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Minireview

# Plant Stem Cells

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Among the trending topics in the life sciences, stem cells have received a fair share of attention in the public debate — mostly in connection with their potential for biomedical application and therapies. While the promise of organ regeneration and the end of cancer have captured our imagination, it has gone almost unnoticed that plant stem cells represent the ultimate origin of much of the food we eat, the oxygen we breathe, as well the fuels we burn. Thus, plant stem cells may be ranked among the most important cells for human well-being. Research by many labs in the last decades has uncovered a set of independent stem cell systems that fulfill the specialized needs of plant development and growth in four dimensions. Surprisingly, the cellular and molecular design of these systems is remarkably similar, even across diverse species. In some long-lived plants, such as trees, plant stem cells remain active over hundreds or even thousands of years, revealing the exquisite precision in the underlying control of proliferation, self-renewal and differentiation. In this minireview, we introduce the basic features of the three major plant stem cell systems building on these facts, highlight their modular design at the level of cellular layout and regulatory underpinnings and briefly compare them with their animal counterparts.

## Introduction

Multicellularity evolved independently in the plant and animal lineages and, thus, developmental strategies and underlying molecular circuits have substantially diverged since the last common ancestor. Against the background of the vast evolutionary distance, it comes as a surprise that the concept of stem cells and even the cellular design of stem cell systems exhibit remarkable similarities between the kingdoms of life [1]. Nevertheless, the particular lifestyles of plants and animals have led to the evolution of distinct features in stem cell control that allow us to challenge the stem cell concept using comparative studies.

As the major organismal group collecting solar energy outside the oceans, plants are not required to hunt for food, but in contrast need to maximize their surface area, and thus are sessile. As a consequence, they have to deal with dramatically changing environments throughout the year, as well as competition, herbivory and pathogen attack — all without the option of moving to a more benign surrounding. Evolution has solved this dilemma by a post-embryonic mode of development, which is the basis for the capacity of plants to form and regenerate organs over their entire life cycle and an unrivalled plasticity in growth and form. At the heart of this developmental strategy are permanently active groups of pluripotent stem cells, embedded in specialized tissues called meristems. Located at the growth points of the plant body (Figure 1), meristems continuously produce cells whose fates are specified by position and can be adapted 'on the fly' to current requirements dictated by environment or developmental stage [2]. The tuning of evolutionarily conserved regulatory circuits during the production of distinct modules by those stem cells — for example, leaves — is the major basis for the tremendous variation of growth forms found among higher plants.

Another important and distinctive fundamental feature we need to consider when studying plant stem cell biology is the decentralized mechanical support of the organism. In contrast to most animals, whose bodies are supported by specialized endo- or exoskeletons, the structural integrity of plants relies on cell walls that encase every single cell. Consequently, plant cells are immobile and the local regulation of cell wall rigidity, cell division plane and ultimately cell size and shape are critical parameters for plant morphology. The physical restrictions imposed by the cell wall preclude lineage-dependent cell-fate specification and subsequent migration, and thus dictate that cell fate is constantly coordinated between tethered neighbors by organism-wide environmental and developmental sensing and signaling.

## Developmental Origin and Function of Plant Stem Cell Systems

In line with the postembryonic mode of development and the plasticity of plant cell fate, stem cells are specified independently at multiple locations and developmental stages. Stem cell systems established during embryogenesis are denoted as 'primary meristems', whereas other meristems, which are established post-embryonically, are designated as 'secondary meristems'. During embryogenesis, only the main stem cell systems for longitudinal growth — the shoot and root apical meristems (SAM and RAM), which produce all above- and below-ground parts of the plant — are specified (Figure 1), but remain largely dormant until germination [3]. Only when the seedling finds itself in the right environment are stem cells activated and can organogenic growth occur [4]. Consequently, in contrast to most animals, whose embryos terminate when stem cell regulators are inactivated, plant embryogenesis is mostly unaffected by mutations in stem cell regulators, and their defects only come to light once post-embryonic programs have been triggered. These programs not only control the formation of the primary growth axes, but also include the initiation of additional growth points in the root and shoot by controlling the development of lateral root meristems and axillary meristems (LRM and AM),

 

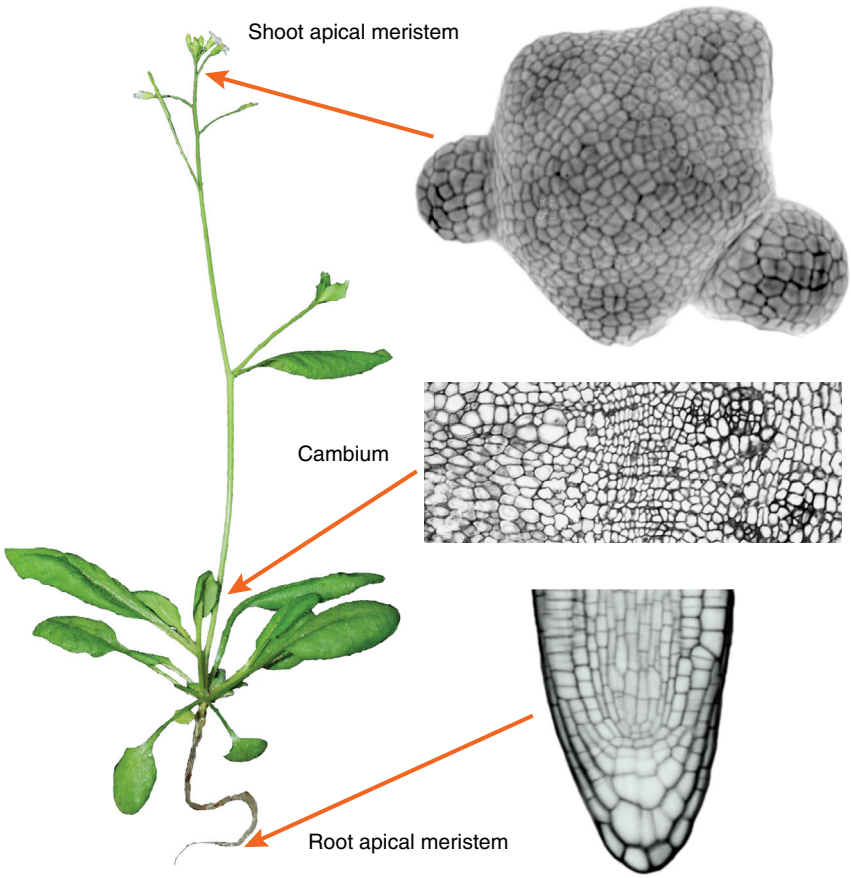


**Figure 1. Location and histology of the three major stem cell systems of *Arabidopsis thaliana*.**
Figure modified from [2].

respectively [5,6]. Although the initial steps in the formation of these secondary meristems are distinct in molecular and anatomical terms from their embryonic counterparts, fully developed AMs and LRMs are undistinguishable from primary SAMs and RAMs. Consequently, AM and LRM initiation have been extremely useful for studying *de novo* stem cell specification in differentiated environments.

In addition to growing longitudinally, plant organs grow radially with the help of a group of cylindrical and concentric meristems located below the organ surfaces. These so-called lateral meristems, of which the cambium is the most prominent (Figure 1) [7], usually display a high degree of anatomical organization because tissue production is strictly radial. Developmentally, the cambium is initiated from procambium cells located in the center of primary vascular bundles and, consistently, the spectrum of cell types produced by the cambium is mostly limited to vascular cells. This contrasts sharply with the SAM and the RAM, which are the origin of all above-ground and below-ground cell types, respectively.

## Cellular and Molecular Design of Stem Cell Niches

Let's have a look at the cellular layout and the major molecular players of the plant stem cell niches. The SAM, located at the shoot apex, is a dome-shaped tissue made of small proliferating cells, which in the reference plant *Arabidopsis thaliana* is defined by the expression of the homeodomain transcription factor *SHOOTMERISTEMLESS* (*STM*). STM suppresses differentiation and maintains the proliferative capacity of meristematic cells [8] and may also integrate mechanical signals acting during lateral organ formation [9]. At the very center of the SAM, the slowly dividing stem cells reside in the three topmost cell layers, which are clonally distinct (Figure 2). As in many animals, stem cells require an inductive niche and in the SAM this role is played by the cells of the organizing center (OC), located basally to the stem cells. At the molecular level, the OC is defined by the highly localized expression of the homeodomain transcription factor WUSCHEL (WUS; Figure 2), which is necessary and sufficient for stem cell maintenance [10,11]. However, in contrast to animal niches, WUS protein does not act through an elaborated signaling cascade, but rather moves to the stem cells through cytoplasmic connections, called plasmodesmata, to directly regulate target genes in niche and stem cells [11–13].

The mobility of WUS is highly directional, but the mechanistic basis for this specificity is unresolved as of now. Similarly, the molecular markup of stem cells is still poorly characterized, but fortunately genetics has identified a major stem cell-derived signal, called CLAVATA3 (CLV3). CLV3 is a short secreted peptide which is processed and post-translationally modified [14,15]. The CLV3 peptide diffuses in the interstitial space and acts by binding to a set of related leucine rich repeat (LRR)-based receptor complexes found in the plasma membrane (Figure 2) [16,17]. The common theme among these receptors is that CLV3 binding results in the activation of an intracellular signaling cascade, the molecular mechanisms of which are only beginning to emerge. However, some of the receptor complexes appear to be homomers of LRR-receptor-like kinases (LRR-RLK), such as CLAVATA1 (CLV1), while others are complexes of LRRs with membrane-bound kinases or pseudokinases, such as in the case of CLAVATA2 (CLV2) and CORYNE (CRN) [18,19]. The net effect of CLV signaling is the reduction in WUS expression [20], thus defining a local negative feed-back loop — WUS migrates from the OC to the stem cells to maintain their fate, stem cells secrete CLV3, and CL-dependent signaling in the OC causes a reduction in WUS activity.

Taking into consideration that cells in all domains of the SAM are continuously dividing at different rates, it follows that the underlying patterning system must be highly dynamic. Indeed, SAM domains are not fixed to certain cells but to a relative

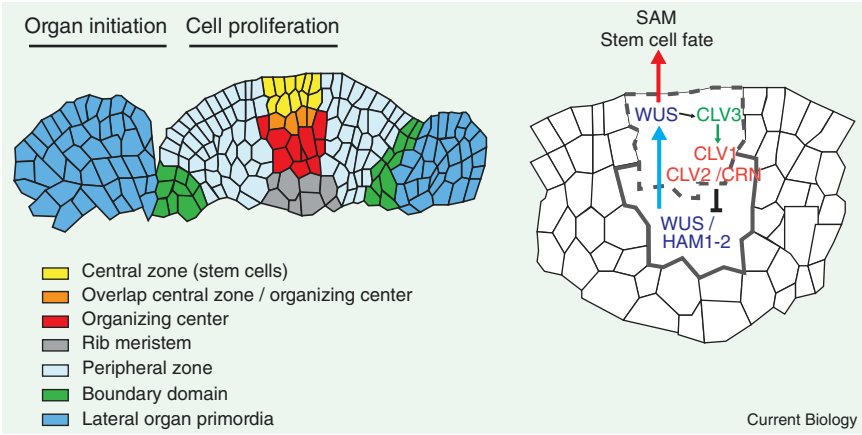


**Figure 2. The shoot apical meristem (SAM).** Schematic representation of a longitudinal section through the center of the SAM displays the functional domains; a central regulatory loop maintaining SAM activity is shown on the right. Figure modified from [2].

position within the tissue, and thus cells born in the stem cell domain will ultimately be 'left behind' by their dividing daughters. As a consequence, these cells will stop expressing stem cell markers and will either assume the identity of the peripheral zone in case they end up laterally to the stem cells, or alternatively, cells ending up basal to the OC will make up the internal tissues of the stem, including the vasculature. In the peripheral zone, cells divide rapidly before being incorporated into developing organs, such as leaves or flowers, once they have reached the boundary of the meristem. How the various subdomains of the SAM are established and maintained in such a plastic cellular environment is still unresolved, and progress on this front is severely hindered by the difficulties of dynamically following cells and their fates with high temporal resolution. Fortunately, elegant ablation experiments have demonstrated the prime influence of relative position on cell identity and the incredible plasticity of the SAM. Removing the central zone will cause the formation of competing stem cell clusters around the site of ablation, with a single center prevailing. Even when stem cells and organizing niche are ablated all together, a fully functional and spatially organized stem cell system will be re-created within days [21]. Unfortunately, the upstream signals for this phenomenal re-programming are still unresolved. However, it has become clear that the epidermal layer is fundamentally important to guide growth and patterning and non-cell-autonomous signals – including plant hormones and microRNAs – have been proposed to contribute to this function [21,22].

Another important aspect is the communication between developing organs at the periphery and stem cells in the center of the SAM, since due to the spatial separation of proliferation and differentiation, local regulatory systems seem insufficient to synchronize stem cell behavior with developmental or environmental inputs. This important function is carried out by plant hormones and among these, auxin and cytokinin have been found to be the most influential so far. In the SAM, cytokinin plays the part of a cell-cycle inducer and is important for the activation of WUS [23,24], while the primary role of auxin is to trigger differentiation at the periphery [25]. Intriguingly, auxin also enhances cytokinin output by directly repressing the expression of negative feedback regulators in cytokinin signaling [23]. Thus, local transcriptional loops are highly connected with more widely active hormone pathways to guide stem cell activity, and this tight network is not only found in the SAM.

Shifting our focus to the RAM, we indeed find almost the same players at work, even though the cellular layout of the root meristem is much more organized when compared with the shoot, at least in *Arabidopsis thaliana* (Figure 3). Again, we find a group of cells act as a niche; in the RAM these cells are termed the quiescent center (QC) and are located in the very center of the root tip. Stem cells, or initial cells, directly surround the QC and maintain a direct cell–cell contact with the niche. This position is essential for stem cell identity and ablation studies have shown that cells can re-acquire stem cell properties once they are brought into this environment [26]. In contrast to the SAM, where auxin triggers differentiation, the hormone is required to specify the niche and to maintain cell proliferation in the RAM [27]. Conversely, differentiation is promoted by cytokinin, which by mutual inhibition with auxin predominantly acts at a distance from the root tip [28]. However, cytokinin has also been shown to counteract the unique attributes of QC cells by reducing the import of auxin from their surroundings and by inducing cell division in this context [29].

While the hormonal influence on stem cells in the root is, by and large, the exact opposite of that observed in the shoot, stem cell maintenance follows a common theme at the transcriptional level. Just as in the shoot, niche cells are specified by a homeodomain transcription factor, which is termed WUSCHEL-RELATED HOMEOBOX 5 (WOX5; Figure 3) [30]. WOX5 not only is closely related to WUS but also has a similar mechanism of action: WOX5 protein moves from the QC into columella stem cells to directly instruct their fate [31]. Furthermore, *WOX5* expression is under the control of a peptide–receptor system just like *WUS*. In the RAM, the CLAVATA3-ESR related 40 (CLE40) peptide signals via CLV1 and the ARABIDOPSIS CRINKLY4 (ACR4) crinkly repeats (CR)-RLK to restrict *WOX5* expression [32]; however, the topology of the module is substantially different from the one found in the SAM. In contrast to CLV3 in the shoot, CLE40 is not expressed in stem cells but in differentiated root cap cells, while the CLV1 and ACR4 receptors are expressed in both populations (Figure 3) [33]. Intriguingly, the receptors are not expressed in the QC but still mediate CLE40-dependent *WOX5* regulation, maybe by preventing *WOX5* expression in stem cells [33]. The commonalities do not end here: WOX5 as well as WUS mainly act as transcriptional repressors and this activity is mediated by physical interaction with proteins encoded by the TOPLESS (TPL) gene family [31,34]. TPLs are members of the group of GROUCHO-type co-repressors and cause de-acetylation of histones through interaction with HISTONE DEACETYLASES (HDACs) [35]. Further

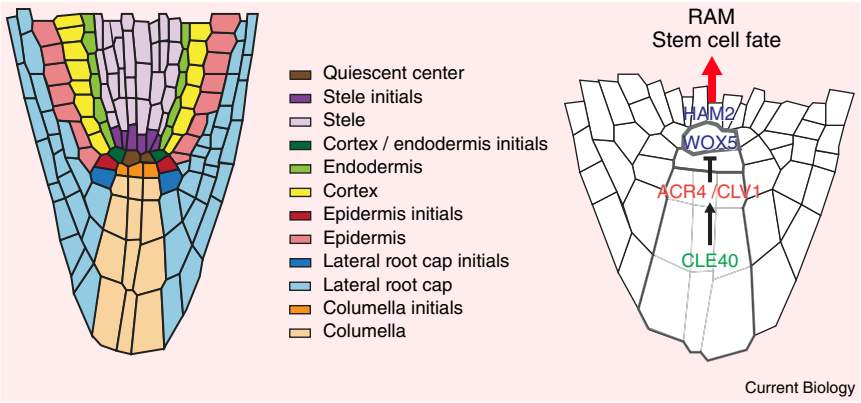


**Figure 3. The root apical meristem (RAM).**
A schematic outline of cell types found in the RAM is shown on the left, and the representation of one of the central regulatory loop maintaining RAM activity is shown on the right. Figure modified from [2].

essential but redundant parts of the WOX regulatory module are the HAIRY MERISTEM (HAM) proteins, GRAS-domain transcription factors directly interacting with WOX proteins (Figures 2–4) [36].

HAMs interact not only with WUS and WOX5 but also with WOX4, another prominent member encoded by the *WOX* gene family [36]. Interestingly, *WOX4* plays essential roles in regulating the activity of the cambium, a purely secondary meristem (Figure 4). Similar to *WUS* and *WOX5* in the two apical meristems, *WOX4* is expressed in the central area of the cambium and is under control of an LRR–CLE signaling cascade [37]. Due to restrictions in the analysis of cell division rates and clonal relationships, it is not yet clear how the terms 'stem cell', 'niche' and 'quiescence' can be applied to the cambium. Nevertheless, CLE41/42/44 peptides are generated in the distal area of the cambium including the differentiated phloem (Figure 4) [38,39], the cambium-derived tissue transporting assimilates and signaling molecules over long distances.

From there, these peptides travel to the undifferentiated cambium cells and bind to the LRR-RLK PHLOEM INTERCALATED WITH XYLEM (PXY, also known as TDR) where *WOX4* transcription is promoted (Figure 4) [37–39]. At the same time, the PXY–CLE41/42/44 module represses xylem differentiation [37,38], the tissue specialized for the long-distance transport of water, produced proximally by the cambium. As for *WUS* and *WOX5*, the intracellular signaling chain connecting the CLE receptor with the transcriptional regulation of *WOX4* has hardly been characterized. However, repression of xylem differentiation is *WOX4*-independent [37] and requires components of the brassinosteroid (BR) signaling cascade [40]. Interestingly, also in the RAM, BR signaling has to be counteracted by the BRAVO transcription factor to maintain QC attributes [41], suggesting that attenuation of BR output is a common feature of plant stem cell niches. Collectively, the PXY–CLE41/42/44 cascade promotes cambium stem cell fate, in contrast to similar cascades in the SAM and the RAM. In addition to the PXY–CLE41/42/44 module, the LRR-RLK MORE LATERAL GROWTH1 (MOL1) acts in the distal cambium area and represses stem cell activity similar to CLV1 in the SAM. In fact, MOL1 and CLV1 are interchangeable, demonstrating that they act by the same mechanisms [42]. The spatially divergent activity of LRR-RLK receptors in the cambium might be due to the bifacial mode of tissue production [42]. With local feedback signaling systems built on the same molecular backbone as in the SAM and RAM, what is the contribution of plant hormones in the cambium? With respect to its dependence on auxin, the cambium resembles the RAM — auxin is crucial for cambium proliferation, and there is a high level of auxin signaling in or next to cambium stem cells [43,44]. *WOX4* serves as an integrator of auxin signaling, a role which is independent of its stimulation by the PXY–CLE41/42/44 module [43] and rather seems similar to the auxin-dependent activity of *WOX5* [30,45].

## Comparative Approaches and Outlook

Despite the massive differences in lifestyle and cellular biophysics between plants and animals, the general design philosophy for their stem cell systems is remarkably similar. Signals emanating from organizing or niche cells non-cell-autonomously control stem cell fate and activity over extended periods of time. Furthermore, although animal cell fate seems to be more stable, ablated somatic multipotent stem cells can be replaced by cells

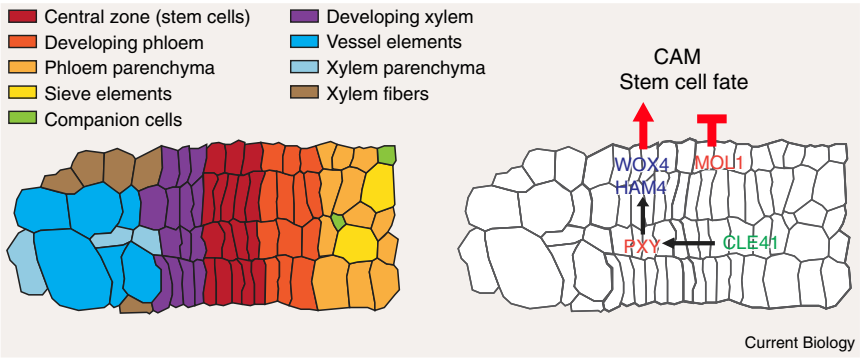


**Figure 4. The cambium.**
A schematic cross-section of the cambium area in the *Arabidopsis* lower stem. The different cell types found in the cambium are shown on the left and the interaction of tissue-specific stem cell regulators is shown on the right.

from their surroundings, highlighting the role of niche signaling in both kingdoms [46].

At the molecular level, however, the divergence is substantial. While mobile transcription factors seem a common theme for stem cell-inducing signals in plants, contact or ligand–receptor-based systems are the norm in animals. These interactions also play a profound role in plants, mostly for the limitation of proliferation, and so far it appears that evolution has adopted LRR-RLKs as the toolbox to equip all plant stem cell systems [47,48].

Another fundamental difference between plants and animals is the aspect of pluripotency — many plant cells even outside the stem cell niches are able to de-differentiate and return to a proliferative pluripotent state, as seen after excessive wounding or in simple tissue culture, whereas in animals this capacity is limited to embryonic stem cells. Thus, *in vitro* reprogramming of differentiated animal cells has opened the door not only for potent therapies, but also to new experiments to dissect the molecular mechanisms of pluripotency using comparative analyses. The finding of distinct histone modifications in undifferentiated cells, massive epigenetic modifications upon reprogramming, or the recruitment of histone deacetylases by stem cell-inducing and plant-specific WOX transcription factors already provide a glimpse of what we might be able to learn from these approaches [31,49,50]. Thus, deciphering the evolutionary signatures hidden in stem cell systems of animals and plants might allow us to identify ancient conserved building blocks, as well as novel, yet similar, regulatory modules shaped by convergent evolution. Ultimately, such information could allow us to travel back in time by revealing the selective forces that acted on the most fundamental cellular system of all higher organisms, including man.

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