Introduction

Stem cells are small populations of relatively undifferentiated dividing cells whose daughters can either remain stem cells or differentiate. In most, but not all cases, they are pluripotent and give rise to several differentiated cell types. The balance between self renewal and differentiation can be coordinated either at the single cell or population level (Fig. 1) (Spradling et al., 2001). In the single cell mechanism, each stem cell division is strictly asymmetric, producing one new stem cell and one differentiating cell. This can occur by asymmetric distribution of intracellular components or by placing of the daughter cells into different microenvironments. By contrast, in a population-based mechanism, the outcome of an individual stem cell division cannot be predicted, but the total number of stem cells is regulated. Regardless of the division mode, however, the emerging picture is that stem cell identity is regulated by signals from surrounding cells (Mayer et al., 1998; Spradling et al., 2001). This is in line with Newman’s proposal that the founder cells in the shoot apex are the ‘temporary occupants of a permanent office’ (Newman, 1965), which anticipated Schofield’s ‘niche concept’ derived from studies of hematopoietic development (Schofield, 1978; Spradling et al., 2001).

The caveat of the above stem cell definition is, however, that it is based on something the stem cell daughters do but tells us little about the nature of a stem cell itself. Can we define a stem cell in molecular terms? In many cases, molecular markers have been identified that allow enrichment for stem cells (Blau et al., 2001; Kornblum and Geschwind, 2001; Lagasse et al., 2000). However, it is often unclear whether such molecules are necessary components of stem cell identity.

In plants, all postembryonically formed cells and organs are ultimately derived from small stem cell populations in the apical shoot and root meristems, which allow generation of new organs over a life span that can be more than a thousand years. In addition, plants possess stem cells that have more tissue-specific functions, such as to provide cells for girdle formation. The apical meristems are especially suitable for studies of stem cell biology. For example, mutant sectors can be generated and the progeny of a single stem cell can be followed. This has allowed determination of the numbers, potency and proliferative properties of shoot meristem stem cells (Furner and Pumfrey, 1992; Irish and Sussex, 1992; Ruth et al., 1985; Stewart and Dermen, 1970). Here, we discuss our current knowledge of stem cell regulation in the shoot meristem. For information on general shoot meristem development and function, the reader is referred to several excellent reviews (Barton, 1998; Bowman and Eshed, 2000; Clark, 1997; Meyerowitz, 1997).

Stem cells in the shoot apical meristem

The shoot meristem contains a central zone (CZ) that harbors pluripotent stem cells and surrounding regions in which cells start to differentiate and organ primordia are initiated (Fig. 2). In most angiosperms, it is also divided into three separate ‘germ’ layers, L1-L3 (Satina et al., 1940). Cells in the outer two layers, L1 and L2, divide predominantly anticlinally (vertical to the surface) to form two sheets of tissue, the epidermis and subepidermal tissue, respectively. By contrast, the underlying L3 cells divide in all directions and give rise to the internal tissues.

Elegant clonal studies demonstrated that within a given layer all cells are ultimately derived from 2-3 long-term stem cells (Furner and Pumfrey, 1992; Irish and Sussex, 1992; Schnitter et al., 1996; Stewart and Dermen, 1970). In addition, their immediate daughter cells can still act as transiently active short-term stem cells, giving rise to a more restricted part of the plant (Stewart and Dermen, 1970). In privet, it has been estimated that the short-term stem cells are replaced on average every 14 days, whereas the long-term stem cells can be active throughout the plants life (Stewart and Dermen, 1970). What could distinguish long-term from short-term stem cells? It is possible that the only difference is their position: the short-term...
cells at the rim of the stem cell pool are next to be ‘pushed out’ by divisions of central cells, whereas the central ones have a better chance of staying for a longer time (Ball, 1960). This division of labor might allow plants to reduce the number of cell divisions of their long-term stem cells and thus maintain them as a relatively error-free genetic blueprint.

The CZ is identified by its relatively weak cytoplasmic staining and low rate of cell division. Although the stem cells cannot be recognized histologically, on the basis of geometrical considerations one can predict that they are located in the three outermost cell layers of the CZ. Thus, if one assumes that the CZ in Arabidopsis it is about 5-6 cells high (Fig. 2) (Vaughan, 1955), the stem cells occupy only about the upper half of it. Are the stem cells different from surrounding cells in the shoot apex? The presumed stem cell region is characterized by the expression of the CLAVATA3 (CLV3) gene, which is thus used as an operational stem cell marker for the shoot meristem (Fletcher et al., 1999). This indicates that the stem cells of the shoot meristem are distinct from the other cells. Note, however, that mutants lacking CLV3 activity possess stem cells, indicating that CLV3 is not essential for stem cell identity (Clark et al., 1995).

Cells that exit the stem cell pool initiate differentiation and form lateral organs (leaves, side shoots and flowers) in the ring-shaped peripheral zone surrounding the CZ, and central stem tissue from the rib zone underneath the CZ. The earliest molecular changes known to occur are the downregulation of CLV3 expression (Fletcher et al., 1999) and the subsequent activation of several genes, such as ZWILLE (ZLL)/PINHEAD (Lynn et al., 1999; Moussian et al., 1998). Eventually expression of the SHOOTMERISTEMLESS (STM) gene is downregulated in organ anlagen, and organ development takes place (Long et al., 1996) (see below).

In summary, the shoot meristem displays a succession of distinct cell states, from the central stem cells to the cells in organ primordia at the periphery, whose proper specification is essential for meristem function.

**Specification of stem cell identity in the shoot meristem**

What keeps the stem cells in an undifferentiated state? Clonal studies have shown that in plants the fate of a dividing cell is determined by its position and not by its origin. Does this also hold true for stem cells?

During shoot meristem initiation, the first organs appear to be formed independently of the stem cells but subsequent organs are not (Fig. 3) (Sussex and Rosenthal, 1973). One can therefore predict that mutants defective in stem cell specification may form seedlings that have a normal pair of first, non-stem-cell-derived ‘leaves’ (the cotyledons) but no functional stem cells. This is the case in Arabidopsis wuschel (wus) mutants, where the putative stem cells are partially differentiated (Laux et al., 1996). WUS encodes a homeodomain protein and is expressed in a group of ~10 cells in the CZ of the meristem (Fig. 4) (Mayer et al., 1998), which are located underneath the three outermost cell layers that contain the stem cells in the vegetative shoot meristem and one
cell layer higher in embryonic and floral meristems. Together with the finding that \textit{WUS} is sufficient to induce expression of \textit{CLV3} (Schoof et al., 2000), these observations suggest that the stem cells of the shoot meristem are specified by signaling from the \textit{WUS}-expressing cells, termed the organizing center (OC; Fig. 4). Studies of the function of the putative \textit{WUS} orthologs in \textit{Petunia} and \textit{Antirrhinum} support this model (M. Kieffer, H. Cook, Y. Stern et al., unpublished; Stuurman et al., 2002). Thus, the shoot meristem provides one of the few examples where the presence of a stem cell niche can be shown genetically by the requirement for non-cell-autonomous activities of neighboring cells to specify stem cell identity.

**Feedback from the stem cells establishes a self-regulatory system**

How are stem cell self renewal and differentiation coordinated in plants? In ferns and other lower plants, the shoot apex displays a single large apical stem cell, the apical mother cell (Golub and Wetmore, 1948). Each division of this cell is strictly asymmetric, giving one differentiating cell while retaining the mother cell at the apex (Fig. 1A). But, the stem cells in multicellular shoot meristems of higher plants work differently: clonal studies indicate that stem cell divisions are not strictly asymmetric but regulated at the population level (Fig. 1B) (Ruth et al., 1985). This requires that the boundaries of the stem cell pool are constantly assessed and stably maintained in a changing cellular context. How is this achieved?

The results of surgical destruction of the shoot meristem apical cells suggested that the stem cells inhibit stem cell fate in their daughters by lateral suppression and thus themselves are involved in controlling the boundaries of the stem cell pool (Loiseau, 1959; Pilkington, 1929). Genetic analysis in \textit{Arabidopsis} has verified this and revealed that the size of the stem cell population is regulated through size regulation of the OC. Mutations in the \textit{CLV} genes result in largely increased shoot and floral meristem sizes owing to accumulation of \textit{CLV3}-expressing stem cells (Fig. 3) (Clark, 1997; Fletcher et al., 1999; Laufs et al., 1998). The \textit{CLV3} gene encodes a small peptide that is secreted into the extracellular space, where it presumably acts as a ligand for the \textit{CLV1} receptor-like kinase, which is expressed throughout most of the shoot meristem (Clark et al., 1997; Fletcher et al., 1999; Rojo et al., 2002; Trotochaud et al., 1999).

Besides \textit{CLV1} and \textit{CLV3}, additional proteins and genetic
locai that participate in CLV-dependent signaling have been identified. CLV1 protein is stabilized by CLV2, a receptor-like molecule lacking the intracellular kinase domain that might form heterodimers with CLV1 (Jeong et al., 1999). Furthermore, SHEPHERD, an HSP90-related protein that is thought to act as an ER-localized chaperone (Ishiguro et al., 2002), is required for CLV signaling, which suggests that it is either necessary for secretion of functional CLV3 protein or for assembly of a functional CLV1-CLV2 receptor complex. Inside the cell, CLV1/CLV3 signaling is negatively regulated by KAPP, a protein phosphatase (Trotochaud et al., 1999), and antagonized by POLTERGEIST, which appears to act downstream of the CLV loci (Yu et al., 2000).

What are the targets of CLV signaling? wus mutations are epistatic to clv, mutations in any of the three CLV genes result in an expanded WUS expression domain, and ectopic expression of CLV3 is sufficient to repress WUS (Brand et al., 2000; Laux et al., 1996; Schoof et al., 2000). These results indicate that CLV3 signaling restricts the size of the stem cell pool by restricting the size of the WUS expression domain. Thus, the balance between stem cells and differentiating cells appears to be dynamically regulated by a negative feedback loop between the OC and stem cells that involves the WUS and CLV3 genes: signaling from the OC confers stem cell identity to the cells in the three outermost layers, which in turn signal back to limit the size of the OC (Fig. 4) (Schoof et al., 2000). If, for example, the number of stem cells is too small, a reduced amount of CLV3 signal will lead to an expanded WUS expression domain, which in turn will result in the induction of more stem cells. This model for size regulation of the stem cell population by the OC is in line with previous findings from periclinal chimaeras in tomato, which showed that the floral meristem size is determined by the genotype of the L3 cells (Szymkowiak and Sussex, 1992).

Targeting the signals

Within the shoot meristem, signaling between stem cells and the OC must be targeted to the right cells and kept away from others. For example, how is stem cell identity restricted to the cells above the OC but not those surrounding it? Since all cells in the shoot apex are able to respond to ectopic WUS expression (Schoof et al., 2000), the WUS-mediated signal must be directed specifically to the apical neighbors. Interestingly, L1 cells within the CZ are effectively coupled by cytoplasmic connections, plasmodesmata, that facilitate intercellular movement of molecules, whereas they are relatively insulated from surrounding peripheral cells (Rinne and van der Schoot, 1998). If the same were true for all cells of the CZ, such a cytoplasmically insulated CZ could explain the restriction of the WUS-dependent signal to target cells within the CZ.

Turning meristem cells into organs

Once cells have left the stem cell pool, changes in their expression pattern indicate the onset of differentiation. However, the cells are kept in a relatively undifferentiated state, and organ formation appears to be inhibited by the activity of the STM gene. STM acts independently of WUS, but both genes together are required for maintaining the shoot meristem (Gallois et al., 2002; Lenhard et al., 2002). STM encodes the Arabidopsis ortholog of the maize homeodomain protein KNOTTED1 (KN1) (Long et al., 1996; Volledrecht et al., 1991). Both genes are expressed throughout the shoot apex to keep cells in an undifferentiated state but are downregulated in the incipient lateral organ primordia (Jackson et al., 1994; Long et al., 1996). Loss of STM function allows organ formation to consume the entire apex (Fig. 3) (Barton and Poethig, 1993; Endrizzi et al., 1996), suggesting that STM negatively regulates organ formation. This regulation involves repression of the organ-promoting ASYMMETRIC LEAVES1 and ASYMMETRIC LEAVES2 genes (Byrne et al., 2000; Byrne et al., 2002). Thus, in contrast to WUS, whose function appears to be restricted to maintaining the stem cells, STM appears to be required in cells throughout the meristem dome to prevent premature organ formation. This regulation could allow meristem cells to amplify to sufficient numbers before organs are initiated (Lenhard et al., 2002).

In addition to STM and WUS activities, maintaining the shoot meristem cells in an undifferentiated state requires signaling from the organ primordia back to the shoot apex (Waitez et al., 1998). In general, adaxial (upper) leaf identity appears to be required for meristem maintenance, whereas abaxial leaf identity is incompatible with it (Bowman and Eshed, 2000; McConnell and Barton, 1998).

Making stem cells

Embryogenesis

Wardlaw named the shoot meristem stem cells 'embryonic initials', taking into account the fact that both embryo cells and stem cells give rise to many cell types and complete organs (Wardlaw, 1957). However, shoot meristem stem cells are not apparent until half way through embryogenesis and their expression profile shows they are different from early embryo cells. The earliest sign of shoot meristem formation is the onset of WUS expression in four subepidermal apical cells of the 16-cell embryo (Fig. 5) (Mayer et al., 1998), which subsequently undergo a series of asymmetric cells divisions with respect to continuing WUS expression. In mid-stage embryos, the shoot meristem becomes discernable and CLV3 expression is initiated (Fig. 5) (Brand et al., 2002). Loss of WUS function results in a failure to express CLV3 and to form a shoot meristem (Brand et al., 2002; Laux et al., 1996). Thus, embryonic formation of shoot meristem stem cells can be divided into two steps: first, a cell lineage that will give rise to the OC is established and presumably preserved by WUS function; and second, stem cell identity is induced in mid-stage embryos. Mutations in other genes important for embryonic shoot meristem development, such as STM, seem not to be required for stem cell initiation but instead to maintain them (Brand et al., 2002; Long and Barton, 1998).

Analysis of the zwillle (zll, also named pinhead) mutant has given some indication of how stem cell initiation is coordinated with the rest of the embryo. In zll embryos, the expression pattern of shoot meristem genes is randomized but still restricted to the shoot apex (Lynn et al., 1999; Moussian et al., 1998). At late stages, shoot meristem gene expression is shut off, and the cells at the stem cell position differentiate (Endrizzi et al., 1996; McConnell and Barton, 1995; Moussian et al., 1998). During early embryo development, ZLL is expressed in
the precursor cells of the vasculature, directly underneath the shoot meristem primordium, and later in the adaxial (upper) side of cotyledonary primordia (Lynn et al., 1999; Moussian et al., 1998). Expression of ZLL in the abaxial (lower) instead of the abaxial side of the cotyledonary primordia resulted in their transformation into indeterminate axes with ectopic shoot meristems (Newman et al., 2002). Together these observations indicate that stem cell formation requires ZLL-dependent signals from neighboring embryonic cells. Similarly, postembryonic ZLL activity in the vascular primordia and/or the adaxial part of leaf primordia is important for the formation of axillary meristems (Lynn et al., 1999).

ZLL encodes one of the name-giving members of a protein family with a PAZ (PIWI ARGONAUTE ZWILLE) domain, which is highly conserved throughout the animal and plant kingdom (Cerutti et al., 2000). Recent evidence shows that some PAZ proteins are members of complexes that bind micro RNAs – small RNA molecules of ~20 nucleotides (Hammond et al., 2001; Mourelatos et al., 2002) – which in turn allow binding to homologous sequences of specific mRNA species. Since one member of the PAZ family is the putative translation initiation factor eIF2C from rabbit (Zou et al., 1998), and double mutants of zll and its relative argonaute produce STM mRNA but no STM protein, an attractive hypothesis is that ZLL functions in translational regulation of specific mRNA species required for shoot meristem development (Lynn et al., 1999).

**Formation of stem cells from differentiated cells**

Plants can also form stem cells de novo from differentiated cells. For example, the expression pattern of meristem genes suggests that floral meristems that arise at the periphery of the inflorescence meristem are not contiguous with the inflorescence meristem but are initiated de novo (Mayer et al., 1998; Otsuga et al., 2001). While the cells that give rise to floral meristems are still relatively undifferentiated, plants clearly can also form meristems from fully differentiated cells. For example, differentiated leaf epidermal cells can give rise to leaf-borne embryos with apical meristems (Taylor, 1967). In the root, lateral root meristems are initiated from differentiated pericycle cells (Malamy and Benfey, 1997). The capacity of differentiated plant cells to dedifferentiate and to give rise to stem cells, either through the induction of meristems or through somatic embryo formation, provides an important tool for regenerative biology. It should be noted, however, that in many cases the cells from which the stem cells ultimately originate and their differentiation state are not precisely known.

**Termination of stem cells**

Flowers are homologous to shoots and it is thus not surprising that the regulatory circuitry that governs stem cell maintenance in the shoot meristem also functions in floral meristems. However, one important difference between shoot and flower development is that the *Arabidopsis* shoot meristem is indeterminate whereas the floral meristem is determinate and gives rise to only a limited number of organs. Thus, at the end of floral meristem activity, the stem cells differentiate and contribute to the central organ, the gynoecium. The MADS box transcription factor AGAMOUS (AG) is required for both specifying floral organ identity and termination of the floral meristem (YanoFSky et al., 1990). The latter involves repression of WUS expression in the OC (Laux et al., 1996; Lenhard et al., 2001; Lohmann et al., 2001). WUS in turn can activate transcription of the AG gene, setting up a suicidal feedback mechanism by which the OC and eventually the stem cells differentiate. Obviously, the correct temporal and spatial control of this mechanism is important. First, stem cells have to be active for long enough to ensure that sufficient cells are generated for all floral organs. A possible mechanism is suggested by the finding that floral determinacy appears to require high levels of AG activity, which might be reached only gradually during flower development (Sieburth et al., 1995). Second, stem cell termination must be restricted to the floral meristem and not occur in the shoot meristem. Genetic interactions indicate that WUS requires the presence of the floral regulator *LEAFY* in order to activate AG expression (Lenhard et al., 2001). However, in vitro both proteins appear to be able to bind the AG promoter independently (Lohmann et al., 2001).

**Common principles in stem cell regulation**

How similar are shoot meristem stem cells to other stem cell systems? The root meristem is thought to have evolved independently of the shoot meristem, but the organization of
both meristems is very similar: In the root meristem, differentiation of stem cells is prevented by signals from a small group of cells, the quiescent center, similar to the function of the OC in the shoot meristem (van den Berg et al., 1997). Whether the regulatory molecules and mechanisms involved are similar to those in the shoot meristems has to await further analysis.

Traditionally plant stem cells have been considered to be fundamentally different from animal stem cells. However, recent advances suggest that plant and animal stem cells are functionally equivalent and regulated by common principles. A major perceived difference is that plant stem cells are regulated by positional information, whereas animal stem cells have been viewed as cell lineages of a fixed fate. However, it now has become clear that at least many animal stem cells are similarly specified by signals from their neighborhood (Spradling et al., 2001). For example, the germ line stem cells in the oviduct of C. elegans are specified by signals from a single cell the distal tip cell, that suppress differentiation (meiosis) and maintain mitotic divisions (Berry et al., 1997; Henderson et al., 1994).

A second apparent difference is that plant stem cells are considered to have a much broader developmental program (they give rise to complete organs) than their animal counterparts, which regenerate cells restricted to one tissue type. However, recent findings have shown that in both cases the developmental capacity of stem cells is not an inherent property of the stem cell but instead dictated by the environment the daughter cells are exposed to, and can be dramatically expanded if this environment is altered (Blau et al., 2001; Morrison, 2001; Steeves and Sussex, 1989).

Are there also molecular similarities? This question is still difficult to answer since we know too little of the molecules that are important for stem cell generation and maintenance. Interestingly, one of the first ZLL-related genes identified, PIWI, functions in the regulation of stem cell maintenance in the Drosophila gerarium (Cox et al., 1999), which suggests that there are at least some similarities. However, there are no obvious candidates for the WUS or CLV3 genes in animals, which could reflect the different cellular constitutions of plant and animal stem cell niches, i.e. a dividing cell population versus a stable cavity.

Conclusion and perspectives
In the past few years, we have gained insights into how stem cells of the shoot meristem are specified and how self-renewal and differentiation are balanced. Most findings demonstrate that a major function in stem cell specification is to suppress differentiation pathways. However, the expression of CLV3 exclusively in the stem cells indicates that the activation of stem-cell-specific gene expression could also play a role. We have obtained an overview about the players and the mechanisms but many details are still to be discovered and genetic screens in selected genetic backgrounds may enable us to identify components missed so far.

Many of the regulatory principles appear to be common to a wide range of stem cell systems in plants and animals. But still we do not know what a stem cell is in molecular terms. What are the molecular factors that impart pluripotency on a cell? Many hypotheses have implicated chromatin structure in cell potency but, although this is an attractive possibility, robust experimental data are not yet available. Do stem cells express specific genes that confer 'stemness' or is it sufficient to protect them against differentiation signals? Is there a universal stem cell factor? Now that we are able to mark and to purify stem cells, their molecular profiles can be obtained that may allow answers to these questions (Phillips et al., 2000; Terskikh et al., 2001).

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