanisms [15]. By the comparative study of plant and animal regeneration, it is expected that new insights into essential mechanisms will be gained. New technologies for making transgenic lines, image analysis and genome-wide transcriptome profiling are providing new views of both plant and animal regeneration. Here, we will review plant and animal regeneration, focusing on the topics of what cells are responsible for regeneration, and how these cells acquire the competency to differentiate into new organs. First, we will introduce various regeneration systems in plants and animals, and then discuss the origin of regenerating cells: de- or trans-differentiation of differentiated cells, or development from pre-existing stem cells.

Regeneration systems in plants and animals

Regeneration in plants can be divided into several types, which are each manifested in a variety of forms: (i) the regeneration of a tissue structure lost by injury, (ii) the *de novo* generation of a new tissue or growth structure not present prior to injury, and (iii) regeneration of an entire plant from a single somatic cell (Figure 1a–c). In this first case, the regeneration of the excised tip of a leaf or root is similar to animal limb regeneration in that a lost part of the body with 3D structure, and containing diverse tissue types, is replaced by regeneration. In contrast to this more classical type of regeneration, plants also commonly regenerate by *de novo* formation of an entire plant from a cut piece of tissue in culture. In this type of regeneration entirely new centers of plant growth are initiated at a site of injury. These centers of growth often develop new stem cell niches (meristems) that enable indeterminate growth potentially in the form of new individual plants. Often, *de novo* regeneration occurs through an intermediate growing cell mass, callus. Callus can also be induced in cell and tissue culture through the use of appropriate ratios of the

Corresponding author: Meyerowitz, E.M. (meyerow@its.caltech.edu).

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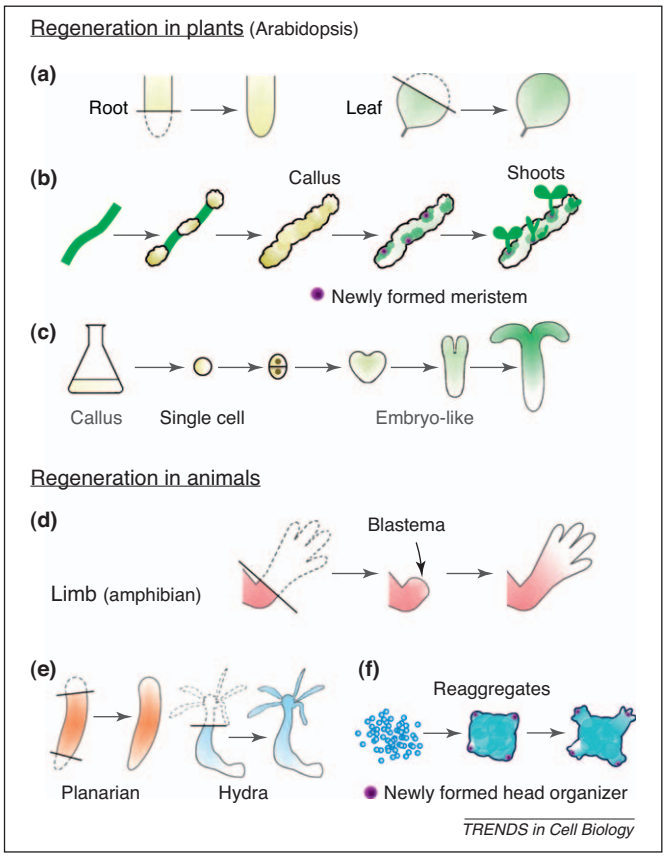

Figure 1. Schematic drawing of various regeneration systems in plants and animals. **(a)** The regeneration of the excised tip of a root and leaf in *Arabidopsis*. **(b)** *Arabidopsis in vitro* shoot regeneration system. An intermediate growing cell mass called callus is induced in the first hormonal treatment. Then the subsequent culture of callus on different media causes the cells to be specified to form entirely new stem cell niches (meristems), from which shoots or roots are derived. **(c)** Somatic embryogenesis. Callus growth in liquid or solid media is transferred to different media (hormone-free or different ratios of hormones) to induce somatic embryogenesis. **(d)** The regeneration of limbs in amphibians. Amputation triggers the formation of a pool of progenitor cells called blastema that regenerates damaged or lost parts of the body. **(e)** Regeneration in *Planaria* and *Hydra*. These invertebrates can regenerate a whole animal from a small piece of almost any part of body, even from dissociated and re-aggregated cells. **(f)** The self-organization system in *Hydra* re-aggregates. Head organizing centers are set up *de novo* after positional cues are destroyed by dissociation and re-aggregation of cells.

plant hormones auxin and cytokinin, and generation of individual leaves, shoot and root meristems, or newly organized embryos, can be elicited from the growing callus by culture in media with different ratios of the same plant hormones [16–18].

In animals, regenerative capability ranges across species and organs. Different tissues use different regenerative strategies. The tail and limb of amphibians such as salamanders, axolotls and *Xenopus* tadpoles (plus heart and lens in newts), fin and heart of zebrafish, gut and germ cells of *Drosophila*, blood, skin and gut in mice and the whole body of planarians and hydra are used widely as model systems (Figure 1d-f) [19].

Analogous between animal and plant regeneration is the intermediate structure: plant callus and animal blastema, a zone of progenitor cells formed at the wound site during regeneration [15,20,21]. Because of its ability to produce various cell types and the lack of characteristic structures, both tissues have been believed to contain undifferentiated cells, which are generated through dedifferentiation of once-differentiated cells into a pluripotent state outside their original lineages. To what extent these cells dedifferentiate, however, and the cells from which they originate have long been unclear. As discussed later, recent reports in plants and animals have clarified these questions for certain regeneration systems.

What does dedifferentiation have to do with it?

Historically, discussion of both plant and animal regeneration has involved the concept of dedifferentiation. Indeed, the earliest entry in the Oxford English Dictionary for the word dedifferentiation, from 1917 [22] states that "dedifferentiation or return to a more embryonic condition probably underlies all types of regeneration" (Figure 2). However, there is little evidence for this concept besides cellular morphology. Moreover, the concept of dedifferentiation itself is vague. Over the intervening decades the word dedifferentiation has taken on a variety of alternative meanings, such as loss of evident differentiated cell type characteristics, or re-entry to the cell cycle of normally non-dividing cells, and consequent acquisition of the ability to grow, each of which is involved in the process of reverting to an earlier differentiation state but represents only parts of the whole event.

In the next sections, we will discuss the case for and against the involvement of dedifferentiation in plant and animal regeneration processes, in view of contemporary work.

Dedifferentiation in plants

Dedifferentiation in plant regeneration has been historically inferred, indirectly through the observation of the renewed ability of previously quiescent cells to divide, and the induction of structural and morphological changes within dividing callus cells. During post-embryonic development, tissues arise through the action of pluripotent stem cells within structures called meristems. Cells within meristems are small, with dense cytoplasm and small vacuoles. By contrast, quiescent cells within mature tissues that differentiate from the meristems are often characterized by larger size, containing larger vacuoles and different plastids and storage products than cells of the meristem [16]. Callus initiation during regeneration leads to cells acquiring features similar to meristematic cells and consequent loss of differentiated cell morphology [16]. These changes in cell morphology have been taken as evidence of a process of dedifferentiation. Nonetheless, these changes in cell structure do not necessarily equate with a cell returning to a fundamentally more embryonic state, or to a developmentally earlier position in their usual lineage.

Callus, a mass of proliferating cells found after wounding and stimulated in culture by the plant hormones auxin and cytokinin, has long been held to be a dedifferentiated tissue [see above]. However, recent work has shown that callus is not dedifferentiated [6,7]. In fact, callus induced in these studies resembles root tissue in its patterns of gene expression and multicellular organization, even when it is generated from aerial organs that are separated from the root lineage from the earliest divisions of embryogenesis [6] (Figure 3a,b). The transcriptome of callus is more

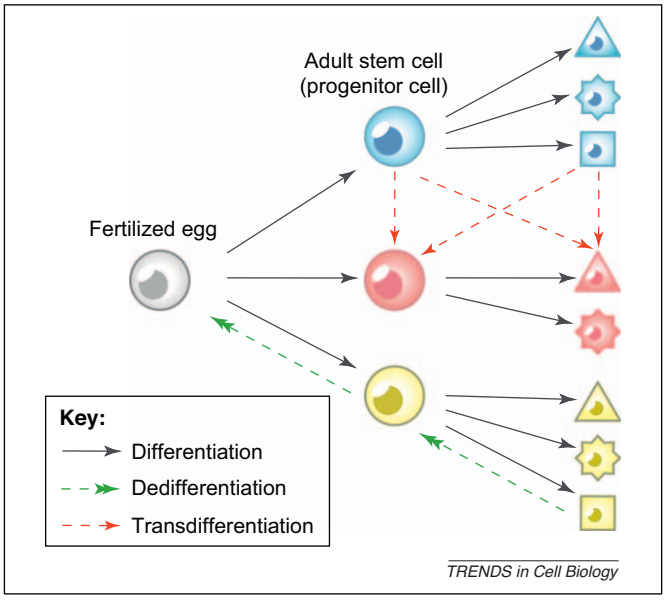

Figure 2. Schematic diagram of cell differentiation, dedifferentiation and transdifferentiation. A single fertilized egg generates various cell lineages (blue, red and yellow clades) and numerous cell types (different shape of differently colored cells) through successive cell division and differentiation (black arrows with solid line). Dedifferentiation is the process by which cells revert to a more embryonic state (green double arrows with dotted line). Transdifferentiation is the process by which cells directly transform into different type of cells outside of their already established differentiation paths (red arrows with dotted line). To regenerate multiple types of cells contained in a lost body part, cells could dedifferentiate or transdifferentiate, or differentiate from stem cells sitting in the adult tissues.

similar to root meristem tissue than shoot meristem or embryonic tissues. Therefore, callus formation is not a simple reprogramming process back to a dedifferentiated or embryonic state.

The regeneration of an entire plant from a single somatic cell could plausibly involve a return to a more embryonic state, and therefore, it is easy to accept the idea that dedifferentiation could play a widespread role in various regeneration processes. This assumption is reinforced by the ability of plant cells to undergo somatic embryogenesis in which somatic cells are stimulated to form embryos in culture [16,18]. Nonetheless, this process remains poorly understood.

Dedifferentiation in animals

As in studies of plant regeneration, arguments for a role of dedifferentiation in animal regeneration have relied on the observation of the renewed ability of previously quiescent cells to divide, and the loss of the most evident structural markers for a given cell type [10,20]. Limb regeneration in *Amblystoma* larvae was proposed to involve dedifferentiation of cartilage cells based on structural and morphological changes of cells [23]. Similarly, the cellularization of multinucleate myocytes, their loss of sarcomeric structure and division have been taken as signs of dedifferentiation [20]. However, loss of structural markers for a given cell's type is not by itself indicative of the exact developmental stage of the cell, as it would be defined today by the list of genes contributing RNA or proteins to the cell.

Recent studies put into question the extent of dedifferentiation in animal regeneration. For example, in salamander limb regeneration, the blastema, previously regarded as a homogeneous cell population, is now known to be a heterogeneous pool of progenitor cells with restricted potential [8]. Careful cell lineage analyses show that the regenerating cells maintain the memory of their earlier cellular identity and give rise to tissues only within their original lineage (one exception is dermal cells, which occasionally switch lineage to cartilage) [8]. Therefore, in this case regeneration is achieved without dedifferentiation back to the earliest pluripotent state as was thought previously. In addition, blastema cells from different tissue types occupy distinct subregions, and also proximo-distal positional identity is retained in some cell types. These mechanisms could be important to the precise spatial patterning of limb regeneration.

Further investigation is required to determine the origin of the muscle progenitor cells in this regeneration system. Because limb muscle fibers and satellite cells (muscle stem cells) were labeled together in the starting tissue, it is not clear whether regenerating muscle derives from dedifferentiated muscle cells, satellite cells, or both. In the case of axolotl tail regeneration, dedifferentiation of mature muscle fibers was confirmed by tracking fluorescently labeled single muscle fibers [24], and by observing mononucleation of muscle fibers, which was reported as the structural marker of a prior state of the cell in classical experiments [25,26]. In support of these cells changing their identity at a molecular level, the homeobox-containing transcription factor *Msx-1,* known to be expressed during embryogenesis in areas of epithelial to mesenchymal transitions, and sufficient to prompt terminally differentiated murine myotubes to dedifferentiate to multipotent cells [27], is also expressed during limb regeneration [28].

Recent cre/lox cell lineage analysis in zebrafish heart regeneration shows that regenerating heart muscles are derived primarily from a subpopulation of cardiomyocytes within the tissue, rather than non-myocyte sources such as stem cells, as previously suggested [9,10]. Wound stimulus triggers cardiomyocytes to express the embryonic heart gene, *gata-4*, disassemble their sarcomeric structure and proliferate, but does not induce the expression of the precardiac mesoderm RNAs of the genes *nkx2.5* and *hand2*. Thus, the cardiomyocytes undergo limited dedifferentiation during heart regeneration.

Therefore, dedifferentiation does occur in some systems of animal regeneration depending on the definition used, but the degree of plasticity that they acquire is often limited compared to that of an embryonic cell.

In summary, new cell lineage analyses have revealed the details of the differentiated states of regenerating cells that have long been masked by the ambiguous term of dedifferentiation. In plants, it appears that dedifferentiation is not an inescapable feature of regeneration. We can say, at least, that reversion to a more embryonic state does not always apply to the entire process of forming competent cell populations. In several animal regeneration systems, dedifferentiation is limited within lineages. Lineage memory and residential segregation of the cells might be involved in the acquisition of positional information during regeneration. Without reverting to the earliest embryonic state, cells re-acquire plasticity to give rise to new tissues.

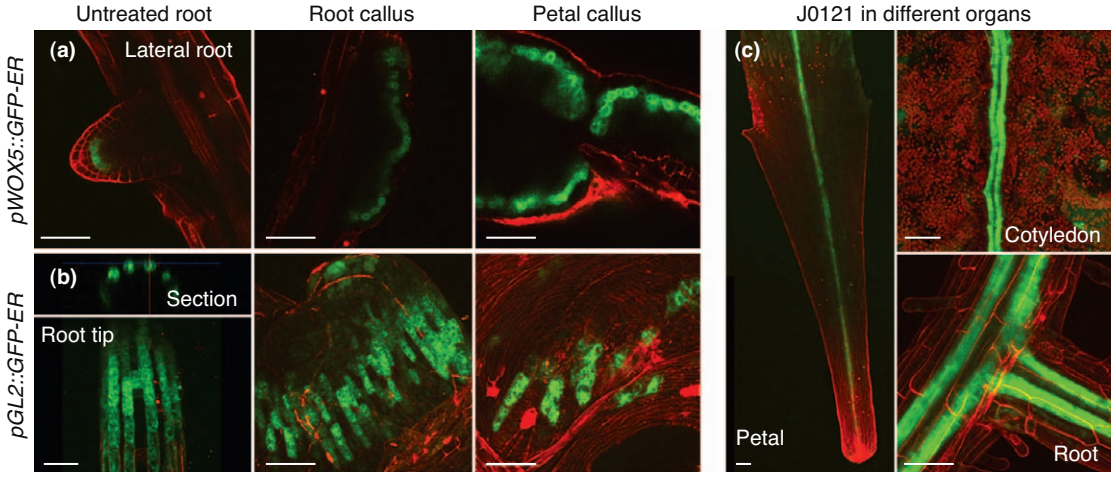

Figure 3. Callus resembles the tip part of the root meristem, which arises from perivascular cells of multiple organs. pWOX5::GFP-ER **(a)** and pGL2::GFP-ER **(b)** marker expression (green) in untreated root (left panels), callus derived from root (middle panels) and petal (right panels). pWOX5::GFP-ER is a root quiescent center (QC)-specific marker, and is expressed broadly in the sub-epidermal layer of callus derived from root and petal. pGL2::GFP-ER marks non-hair epidermal cells of the meristematic zone of the root. Expression is in a striped pattern in the callus epidermis, as in roots. These data and others indicate that callus differentiates as root meristem-like tissue. **(c)** Expression of xylem pole pericycle marker J0121 (green) in untreated petal, cotyledon and root. Although pericycle cells have been described previously as a root tissue, the marker signal is also detected along the midvein of aerial organs. Cellular outlines were visualized with propidium iodide staining (red) in all the panels except the cotyledon panel of **(c)**, in which chlorophyll autofluorescence is in red. Scale bars: 50 μm. Images are reprinted with permission from [6].

Again, what is occurring is more complex than what is generally meant by dedifferentiation, and it might be time to retire this term in favor of a more precise description.

Is transdifferentiation more the case?

Transdifferentiation was defined by Okada as the irreversible switch of one differentiated cell type into another [29] (Figure 2). In some cases, the presence of switches in cell-type identity, combined with the apparent lack of dedifferentiation processes, suggests that transdifferentiation could better approximate the molecular changes occurring as one cell type switches its state to that characteristic of another lineage [6–8,30,31].

In plant regeneration, transdifferentiation appears to be the process of regeneration in at least some recently studied cases. Time course experiments during root tip regeneration show that cell type-specific markers for lost cell types are induced rapidly within 5 h of wounding [5]. Furthermore, newly specified cells are functional within 24 h of regeneration [5]. Observation of cell-type markers over time and the speed of cell respecification argue against the occurrence of dedifferentiation, and argue for transdifferentiation in this system.

This also appears to be the case in the formation of new shoot meristems from the surface of callus. In the model plant, *Arabidopsis*, root and shoot lineages are separated from the earliest stages of embryogenesis, and do not normally interconvert. Given that callus largely has root identity as described above, the induction of shoots from callus through application of the plant hormone cytokinin might be a transdifferentiation process.

In animals, there is some evidence that transdifferentiation contributes to blastema formation. In the case of salamander tail regeneration, spinal cord cells were observed occasionally to migrate out of the regenerating spinal cord, and to dramatically switch lineage and participate in the regeneration of muscle and cartilage tissue [30]. Differentiation of cells of dermal origin into cartilage in axolotl limb regeneration is also such a case [8].

Historically, transdifferentiation has long been known to occur during newt lens regeneration, as pigmented epithelial cells from the dorsal iris enter the cell cycle, lose their pigmentation and transdifferentiate into lens cells [29,32,33]. Furthermore, if iris epithelial cells are transplanted into the limb blastema, they give rise to a lens, and cells from limb blastemas always give rise to a limb even if they are transplanted to the eye [34,35]. A recent study indicates that the oocyte-specific linker histone B4, which is known to be associated with reprogramming mediated by somatic cell nuclear transfer into oocyte, is expressed and required for transdifferentiation and lens regeneration [36]. This result suggests that transdifferentiation in newt lens regeneration requires a phase of reprogramming as a cell switches its identity, similar to what is observed after nuclear transfer to an oocyte.

What is the molecular mechanism of reprogramming? Is dedifferentiation always required prior to a lineage switch? Similarly to nuclear transfer to an oocyte, direct reprogramming of adult mammalian cells into a pluripotent state can be done by forced expression of only four transcription factors expressed specifically in embryonic stem (ES) cells [11]. Since this landmark discovery, applying the same screening strategy (genome-wide expression analysis and *in vivo* elimination protocol), three groups have successfully defined specific combinations of factors that convert pancreatic exocrine cells into β cells, fibroblasts into neurons, and fibroblasts into cardiomyocytes, respectively [12–14,37]. In each case, cells are reprogrammed directly by only three factors without reverting to stem cell progenitors. Therefore, animal cells maintain potential transdifferentiation ability, and the mechanisms of lineage commitment and fate determination of cells could be simpler than we have thought. There could be a similar mechanism underlying shoot regeneration from root-like

callus in plants, although in this case transcription factors are not induced exogenously by transfection, but endogenously by hormone treatment.

Stem cells in regeneration

In addition to dedifferentiation and transdifferentiation as discussed above, there is another possibility for the origin of regenerating tissues: pre-existing stem cells that proliferate and differentiate into new organs (Figure 2).

Stem cells in animals

Stem cells are cells with the capacity of self-renewal that can produce multiple types of descendant cells by differentiation. In mammalian studies, it has been generally thought that the regeneration capability of each tissue upon injury depends on the presence of adult stem cell populations in it. Tissues such as pancreas in mammals hardly regenerate lost parts, and whether stem cells exist in these tissues is still controversial [38]. In contrast, tissue turnover takes place constantly in blood, skin and intestine, and the resident stem cells of these tissues have been well documented [39,40]. Those stem cells reside in the special microenvironment called the stem cell niche, which provides stem cells with external signals and regulates the behavior of the progenitor cells [41]. Advances in lineage-tracing techniques, cell manipulation and imaging technologies have gradually revealed where stem cells and their niches reside within tissues [42]. Several types of stem cell niches appear closely associated with the vasculature in multiple tissues [43–45], and the activity of stem cells and/or niche cells are regulated by soluble factors released from the vasculature, such as IGF-1, VEGF and Wnt signaling molecules [43–45]. The vasculature simultaneously provides these common regulatory factors to several organ systems throughout the body. Also, stem cells themselves migrate on blood vessels. Neuroblasts have been observed to migrate from the posterior subventricular zone to the anterior olfactory zone along blood vessels in the adult mammalian forebrain [46]. Thus the vasculature could play a major role in coordinating stem cell activities across organs in a dynamic fashion in response to systemic changes, such as the decline of regenerative potential of multiple organs with age.

Among the amphibian limb or tail regeneration systems, only few examples of stem cell-based regeneration have been observed. The *Xenopus* tadpole completely regenerates its limb and tail only during early stages of development, until metamorphosis. Unlike axolotl limb or tail regeneration (discussed above), there seems to be little or no dedifferentiation or transdifferentiation in the *Xenopus* tail regeneration system. Instead, cells regenerate from pre-existing precursors in the same lineages (stem cell or not stem cell): The spinal cord and notochord regenerate from the same tissue type [47], the muscle regenerates from muscle satellite cells [48], and the melanophore regenerates from melanophore precursors [49]. Therefore tadpole regeneration is similar to the normal mode of tail growth or tissue turnover seen in mammals. Thinking of the capacity and the strategy of regeneration, the anuran amphibian is seated at an intermediate position between the urodele amphibian and mammals.

In planaria and in hydra, adult stem cells are distributed almost throughout the body, which leads to the remarkable ability of these organisms to regenerate [50–52]. Planarian neoblasts are the only known mitotically active somatic stem cells competent to become all types of cells observed in the mesenchymal space of the body, except the pharyngeal and eye regions. Hydra interstitial cells are uniformly distributed along the body column but are absent from the head and foot. Both planarian neoblasts and hydra interstitial cells are suggested to migrate to wound sites where they replace missing tissues [53,54]. What types of signals maintain these cells as stem cells in the adult body and control their activity after injury, and whether there are special stem cell niches nursing these cells, is still not clear. Stem cell-specific markers indentified in this decade and novel imaging technologies are expected to find the answers to these questions in the future [50,51]. In the hydra head regeneration system, a recent study has shown that apoptosis of injured cells releases Wnt3, which induces the recruitment of interstitial cells to the wounding site and their subsequent proliferation [54].

Stem cells in plants

In plants, regenerative ability has been demonstrated with the rooting of cuttings taken from almost every organ – stem, root, leaf, hypocotyl, floral axis and flowers [55]. Because of the ease with which plant regeneration can be induced, it is often inferred that all plant cells are totipotent (see above). However, this notion has not been proven. The inability to follow individual cells from the beginning to the end of the process in classical experiments prevented the validation of this idea [15,56]. In contrast to earlier beliefs, recent data suggest that stem cells might be responsible for this dramatic regeneration ability. The cells from which callus forms in roots, hypocotyls, cotyledons and petals are in fact specific cells surrounding the vasculature. In roots and hypocotyls, these are the xylem pole pericycle cells [6,7,31,57]. In other organs, these callus-forming cells share expression of at least one reporter gene with xylem pole pericycle cells; because these cells have not been described previously in aerial organs, there is as yet no standard name for them [6] (Figure 3c). Similar to mammalian stem cell niches that are often found around the vasculature, these plant pericycle-like cells appear to exist surrounding the vasculature of various organ types, and serve as the origin of regenerating tissues. Although the role of pericycle cells in regeneration has been established only recently, these cells have long been known to be the stem cells for the formation of lateral roots [58]. In lateral root formation, a limited number of pericycle cells adjacent to the two xylem poles undergo ordered cell divisions and differentiation, and produce all of the cell layers present in a root as it forms a lateral root primordium (LRP) [59,60]. As in animals, this stem cell niche is regulated by diffusible substances from other cells; hormones have been shown to be involved in different steps of LRP formation from pericycle cells [61,62]. Auxin positively regulates the initiation and development of each LRP. Local auxin accumulation in pericycle cells is the initial trigger of LRP formation [62]. Cytokinin negatively

regulates LRP formation by altering the expression of auxin transporter PIN proteins, preventing the establishment of an auxin gradient and thereby allowing reorganization of the root [63]. Similarly, callus formation in culture requires the application of exogenous hormones from the media. Callus formation recapitulates the lateral root development program at the initial step, even when it is derived from aerial organs. This is demonstrated by the fact that a mutant defective in lateral root formation also exhibits defects in callus formation [6], and that roots from seedlings with the pericycle cells specifically ablated by expression of a diphtheria toxin gene fail to form callus [57]. Therefore, in this system, the differentiation of pericycle-like cells toward root meristem-like tissue is the common mechanism of callus formation from various organs. Furthermore, it has been shown recently that root pericycle cells also have the potential to form shoots directly upon cytokinin-rich media in the sites where LRP would have formed [7].

Thus, in plants, as well as in many examples in animals, the regeneration of at least some tissues involves special populations of starting cells that can be considered adult stem cells, and that lead to regenerated material by differentiating (or perhaps transdifferentiating from a different state – little is known as yet about these cells), not dedifferentiating. Unlike vertebrate animals, in plants one common type of adult stem cell is distributed throughout the entire body along the vasculature. This accessibility of the adult stem cells might be one of the reasons for the high plasticity of plants, relative to vertebrates.

Concluding remarks

Response to injury or other cues mobilizes certain cell populations to give rise to progenitors that participate in regeneration of lost or damaged parts. In some regeneration systems, progenitors are derived from previously quiescent differentiated cells whereas in others, progenitors arise from the activity of stem cells. The previous literature has assumed that quiescent differentiated cells give rise to progenitors of regenerating parts through a process of dedifferentiation. Current genomic and imaging technologies are allowing researchers to re-approach model systems of regeneration and access the molecular state of cells participating in the regeneration process in real time, as regeneration occurs. The widespread use of real-time imaging and multiple molecular markers will allow a more complete description of the state of regenerating cells and their relation to precursors within and outside their lineage. The utility of this approach is highlighted by recent studies in plants and animals that show that generation of progenitor cells from quiescent differentiated tissues involves mechanisms other than dedifferentiation, or dedifferentiation at a different level than previously thought. The utility of comparison between plant and animal regeneration systems is also highlighted by recent work: although the exact mechanisms are different, the principles and concepts are closely related, and work in each highlights processes and ways of thinking that can be useful in both arenas. Further work will lead to a much more precise understanding of the changes in gene activity that accompany regeneration, and of the signals that prevent cells of uninjured tissues from regeneration activity. Understanding these signals could lead to the ability to induce regeneration at will.

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References

1 Nabors, M.W. (2004) *Introduction to Botany*, Pearson/Benjamin Cummings
2 Raven, P.H. *et al.* (1986) *Biology of Plants*, Worth Publishers, Inc.
3 Rost, T.L. *et al.* (1998) In *Plant Biology*, Wadsworth Publishing Company
4 Steeves, T.A. and Sussex, I.M. (1972) *Patterns in Plant Development*, Prentice-Hall, Inc.
5 Sena, G. *et al.* (2009) Organ regeneration does not require a functional stem cell niche in plants. *Nature* 457, 1150–1153
6 Sugimoto, K. *et al.* (2010) *Arabidopsis* regeneration from multiple tissues occurs via a root development pathway. *Dev. Cell* 18, 463–471
7 Atta, R. *et al.* (2009) Pluripotency of *Arabidopsis* xylem pericycle underlies shoot regeneration from root and hypocotyl explants grown *in vitro*. *Plant J.* 57, 626–644
8 Kragl, M. *et al.* (2009) Cells keep a memory of their tissue origin during axolotl limb regeneration. *Nature* 460, 60–65
9 Kikuchi, K. *et al.* (2010) Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. *Nature* 464, 601–605
10 Jopling, C. *et al.* (2010) Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. *Nature* 464, 606–609
11 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
12 Ieda, M. *et al.* (2010) Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell* 142, 375–386
13 Zhou, Q. *et al.* (2008) *In vivo* reprogramming of adult pancreatic exocrine cells to beta-cells. *Nature* 455, 627–632
14 Vierbuchen, T. *et al.* (2010) Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* 463, 1035–1041
15 Birnbaum, K.D. and Sanchez Alvarado, A. (2008) Slicing across kingdoms: regeneration in plants and animals. *Cell* 132, 697–710
16 Street, H.E. (ed.) (1977) *Plant Tissue and Cell Culture*, Blackwell Scientific Publications
17 Skoog, F. and Miller, C.O. (1957) Chemical regulation of growth and organ formation in plant tissues cultured *in vitro*. *Symp. Soc. Exp. Biol.* 54, 118–130
18 Gautheret, R.J. (2003) Plant tissue culture: the history, In *Plant Tissue Culture: 100 Years since Gottlieb Haberlandt*, SpringerWien
19 Poss, K.D. (2010) Advances in understanding tissue regenerative capacity and mechanisms in animals. *Nat. Rev. Genet.* 11, 710–722
20 Brockes, J.P. and Kumar, A. (2002) Plasticity and reprogramming of differentiated cells in amphibian regeneration. *Nat. Rev. Mol. Cell Biol.* 3, 566–574
21 Odelberg, S.J. (2004) Unraveling the molecular basis for regenerative cellular plasticity. *PLoS Biol.* 2, E232
22 Lewis, W.H. and Lewis, M.R. (1917) Behavior of cross striated muscle in tissue cultures. *Am. J. Anat.* 22, 169–180
23 Butler, E.G. (1933) The effects of X-radiation on the regeneration of the fore limb of amblystoma larvae. *J. Exp. Zool.* 65, 271–315
24 Echeverri, K. *et al.* (2001) *In vivo* imaging indicates muscle fiber dedifferentiation is a major contributor to the regenerating tail blastema. *Dev. Biol.* 236, 151–164
25 Hay, E.D. (1959) Microscopic observations of muscle dedifferentiation in regenerating *Amblystoma* limbs. *Dev. Biol.* 1, 555–585
26 Hay, E.D. and Fischman, D.A. (1961) Origin of the blastema in regenerating limbs of the newt *Triturus viridescens*. An autoradiographic study using tritiated thymidine to follow cell proliferation and migration. *Dev. Biol.* 3, 26–59
27 Odelberg, S.J. *et al.* (2000) Dedifferentiation of mammalian myotubes induced by *msx1*. *Cell* 103, 1099–1109
28 Koshiba, K. *et al.* (1998) Expression of Msx genes in regenerating and developing limbs of axolotl. *J. Exp. Zool.* 282, 703–714
29 Okada, T.S. (1991) *Transdifferentiation*, Clarendon

30 Echeverri, K. and Tanaka, E.M. (2002) Ectoderm to mesoderm lineage switching during axolotl tail regeneration. *Science* 298, 1993–1996
31 Gordon, S.P. *et al.* (2007) Pattern formation during *de novo* assembly of the *Arabidopsis* shoot meristem. *Development* 134, 3539–3548
32 Eguchi, G. and Okada, T.S. (1973) Differentiation of lens tissue from the progeny of chick retinal pigment cells cultured *in vitro*: a demonstration of a switch of cell types in clonal cell culture. *Proc. Natl. Acad. Sci. U.S.A.* 70, 1495–1499
33 Eguchi, G. *et al.* (1974) Differentiation of lens-like structures from newt iris epithelial cells *in vitro*. *Proc. Natl. Acad. Sci. U.S.A.* 71, 5052–5056
34 Reyer, R.W. *et al.* (1973) Stimulation of lens regeneration from the newt dorsal iris when implanted into the blastema of the regenerating limb. *Dev. Biol.* 32, 258–281
35 Ito, M. *et al.* (1999) Lens formation by pigmented epithelial cell reaggregate from dorsal iris implanted into limb blastema in the adult newt. *Dev. Growth Differ.* 41, 429–440
36 Maki, N. *et al.* (2010) Oocyte-type linker histone B4 is required for transdifferentiation of somatic cells in vivo. *FASEB J.* 24, 3462–3467
37 Passier, R. and Mummery, C. (2010) Getting to the heart of the matter: direct reprogramming to cardiomyocytes. *Cell Stem Cell* 7, 139–141
38 Dor, Y. *et al.* (2004) Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. *Nature* 429, 41–46
39 Li, L. and Clevers, H. (2010) Coexistence of quiescent and active adult stem cells in mammals. *Science* 327, 542–545
40 Wilson, A. *et al.* (2009) Balancing dormant and self-renewing hematopoietic stem cells. *Curr. Opin. Genet. Dev.* 19, 461–468
41 Watt, F.M. and Hogan, B.L. (2000) Out of Eden: stem cells and their niches. *Science* 287, 1427–1430
42 Voog, J. and Jones, D.L. (2010) Stem cells and the niche: a dynamic duo. *Cell Stem Cell* 6, 103–115
43 Massouh, M. and Saghatelyan, A. (2010) De-routing neuronal precursors in the adult brain to sites of injury: role of the vasculature. *Neuropharmacology* 58, 877–883
44 Gopinath, S.D. and Rando, T.A. (2008) Stem cell review series: aging of the skeletal muscle stem cell niche. *Aging Cell* 7, 590–598
45 Mayack, S.R. *et al.* (2010) Systemic signals regulate ageing and rejuvenation of blood stem cell niches. *Nature* 463, 495–500
46 Snapyan, M. *et al.* (2009) Vasculature guides migrating neuronal precursors in the adult mammalian forebrain via brain-derived neurotrophic factor signaling. *J. Neurosci.* 29, 4172–4188
47 Gargioli, C. and Slack, J.M. (2004) Cell lineage tracing during *Xenopus* tail regeneration. *Development* 131, 2669–2679
48 Chen, Y. *et al.* (2006) Control of muscle regeneration in the *Xenopus* tadpole tail by Pax7. *Development* 133, 2303–2313
49 Lin, G. *et al.* (2007) Regeneration of neural crest derivatives in the *Xenopus* tadpole tail. *BMC Dev. Biol.* 7, 56
50 Shibata, N. *et al.* (2010) Cellular and molecular dissection of pluripotent adult somatic stem cells in planarians. *Dev. Growth Differ.* 52, 27–41
51 Bosch, T.C. *et al.* (2010) The *Hydra* polyp: nothing but an active stem cell community. *Dev. Growth Differ.* 52, 15–25
52 Galliot, B. *et al.* (2006) *Hydra*, a niche for cell and developmental plasticity. *Semin. Cell Dev. Biol.* 17, 492–502
53 Wenemoser, D. and Reddien, P.W. (2010) Planarian regeneration involves distinct stem cell responses to wounds and tissue absence. *Dev. Biol.* 344, 979–991
54 Chera, S. *et al.* (2009) Apoptotic cells provide an unexpected source of Wnt3 signaling to drive hydra head regeneration. *Dev. Cell* 17, 279–289
55 Sinnott, W.E. (1960) *Plant Morphogenesis*, McGraw-Hill Book Company, Inc.
56 Steward, F.C. *et al.* (1970) Growth and development of totipotent cells: Some problems, procedures, and perspectives. *Ann. Bot.* 34, 761–787
57 Che, P. *et al.* (2007) Developmental steps in acquiring competence for shoot development in *Arabidopsis* tissue culture. *Planta* 226, 1183–1194
58 Laplaze, L. *et al.* (2005) GAL4-GFP enhancer trap lines for genetic manipulation of lateral root development in *Arabidopsis thaliana*. *J. Exp. Bot.* 56, 2433–2442
59 Malamy, J.E. and Benfey, P.N. (1997) Organization and cell differentiation in lateral roots of *Arabidopsis thaliana*. *Development* 124, 33–44
60 Kurup, S. *et al.* (2005) Marking cell lineages in living tissues. *Plant J.* 42, 444–453
61 Fukaki, H. and Tasaka, M. (2009) Hormone interactions during lateral root formation. *Plant Mol. Biol.* 69, 437–449
62 Dubrovsky, J.G. *et al.* (2008) Auxin acts as a local morphogenetic trigger to specify lateral root founder cells. *Proc. Natl. Acad. Sci. U.S.A.* 105, 8790–8794
63 Laplaze, L. *et al.* (2007) Cytokinins act directly on lateral root founder cells to inhibit root initiation. *Plant Cell* 19, 3889–3900