Stem Cell Research Literatures

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Ahmed, I., et al. (2016). "An ornamental plant targets epigenetic signaling to block cancer stem cell-driven colon carcinogenesis." Carcinogenesis **37**(4): 385-396.

Phytochemicals modulate key cellular signaling pathways and have proven anticancer effects. Alcea rosea(AR; Hollyhock) is an ornamental plant with known anti-inflammatory properties. This study explored its role as an anticancer agent. The AR seed extract (AR extract) inhibited proliferation and colony formation in a dose- and time-dependent manner and promoted apoptosis as was evidenced by cleavage of PARP and increased expression of Bax accompanying reduced levels of BCL-xl protein in HCT116 and SW480 cells, respectively. In addition, AR extract-arrested cells at Go/G1 phase of cell cycle and exhibited decreases in Cyclin D1. AR extract-treated cells exhibited reduced number and size of colonospheres in a dose-dependent manner concomitant with decreases in cancer stem cell (CSC) markers ALDH1A1 and Dclk1. Relative levels of beta-catenin, Notch-ICD, Hes1 and EZH2 were also attenuated by AR extract. TOP-flash reporter activity, a measure of Wnt signaling, decreased significantly in response to treatment while overexpression of wild type but not mutant EZH2, reversed the inhibitory effects. Moreover, WIF1 (a Wnt antagonist) promoter activity increased dramatically following treatment with AR extract which phenocopied increases in WIF1 reporter activity following EZH2 knockdown.In vivo, AR extract attenuated tumor growth due probably to reduced levels of EZH2, beta-catenin, CyclinD1 and Ki-67 along with reduced levels of CSC markers. Since partial purification via HPLC yielded a prominent peak, efforts are underway to identify the active ingredient(s). Taken together, the results clearly suggest that AR extract/active component(s) can be an effective preventative/therapeutic agent to target colon cancer.

Aichinger, E., et al. (2012). "Plant stem cell niches." Annu Rev Plant Biol **63**: 615-636.

Multicellular organisms possess pluripotent stem cells to form new organs, replenish the daily loss of cells, or regenerate organs after injury. Stem cells are maintained in specific environments, the stem cell niches, that provide signals to block differentiation. In plants, stem cell niches are situated in the shoot, root, and vascular meristems-self-perpetuating units of organ formation. Plants' lifelong activity-which, as in the case of trees, can extend over more than a thousand years-requires that a robust regulatory network keep the balance between pluripotent stem cells and differentiating descendants. In this review, we focus on current models in plant stem cell

research elaborated during the past two decades, mainly in the model plant Arabidopsis thaliana. We address the roles of mobile signals on transcriptional modules involved in balancing cell fates. In addition, we discuss shared features of and differences between the distinct stem cell niches of Arabidopsis.

Baumann, K. (2013). "Plant cell biology: mobile miRNAs for stem cell maintenance." Nat Rev Mol Cell Biol **14**(3): 128.

Bennett, T., et al. (2014). "Precise control of plant stem cell activity through parallel regulatory inputs." Development **141**(21): 4055-4064.

The regulation of columella stem cell activity in the Arabidopsis root cap by a nearby organizing centre, the quiescent centre, has been a key example of the stem cell niche paradigm in plants. Here, we investigate interactions between transcription factors that have been shown to regulate columella stem cells using a simple quantification method for stem cell activity in the root cap. Genetic and expression analyses reveal that the RETINOBLASTOMA-RELATED protein, the FEZ and SOMBRERO NAC-domain transcription factors, the ARF10 and ARF16 auxin response factors and the quiescent centre-expressed WOX5 homeodomain protein each provide independent inputs to regulate the number of columella stem cells. Given the tight control of columella development, we found that these inputs act in a surprisingly parallel manner. Nevertheless, important points of interaction exist; for example, we demonstrate the repression of SMB activity by non-autonomous action of WOX5. Our results suggest that the developmental progression of columella stem cells may be quantitatively regulated by several more broadly acting transcription factors rather than by a single intrinsic stem cell factor, which raises questions about the special nature of the stem cell state in plants.

Beri, K. and S. S. Milgraum (2015). "Neocollagenesis in Deep and Superficial Dermis by Combining Fractionated Q-Switched ND:YAG 1,064-nm With Topical Plant Stem Cell Extract and N-Acetyl Glucosamine: Open Case Series." J Drugs Dermatol **14**(11): 1342-1346.

INTRODUCTION: As we enter a new age of increasing demand in novel cosmetic therapies, we are challenged to provide excellent results with minimal downtime and safety in all skin types. In this open case series we are studying the improvement in rhytides by combining a novel, FDA-approved, non-ablative fractionated Q-switched ND: YAG 1,064-nm laser that acts in the deep dermis, with a topical containing plant stem cell extract and N-acetyl glucosamine (NAG) that acts in the superficial dermis. METHOD: Six healthy females (Skin types III - V) were selected for the study with mean average age of 56 years +/- 11 years. The rhytides on the face and neck were assessed using a comprehensive grading scale. Patients were then divided into two groups, one received only laser treatment with the fractionated QSW 1,064 nm laser and the other group received combined treatment with the laser and topical. Patients were assessed again at 4 and 8 weeks. RESULTS: We observed an enhanced anti-aging effect of the laser in the patients with combined treatment. DISCUSSION: Understanding the effect of this novel laser therapy on human stem cells and investigating the basis of its synergistic effect with plant stem cell extract and NAG will lead us to better understand stem cell activity. Non-ablative tissue regeneration is the next step in providing optimal anti-aging treatments.

Biedermann, S. and T. Laux (2018). "Plant Development: Adding HAM to Stem Cell Control." Curr Biol **28**(21): R1261-R1263.

The stem cell niche of the shoot meristem is stably maintained despite a rapidly changing cellular context. Recent papers reveal a mechanism controlling the spatial patterning of the stem cell niche that prevents its self-termination.

Bleckmann, A. and R. Simon (2009). "Interdomain signaling in stem cell maintenance of plant shoot meristems." Mol Cells **27**(6): 615-620.

The plant shoot meristem maintains a group of stem cells that remain active throughout the plant life. They continuously generate new cells that are then recruited for organ initiation in the peripheral zone. Stem cell proliferation and daughter cell differentiation has to be integrated with overall growth and development of the diverse functional domains within the shoot apex. Several studies have revealed extensive communication between these domains. The signaling mechanisms employed comprise diffusible peptides, directional transport of plant hormones, but also complex interactions between transcription factors, that together establish a panoply of regulatory inputs that fine-tune stem cell behavior in the shoot meristem.

Bonturi, C. R., et al. (2018). "Could a plant derived protein potentiate the anticancer effects of a stem cell in brain cancer?" Oncotarget **9**(30): 21296-21312.

Glioblastoma is the most aggressive brain tumor with poor overall survival bellow 2 years. The natural compounds with anti-cancer properties, are thus gaining attention for possible adjuvant GBM treatment. In various cancer models Enterolobium contortisiliquum Trypsin Inhibitor (EcTI) proved to have anti-cancer effects. Here, we investigated the EcTI effects on GBM U87 cells and on mesenchymal stem cells (MSC) compared to their direct coculture (MSC/U87). MSC are present in tumor stroma, modulating GBM cells phenotype, and also represent potential drug delivery vehicle due to their tumor tropism. We showed that in p53-wild type U87 cells, metabolic activity was less affected by EcTI as in MSC monocuture, but the metabolic rate of mixed coculture was significantly reduced at lower EcTI concentration. Under coculture condition, EcTI potentiated MSC induced cell cycle arrest, possible due to highly increased p53, p21 and lower D1 expression, but there was no effect on apoptosis. Accordingly, in the coculture EcTI also enhanced Ca(2+) signalling mediated via bradykinin receptor 2, being associated with nitric oxide release that highly impaired proliferation and invasion. The mechanism did not seem to involve changes in cell adhesion but rather it down-regulated the beta1 integrin signaling with associated p-FAK in U87 cells, both supporting inhibition of invasion. Finally, some cytokines were down-regulated, indicating that EcTI inhibition of signalling might be mediated by cytokines. In conclusion, these results indicate that in cocultured MSC/U87 cells EcTI impairs the metabolic activity, proliferation, and reduced invasion, possibly associated with observed cytokines secretion. In this context, we confirmed that the plant derived protein potentiated the anticancer effects, induced by MSC, as represented by GBM U87 cell line.

Burian, A., et al. (2016). "Patterns of Stem Cell Divisions Contribute to Plant Longevity." Curr Biol **26**(11): 1385-1394.

The lifespan of plants ranges from a few weeks in annuals to thousands of years in trees. It is hard to explain such extreme longevity considering that DNA replication errors inevitably cause mutations. Without purging through meiotic recombination, the accumulation of somatic mutations will eventually result in mutational meltdown, a phenomenon known as Muller's ratchet. Nevertheless, the lifespan of trees is limited more often by incidental disease or structural damage than by genetic aging. The key determinants of tree architecture are the axillary meristems, which form in the axils of leaves and grow out to form branches. The number of branches is low in annual plants, but in perennial plants iterative branching can result in thousands of terminal branches. Here, we use stem cell ablation and quantitative cell-lineage analysis to show that axillary meristems are set aside early, analogous to the metazoan germline. While neighboring cells divide vigorously, axillary meristem precursors maintain a quiescent state, with only 7-9 cell divisions occurring between the apical and axillary meristem. During iterative branching, the number of branches increases exponentially, while the number of cell divisions increases linearly. Moreover, computational modeling shows that stem cell arrangement and positioning of axillary meristems distribute somatic mutations around the main shoot, preventing their fixation and maximizing genetic heterogeneity. These features slow down Muller's ratchet and thereby extend lifespan.

Busch, W., et al. (2010). "Transcriptional control of a plant stem cell niche." Dev Cell **18**(5): 849-861.

Despite the independent evolution of multicellularity in plants and animals, the basic organization of their stem cell niches is remarkably similar. Here, we report the genome-wide regulatory potential of WUSCHEL, the key transcription factor for stem cell maintenance in the shoot apical meristem of the reference plant Arabidopsis thaliana. WUSCHEL acts by directly binding to at least two distinct DNA motifs in more than 100 target promoters and preferentially affects the expression of genes with roles in hormone signaling, metabolism, and development. Striking examples are the direct transcriptional repression of CLAVATA1, which is part of a negative feedback regulation of WUSCHEL, and the immediate regulation of transcriptional repressors of the TOPLESS family, which are involved in auxin signaling. Our results shed light on the complex transcriptional programs required for the maintenance of a dynamic and essential stem cell niche.

Chakraborty, A., et al. (2012). "Computational tools for quantitative analysis of cell growth patterns and morphogenesis in actively developing plant stem cell niches." Methods Mol Biol **876**: 217-227.

Pattern formation in developmental fields involves precise spatial arrangement of different cell types in a dynamic landscape wherein cells exhibit a variety of behaviors, such as cell division, cell expansion, and cell migration [Reddy (Curr Opin Plant Biol 11:88-931, 2008) and Meyerowitz (Cell 88:299-3082, 2007)]. The information is exchanged between multiple cell layers through cell-cell communication processes to regulate gene expression and cell behaviors in specifying distinct cell types. Therefore, a quantitative and dynamic understanding

of the spatial and temporal organization of gene expression and cell behavioral patterns within multilayered and actively growing developmental fields is crucial to model the process of development. The quantification of spatiotemporal dynamics of cell behaviors requires computational tools in image analysis, statistical modeling, pattern recognition, machine learning, and dynamical system identification. Here, we give a brief account of recently developed methods in analyzing both local and global growth patterns in Arabidopsis shoot apical meristems. The computational toolkit can be used to gain new insights into causal relationships among cell growth, cell division, changes in gene expression patterns, and organ development by analyzing various mutants that affect these processes. This may allow us to develop function space models that capture variations in several growth parameters both at local/single-cell level and at global/organ level. In the long run, this may enable clustering of molecular pathways that mediate distinct cell behaviors.

Crawford, B. C., et al. (2015). "Plant development. Genetic control of distal stem cell fate within root and embryonic meristems." Science **347**(6222): 655-659.

The root meristem consists of populations of distal and proximal stem cells and an organizing center known as the quiescent center. During embryogenesis, initiation of the root meristem occurs when an asymmetric cell division of the hypophysis forms the distal stem cells and quiescent center. We have identified NO TRANSMITTING TRACT (NTT) and two closely related paralogs as being required for the initiation of the root meristem. All three genes are expressed in the hypophysis, and their expression is dependent on the auxin-signaling pathway. Expression of these genes is necessary for distal stem cell fate within the root meristem, whereas misexpression is sufficient to transform other stem cell populations to a distal stem cell fate in both the embryo and mature roots.

Dinneny, J. R. and P. N. Benfey (2008). "Plant stem cell niches: standing the test of time." Cell **132**(4): 553-557.

Similar to animal stem cells, plant stem cells require special niche microenvironments to continuously generate the tissues that constitute the plant body. Recent work using computer modeling and live imaging is helping to elucidate some of the mechanisms responsible for the specification and maintenance of stem cells in the root and shoot.

Doerner, P. (2006). "Plant meristems: the fiendish SU DOKU of stem-cell maintenance." Curr Biol **16**(6): R199-201.

Three recent studies have uncovered effector mechanisms and novel pathways in the regulation of the dynamic changes to cell behaviour that occur in plant meristems. The results show how exquisite regulation of cell-cycle mechanisms is central to root stem cell homeostasis.

Dong, R., et al. (2018). "Extract of the Medicinal Plant Pao Pereira Inhibits Pancreatic Cancer Stem-Like Cell In Vitro and In Vivo." Integr Cancer Ther **17**(4): 1204-1215.

Pancreatic cancers are enriched with cancer stem-like cells (CSCs), which are resistant to chemotherapies, and responsible for tumor metastasis and recurrence. Here, we investigated the extract of a medicinal plant Pao Pereira (Pao) for its activity against pancreatic CSCs. Pao inhibited overall proliferation of human pancreatic cancer cell lines with IC50 ranging from 125 to 325 mug/mL and had limited cytotoxicity to normal epithelial cells. Pancreatic CSC population, identified using surface markers CD24+ CD44+ EpCam+ or tumor spheroid formation assay, was significantly reduced, with IC50s of ~100 mug/mL for 48 hours treatment, and ~27 mug/mL for long-term treatment. Nuclear beta-catenin levels were decreased, suggesting suppression of Wnt/beta-catenin signaling pathway. In vivo, Pao at 20 mg/kg, 5 times/week gavage, significantly reduced tumorigenicity of PANC-1 cells in immunocompromised mice, indicating inhibition of CSCs in vivo. Further investigation is warranted in using Pao as a novel treatment targeting pancreatic CSCs.

Elo, A., et al. (2009). "Stem cell function during plant vascular development." Semin Cell Dev Biol **20**(9): 1097-1106.

While many regulatory mechanisms controlling the development and function of root and shoot apical meristems have been revealed, our knowledge of similar processes in lateral meristems, including the vascular cambium, is still limited. Our understanding of even the anatomy and development of lateral meristems (procambium or vascular cambium) is still relatively incomplete, let alone their genetic regulation. Research into this particular tissue type has been mostly hindered by a lack of suitable molecular markers, as well as the fact that thus far very few mutants affecting plant secondary development have been described. The development of suitable molecular markers is a high priority in order to help define the anatomy, especially the location and identity of

cambial stem cells and the developmental phases and molecular regulatory mechanisms of the cambial zone. To date, most of the advances have been obtained by studying the role of the major plant hormones in vascular development. Thus far auxin, cytokinin, gibberellin and ethylene have been implicated in regulating the maintenance and activity of cambial stem cells; the most logical question in research would be how these hormones interact during the various phases of cambial development.

Fulcher, N. and R. Sablowski (2009). "Hypersensitivity to DNA damage in plant stem cell niches." Proc Natl Acad Sci U S A **106**(49): 20984-20988.

The growing apices of plants contain stem cells that continually produce tissues, which, in the shoot, include the germline. These stem cell populations remain active throughout the plant's life, which can last for centuries, and are particularly exposed to environmental hazards that cause DNA damage and mutations. It is not known whether plants have mechanisms to safeguard the genome specifically in these crucial cell populations. Here, we show that root and shoot stem cells and their early descendants are selectively killed by mild treatment with radiomimetic drugs, x-rays, or mutations that disrupt DNA repair by nonhomologous end-joining. Stem cell death required transduction of DNA damage signals by the ATAXIA-TELANGIECTASIA MUTATED (ATM) kinase and, specifically in the root, also the ATM/RAD3-RELATED (ATR) kinase. Consistent with the absence of p53 and the core apoptotic machinery in plants, death of the stem cells did not show apoptotic but autolytic features as seen in other cases of plant developmentally programmed cell death. We propose that plants have independently evolved selective death as a stringent mechanism to safeguard genome integrity in their stem cell populations.

Geier, F., et al. (2008). "A quantitative and dynamic model for plant stem cell regulation." PLoS One **3**(10): e3553.

Plants maintain pools of totipotent stem cells throughout their entire life. These stem cells are embedded within specialized tissues called meristems, which form the growing points of the organism. The shoot apical meristem of the reference plant Arabidopsis thaliana is subdivided into several distinct domains, which execute diverse biological functions, such as tissue organization, cell-proliferation and differentiation. The number of cells required for growth and organ formation changes over the course of a plants life, while the structure of the meristem remains remarkably constant. Thus, regulatory systems must be in place, which allow for an adaptation of cell proliferation within the shoot apical meristem, while maintaining the organization at the tissue level. To advance our understanding of this dynamic tissue behavior, we measured domain sizes as well as cell division rates of the shoot apical meristem under various environmental conditions, which cause adaptations in meristem size. Based on our results we developed a mathematical model to explain the observed changes by a cell pool size dependent regulation of cell proliferation and differentiation, which is able to correctly predict CLV3 and WUS over-expression phenotypes. While the model shows stem cell homeostasis under constant growth conditions, it predicts a variation in stem cell number under changing conditions. Consistent with our experimental data this behavior is correlated with variations in cell proliferation. Therefore, we investigate different signaling mechanisms, which could stabilize stem cell number despite variations in cell proliferation. Our results shed light onto the dynamic constraints of stem cell pool maintenance in the shoot apical meristem of Arabidopsis in different environmental conditions and developmental states.

Grafi, G., et al. (2011). "The stem cell state in plant development and in response to stress." Front Plant Sci **2**: 53.

Stem cells are commonly defined by their developmental capabilities, namely, self-renewal and multitype differentiation, yet the biology of stem cells and their inherent features both in plants and animals are only beginning to be elucidated. In this review article we highlight the stem cell state in plants with reference to animals and the plastic nature of plant somatic cells often referred to as totipotency as well as the essence of cellular dedifferentiation. Based on recent published data, we illustrate the picture of stem cells with emphasis on their open chromatin conformation. We discuss the process of dedifferentiation and highlight its transient nature, its distinction from re-entry into the cell cycle and its activation following exposure to stress. We also discuss the potential hazard that can be brought about by stress-induced dedifferentiation and its major impact on the genome, which can undergo stochastic, abnormal reorganization leading to genetic variation by means of DNA transposition and/or DNA recombination.

Gruel, J., et al. (2018). "The interaction of transcription factors controls the spatial layout of plant aerial stem cell niches." NPJ Syst Biol Appl **4**: 36.

The plant shoot apical meristem holds a stem cell niche from which all aerial organs originate. Using a computational approach we show that a mixture of monomers and heterodimers of the transcription factors

WUSCHEL and HAIRY MERISTEM is sufficient to pattern the stem cell niche, and predict that immobile heterodimers form a regulatory "pocket" surrounding the stem cells. The model achieves to reproduce an array of perturbations, including mutants and tissue size modifications. We also show its ability to reproduce the recently observed dynamical shift of the stem cell niche during the development of an axillary meristem. The work integrates recent experimental results to answer the longstanding question of how the asymmetry of expression between the stem cell marker CLAVATA3 and its activator WUSCHEL is achieved, and recent findings of plasticity in the system.

Ito, Y., et al. (2006). "Dodeca-CLE peptides as suppressors of plant stem cell differentiation." Science **313**(5788): 842-845.

In plants and animals, small peptide ligands that signal in cell-cell communication have been suggested to be a crucial component of development. A bioassay of single-cell transdifferentation demonstrates that a dodecapeptide with two hydroxyproline residues is the functional product of genes from the CLE family, which includes CLAVATA3 in Arabidopsis. The dodecapeptide suppresses xylem cell development at a concentration of 10(-11) M and promotes cell division. An application, corresponding to all 26 Arabidopsis CLE protein family members, of synthetic dodecapeptides reveals two counteracting signaling pathways involved in stem cell fate.

Jeon, H. Y., et al. (2017). "BRM270, a Compound from Natural Plant Extracts, Inhibits Glioblastoma Stem Cell Properties and Glioblastoma Recurrence." J Med Food **20**(9): 838-845.

Glioblastoma multiforme (GBM) is one of the most aggressive and lethal human brain tumors, and the median survival of patients with GBM is only 14 months. Glioblastoma stem cells (GSCs) are regarded as a main cause of GBM recurrence, because of their self-renewal and drug resistance properties. Therefore, targeting GSCs is an important therapeutic strategy for GBM. In this study, we show the effects of BRM270, a compound from natural plant extracts, on GSCs in vitro and GBM recurrence in vivo. BRM270 induced apoptotic cell death and inhibited cell growth and "stemness" both in vitro and in vivo. Combining BRM270 treatment with concurrent chemoradiotherapy (CCRT) dramatically increased mice survival and tumor growth inhibition. Taken together, our results suggested that BRM270 synergizes with CCRT as a therapeutic agent to target GSCs.

Jiang, F., et al. (2015). "Involvement of Plant Stem Cells or Stem Cell-Like Cells in Dedifferentiation." Front Plant Sci **6**: 1028.

Dedifferentiation is the transformation of cells from a given differentiated state to a less differentiated or stem cell-like state. Stem cell-related genes play important roles in dedifferentiation, which exhibits similar histone modification and DNA methylation features to stem cell maintenance. Hence, stem cell-related factors possibly synergistically function to provide a specific niche beneficial to dedifferentiation. During callus formation in Arabidopsis petioles, cells adjacent to procambium cells (stem cell-like cells) are dedifferentiated and survive more easily than other cell types. This finding indicates that stem cells or stem cell-like cells may influence the dedifferentiating niche. In this paper, we provide a brief overview of stem cell maintenance and dedifferentiation regulation. We also summarize current knowledge of genetic and epigenetic mechanisms underlying the balance between differentiation and dedifferentiation. Furthermore, we discuss the correlation of stem cells or stem cell-like cells with dedifferentiation.

Kiss, I., et al. (2010). "Enhancement of organ regeneration in animal models by a stem cell-stimulating plant mixture." J Med Food **13**(3): 599-604.

Adult stem cells play an important role in the regeneration of damaged organs. Attempts have already been made to enhance stem cell production by cytokines, in order to increase the improvement of cardiac functions after myocardial infarction. In our present study we investigated the possibility whether instead of cytokine injection dietary stimulation of stem cell production accelerates the organ regeneration in animals. A dietary supplement, Olimpiq StemXCell (Crystal Institute Ltd., Eger, Hungary), containing plant extracts (previously proved to increase the number of circulating CD34(+) cells) was consumed in human equivalent doses by the experimental animals. In the first experiment carbon tetrachloride was applied to CBA/Ca mice, to induce liver damage, and liver weights between StemXCell-fed and control animals were compared 10 days after the treatment. In the second model experimental diabetes was induced in F344 rats by alloxan. Blood sugar levels were measured for 5 weeks in the control and StemXCell-fed groups. The third part of the study investigated the effect of StemXCell on cardiac functions. Eight weeks after causing a myocardial infarction in Wistar rats by isoproterenol, left ventricular ejection fraction was determined as a functional parameter of myocardial regeneration. In all three animal models StemXCell

consumption statistically significantly improved the organ regeneration (relative liver weights, 4.78 +/-0.06 g/100 g vs. 4.97 +/- 0.07 g/100 g; blood sugar levels at week 5, 16 +/- 1.30 mmol/L vs. 10.2 +/- 0.92 mmol/L; ejection fraction, 57.5 +/- 2.23 vs. 68.2 +/- 4.94; controls vs. treated animals, respectively). Our study confirms the hypothesis that dietary enhancement of stem cell production may protect against organ injuries and helps in the regeneration.

Kumar, A., et al. (2019). "Identification and co-evolution pattern of stem cell regulator miR394s and their targets among diverse plant species." BMC Evol Biol **19**(1): 55.

BACKGROUND: Micro RNAs (miRNAs), a class of small non-coding RNAs, have been implicated in various aspects of plant development. miR394 is required for shoot apical meristem organization, stem cell maintenance and abiotic stress responses in Arabidopsis, where it functions by negatively regulating the transcript level of target LEAF CURLING RESPONSIVENESS (LCR), which is an F-box protein-coding gene. The evolutionary conservation of stem cell regulatory miR394-LCR module among plants remains elusive. RESULTS: Our study has identified 79 miR394 and 43 target sequences across 40 plant species using various homology based search tools and databases, and analysed their co-evolution pattern. We customised an annotation workflow which computationally validates 20 novel miR394s from 14 plant species. Independent phylogenetic trees were reconstructed with precursor MIR394s, mature miR394s, and their target sequences along with complementary miR394 binding sites. The phylogeny revealed that mature sequences of miR394s as well as their targets belonging to the F-box protein encoding gene families, were highly conserved. Though, miR394-3p were complementary to miR394s/miR394-5p, they clustered separately. CONCLUSION: The existence and separate clustering of miR394-3p and miR394s/miR394-5p indicate their independent regulation. The phylogeny also suggests that miR394s had evolved at the beginning of gymnosperm-angiosperm divergence. Despite strong conservation, some level of sequence variation in miR394s and the complementary binding sites of their targets suggests possible functional diversification of miR394-LCR mediated stem cell regulation in plants.

Lawrenz, A., et al. (2012). "Geometrical effects in microfluidic-based microarrays for rapid, efficient single-cell capture of mammalian stem cells and plant cells." Biomicrofluidics **6**(2): 24112-2411217.

In this paper, a detailed numerical and experimental investigation into the optimisation of hydrodynamic micro-trapping arrays for high-throughput capture of single polystyrene (PS) microparticles and three different types of live cells at trapping times of 30 min or less is described. Four different trap geometries (triangular, square, conical, and elliptical) were investigated within three different device generations, in which device architecture, channel geometry, inter-trap spacing, trap size, and trap density were varied. Numerical simulation confirmed that (1) the calculated device dimensions permitted partitioned flow between the main channel and the trap channel, and further, preferential flow through the trap channel in the absence of any obstruction; (2) different trap shapes, all having the same dimensional parameters in terms of depth, trapping channel lengths and widths, main channel lengths and widths, produce contrasting streamline plots and that the interaction of the fluid with the different geometries can produce areas of stagnated flow or distorted field lines; and (3) that once trapped, any motion of the trapped particle or cell or a shift in its configuration within the trap can result in significant increases in pressures on the cell surface and variations in the shear stress distribution across the cell's surface. Numerical outcomes were then validated experimentally in terms of the impact of these variations in device design elements on the percent occupancy of the trapping array (with one or more particles or cells) within these targeted short timeframes. Limitations on obtaining high trap occupancies in the devices were shown to be primarily a result of particle aggregation, channel clogging and the trap aperture size. These limitations could be overcome somewhat by optimisation of these device design elements and other operational variables, such as the average carrier fluid velocity. For example, for the 20 mum polystyrene microparticles, the number of filled traps increased from 32% to 42% during 5-10 min experiments in devices with smaller apertures. Similarly, a 40%-60% reduction in trapping channel size resulted in an increase in the amount of filled traps, from 0% to almost 90% in 10 min, for the human bone marrow derived mesenchymal stem cells, and 15%-85% in 15 min for the human embryonic stem cells. Last, a reduction of the average carrier fluid velocity by 50% resulted in an increase from 80% to 92% occupancy of single algae cells in traps. Interestingly, changes in the physical properties of the species being trapped also had a substantial impact, as regardless of the trap shape, higher percent occupancies were observed with cells compared to single PS microparticles in the same device, even though they are of approximately the same size. This investigation showed that in microfluidic single cell capture arrays, the trap shape that maximizes cell viability is not necessarily the most efficient for high-speed single cell capture. However, high-speed trapping configurations for delicate

mammalian cells are possible but must be optimised for each cell type and designed principally in accordance with the trap size to cell size ratio.

Li, T., et al. (2019). "Calcium signals are necessary to establish auxin transporter polarity in a plant stem cell niche." Nat Commun **10**(1): 726.

In plants mechanical signals pattern morphogenesis through the polar transport of the hormone auxin and through regulation of interphase microtubule (MT) orientation. To date, the mechanisms by which such signals induce changes in cell polarity remain unknown. Through a combination of time-lapse imaging, and chemical and mechanical perturbations, we show that mechanical stimulation of the SAM causes transient changes in cytoplasmic calcium ion concentration (Ca(2+)) and that transient Ca(2+) response is required for downstream changes in PIN-FORMED 1 (PIN1) polarity. We also find that dynamic changes in Ca(2+) occur during development of the SAM and this Ca(2+) response is required for changes in PIN1 polarity, though not sufficient. In contrast, we find that Ca(2+) is not necessary for the response of MTs to mechanical perturbations revealing that Ca(2+) specifically acts downstream of mechanics to regulate PIN1 polarity response.

Liang, Z., et al. (2015). "Calpain-Mediated Positional Information Directs Cell Wall Orientation to Sustain Plant Stem Cell Activity, Growth and Development." Plant Cell Physiol **56**(9): 1855-1866.

Eukaryotic development and stem cell control depend on the integration of cell positional sensing with cell cycle control and cell wall positioning, yet few factors that directly link these events are known. The DEFECTIVE KERNEL1 (DEK1) gene encoding the unique plant calpain protein is fundamental for development and growth, being essential to confer and maintain epidermal cell identity that allows development beyond the globular embryo stage. We show that DEK1 expression is highest in the actively dividing cells of seeds, meristems and vasculature. We further show that eliminating Arabidopsis DEK1 function leads to changes in developmental cues from the first zygotic division onward, altered microtubule patterns and misshapen cells, resulting in early embryo abortion. Expression of the embryonic marker genes WOX2, ATML1, PIN4, WUS and STM, related to axis organization, cell identity and meristem functions, is also altered in dek1 embryos. By monitoring cell layer-specific DEK1 down-regulation, we show that L1- and 35S-induced down-regulation mainly affects stem cell functions, causing severe shoot apical meristem phenotypes. These results are consistent with a requirement for DEK1 to direct layer-specific cellular activities and set downstream developmental cues. Our data suggest that DEK1 may anchor cell wall positions and control cell division and differentiation, thereby balancing the plant's requirement to maintain totipotent stem cell reservoirs while simultaneously directing growth and organ formation. A role for DEK1 in regulating microtubule-orchestrated cell wall orientation during cell division can explain its effects on embryonic development, and suggests a more general function for calpains in microtubule organization in eukaryotic cells.

Liu, L., et al. (2018). "[Advances in plant stem cell culture]." Sheng Wu Gong Cheng Xue Bao **34**(11): 1734-1741.

Plant stem cells are the cells that are located in meristems and are kept in a state of undifferentiation. Plant stem cell possesses lower vacuolization, higher mitochondrial activity, more genetic stability and stronger self-renewal capacity compared with calli. Plant stem cell culture has a wide application in pharmaceutical, functional food as well as cosmetic industries. Here we describe the procedure of induction, isolation and identification of plant stem cells, to provide a reference for further research in this field.

Ma, J., et al. (2018). "Histone chaperones play crucial roles in maintenance of stem cell niche during plant root development." Plant J **95**(1): 86-100.

Stem cells in both plant and animal kingdoms reside in a specialized cellular context called the stem cell niche (SCN). SCN integrity is crucial for organism development. Here we show that the H3/H4 histone chaperone CHROMATIN ASSEMBLY FACTOR-1 (CAF-1) and the H2A/H2B histone chaperone NAP1-RELATED PROTEIN1/2 (NRP1/2) play synergistic roles in Arabidopsis root SCN maintenance. Compared with either the m56-1 double mutant deprived of NRP1 and NRP2 or the fas2-4 mutant deprived of CAF-1, the combined m56-1fas2-4 triple mutant displayed a much more severe short-root phenotype. The m56-1fas2-4 mutant root lost the normal organizing center Quiescent Center (QC), and some initial stem cells differentiated precociously. Microarray analysis unraveled the deregulation of 2735 genes within the Arabidopsis genome (representing >8% of all genes) in the m56-1fas2-4 mutant roots. Expression of some SCN key regulatory genes (e.g. WOX5, PLT1, SHR) was not limiting, rather the plant hormone auxin gradient maximum at QC was impaired. The mutant roots showed programmed cell death and high levels of the DNA damage marked histone H2A.X phosphorylation (gamma-H2A.X). Knockout of either ATAXIA-TELANGIECTASIA MUTATED (ATM) or ATR, encoding a DNA damage

response kinase, rescued in part the cell death and the short-root phenotype of the m56-1fas2-4 mutant. Collectively, our study indicated that NRP1/2 and CAF-1 act cooperatively in regulating proper genome transcription, in sustaining chromatin replication and in maintaining genome integrity, which are crucial for proper SCN function during continuous post-embryonic root development.

Marhava, P., et al. (2019). "Re-activation of Stem Cell Pathways for Pattern Restoration in Plant Wound Healing." Cell **177**(4): 957-969 e913.

Patterning in plants relies on oriented cell divisions and acquisition of specific cell identities. Plants regularly endure wounds caused by abiotic or biotic environmental stimuli and have developed extraordinary abilities to restore their tissues after injuries. Here, we provide insight into a mechanism of restorative patterning that repairs tissues after wounding. Laser-assisted elimination of different cells in Arabidopsis root combined with live-imaging tracking during vertical growth allowed analysis of the regeneration processes in vivo. Specifically, the cells adjacent to the inner side of the injury re-activated their stem cell transcriptional programs. They accelerated their progression through cell cycle, coordinately changed the cell division orientation, and ultimately acquired de novo the correct cell fates to replace missing cells. These observations highlight existence of unknown intercellular positional signaling and demonstrate the capability of specified cells to re-acquire stem cell programs as a crucial part of the plant-specific mechanism of wound healing.

Miyashima, S., et al. (2013). "Stem cell function during plant vascular development." EMBO J **32**(2): 178-193.

The plant vascular system, composed of xylem and phloem, evolved to connect plant organs and transport various molecules between them. During the post-embryonic growth, these conductive tissues constitutively form from cells that are derived from a lateral meristem, commonly called procambium and cambium. Procambium/cambium contains pluripotent stem cells and provides a microenvironment that maintains the stem cell population. Because vascular plants continue to form new tissues and organs throughout their life cycle, the formation and maintenance of stem cells are crucial for plant growth and development. In this decade, there has been considerable progress in understanding the molecular control of the organization and maintenance of stem cells in vascular plants. Noticeable advance has been made in elucidating the role of transcription factors and major plant hormones in stem cell maintenance and vascular tissue differentiation. These studies suggest the shared regulatory mechanisms among various types of plant stem cell pools. In this review, we focus on two aspects of stem cell function in the vascular cambium, cell proliferation and cell differentiation.

Mosquna, A., et al. (2009). "Regulation of stem cell maintenance by the Polycomb protein FIE has been conserved during land plant evolution." Development **136**(14): 2433-2444.

The Polycomb group (PcG) complex is involved in the epigenetic control of gene expression profiles. In flowering plants, PcG proteins regulate vegetative and reproductive programs. Epigenetically inherited states established in the gametophyte generation are maintained after fertilization in the sporophyte generation, having a profound influence on seed development. The gametophyte size and phase dominance were dramatically reduced during angiosperm evolution, and have specialized in flowering plants to support the reproductive process. The moss Physcomitrella patens is an ideal organism in which to study epigenetic processes during the gametophyte stage, as it possesses a dominant photosynthetic gametophytic haploid phase and efficient homologous recombination, allowing targeted gene replacement. We show that P. patens PcG protein FIE (PpFIE) accumulates in haploid meristematic cells and in cells that undergo fate transition during dedifferentiation programs in the gametophyte. In the absence of PpFIE, meristems overproliferate and are unable to develop leafy gametophytes or reach the reproductive phase. This aberrant phenotype might result from failure of the PcG complex to repress proliferation and differentiation of three-faced apical stem cells, which are designated to become lateral shoots. The PpFIE phenotype can be partially rescued by FIE of Arabidopsis thaliana, a flowering plant that diverged >450 million years ago from bryophytes. PpFIE can partially complement the A. thaliana fie mutant, illustrating functional conservation of the protein during evolution in regulating the differentiation of meristematic cells in gametophyte development, both in bryophytes and angiosperms. This mechanism was harnessed at the onset of the evolution of alternating generations, facilitating the establishment of sporophytic developmental programs.

Naseem, M., et al. (2014). "Stem-cell-triggered immunity safeguards cytokinin enriched plant shoot apexes from pathogen infection." Front Plant Sci **5**: 588.

Intricate mechanisms discriminate between friends and foes in plants. Plant organs deploy overlapping and distinct protection strategies. Despite vulnerability to a plethora of pathogens, the growing tips of plants grow

bacteria free. The shoot apical meristem (SAM) is among three stem cells niches, a self-renewable reservoir for the future organogenesis of leaf, stem, and flowers. How plants safeguard this high value growth target from infections was not known until now. Recent reports find the stem cell secreted 12-amino acid peptide CLV3p (CLAVATA3 peptide) is perceived by FLS2 (FLAGELLIN SENSING 2) receptor and activates the transcription of immunity and defense marker genes. No infection in the SAM of wild type plants and bacterial infection in clv3 and fls2 mutants illustrate this natural protection against infections. Cytokinins (CKs) are enriched in the SAM and regulate meristem activities by their involvement in stem cell signaling networks. Auxin mediates plant susceptibility to pathogen infections while CKs boost plant immunity. Here, in addition to the stem-cell-triggered immunity we also highlight a potential link between CK signaling and CLV3p mediated immune response in the SAM.

Nimchuk, Z. L., et al. (2011). "Plant stem cell signaling involves ligand-dependent trafficking of the CLAVATA1 receptor kinase." Curr Biol **21**(5): 345-352.

BACKGROUND: Cell numbers in above-ground meristems of plants are thought to be maintained by a feedback loop driven by perception of the glycopeptide ligand CLAVATA3 (CLV3) by the CLAVATA1 (CLV1) receptor kinase and the CLV2/CORYNE (CRN) receptor-like complex. CLV3 produced in the stem cells at the meristem apex limits the expression level of the stem cell-promoting homeodomain protein WUSCHEL (WUS) in the cells beneath, where CLV1 and WUS RNA are localized. WUS downregulation nonautonomously reduces stem cell proliferation. Overexpression of CLV3 eliminates the stem cells, causing meristem termination, and loss of CLV3 function allows meristem overproliferation. There are many questions regarding the CLV3/CLV1 interaction, including where in the meristem it occurs, how it is regulated, and how it is that a large range of CLV3 concentrations gives no meristem size phenotype. RESULTS: Here we use genetics and live imaging to examine the cell biology of CLV1 in Arabidopsis meristematic tissue. We demonstrate that plasma membrane-localized CLV1 is reduced in concentration by CLV3, which causes trafficking of CLV1 to lytic vacuoles. We find that changes in CLV2 activity have no detectable effects on CLV1 levels. We also find that CLV3 appears to diffuse broadly in meristems, contrary to a recent sequestration model. CONCLUSIONS: This study provides a new model for CLV1 function in plant stem cell maintenance and suggests that downregulation of plasma membrane-localized CLV1 by its CLV3 ligand can account for the buffering of CLV3 signaling in the maintenance of stem cell pools in plants.

Nimchuk, Z. L., et al. (2015). "Plant stem cell maintenance by transcriptional cross-regulation of related receptor kinases." Development **142**(6): 1043-1049.

The CLAVATA3 (CLV3)-CLAVATA1 (CLV1) ligand-receptor kinase pair negatively regulates shoot stem cell proliferation in plants. clv1 null mutants are weaker in phenotype than clv3 mutants, but the clv1 null phenotype is enhanced by mutations in the related receptor kinases BARELY ANY MERISTEM 1, 2 and 3 (BAM1, 2 and 3). The basis of this genetic redundancy is unknown. Here, we demonstrate that the apparent redundancy in the CLV1 clade is in fact due to the transcriptional repression of BAM genes by CLV1 signaling. CLV1 signaling in the rib meristem (RM) of the shoot apical meristem is necessary and sufficient for stem cell regulation. CLV3-CLV1 signaling in the RM represses BAM expression in wild-type Arabidopsis plants. In clv1 mutants, ectopic BAM expression in the RM partially complements the loss of CLV1. BAM regulation by CLV1 is distinct from CLV1 regulation of WUSCHEL, a proposed CLV1 target gene. In addition, quadruple receptor mutants are stronger in phenotype than clv3, pointing to the existence of additional CLV1/BAM ligands. These data provide an explanation for the genetic redundancy seen in the CLV1 clade and reveal a novel feedback operating in the control of plant stem cells.

Reynertson, K. A., et al. (2011). "Induction of murine embryonic stem cell differentiation by medicinal plant extracts." Exp Cell Res **317**(1): 82-93.

Epidemiological evidence indicates that diets high in fruits and vegetables provide a measure of cancer chemoprevention due to phytochemical constituents. Natural products are a rich source of cancer chemotherapy drugs, and primarily target rapidly cycling tumor cells. Increasing evidence indicates that many cancers contain small populations of resistant, stem-like cells that have the capacity to regenerate tumors following chemotherapy and radiation, and have been linked to the initiation of metastases. Our goal is to discover natural product-based clinical or dietary interventions that selectively target cancer stem cells, inducing differentiation. We adapted an alkaline phosphatase (AP) stain to assay plant extracts for the capacity to induce differentiation in embryonic stem (ES) cells. AP is a characteristic marker of undifferentiated ES cells, and this represents a novel approach to screening medicinal plant extracts. Following a survey of approximately 100 fractions obtained from 12 species of ethnomedically utilized plants, we found fractions from 3 species that induced differentiation, decreasing AP and

transcript levels of pluripotency markers (Nanog, Oct-4, Rex-1). These fractions affected proliferation of murine ES, and human embryonal, prostate, and breast carcinoma cells in a dose-dependent manner. Several phytochemical constituents were isolated; the antioxidant phytochemicals ellagic acid and gallic acid were shown to affect viability of cultured breast carcinoma cells.

Rodriguez-Leal, D., et al. (2019). "Evolution of buffering in a genetic circuit controlling plant stem cell proliferation." Nat Genet **51**(5): 786-792.

Precise control of plant stem cell proliferation is necessary for the continuous and reproducible development of plant organs(1,2). The peptide ligand CLAVATA3 (CLV3) and its receptor protein kinase CLAVATA1 (CLV1) maintain stem cell homeostasis within a deeply conserved negative feedback circuit(1,2). In Arabidopsis, CLV1 paralogs also contribute to homeostasis, by compensating for the loss of CLV1 through transcriptional upregulation(3). Here, we show that compensation(4,5) operates in diverse lineages for both ligands and receptors, but while the core CLV signaling module is conserved, compensation mechanisms have diversified. Transcriptional compensation between ligand paralogs operates in tomato, facilitated by an ancient gene duplication that impacted the domestication of fruit size. In contrast, we found little evidence for transcriptional compensation between ligands in Arabidopsis and maize, and receptor compensation differs between tomato and Arabidopsis. Our findings show that compensation among ligand and receptor paralogs is critical for stem cell homeostasis, but that diverse genetic mechanisms buffer conserved developmental programs.

Sablowski, R. (2007). "The dynamic plant stem cell niches." Curr Opin Plant Biol **10**(6): 639-644.

Stem cells exist in specific locations called niches, where extracellular signals maintain stem cell division and prevent differentiation. In plants, the best characterised niches are within the shoot and root meristems. Networks of regulatory genes and intercellular signals maintain meristem structure in spite of constant cell displacement by division. Recent works have improved our understanding of how these networks function at the cellular and molecular levels, particularly in the control of the stem cell population in the shoot meristem. The meristem regulatory genes have been found to function partly through localised control of widely used signals such as cytokinin and auxin. The retinoblastoma protein has also emerged as a key regulator of cell differentiation in the meristems.

Sablowski, R. (2011). "Plant stem cell niches: from signalling to execution." Curr Opin Plant Biol **14**(1): 4-9.

The shoot and root meristems contain small populations of stem cells that constantly renew themselves while providing precursor cells to build all other plant tissues and organs. Cell renewal, growth and differentiation in the meristems are co-ordinated by networks of transcription factors and intercellular signals. The past two years have revealed how auxin and cytokinin signals are integrated with each other and with regulatory genes in the shoot and root meristems. Small RNAs have also emerged as novel intercellular signals. Downstream of meristem regulatory genes, links have been made to cell division control and chromatin function. Protection of genome integrity, partly through programmed cell death after DNA damage, has recently been revealed as a specialised function in plant stem cells.

Sahlin, P., et al. (2011). "Models of sequestration and receptor cross-talk for explaining multiple mutants in plant stem cell regulation." BMC Syst Biol **5**: 2.

BACKGROUND: Stem cells reside in a plant's shoot meristem throughout its life and are main regulators of above-ground plant development. The stem cell maintenance depends on a feedback network between the CLAVATA and WUSCHEL genes. The CLAVATA3 peptide binds to the CLAVATA1 receptor leading to WUSCHEL inhibition. WUSCHEL, on the other hand, activates CLAVATA3 expression. Recent experiments suggest a second pathway where CLAVATA3 inhibits WUSCHEL via the CORYNE receptor pathway. An interesting question, central for understanding the receptor signaling, is why the clavata1-11 null mutant has a weaker phenotype compared with the clavata1-1 non-null mutant. It has been suggested that this relies on interference from the mutated CLAVATA1 acting on the CORYNE pathway. RESULTS: We present two models for the CLAVATA-WUSCHEL feedback network including two receptor pathways for WUSCHEL repression and differing only by the hypothesized mechanisms for the clavata1-1 non-null mutant. The first model is an implementation of the previously suggested interference mechanism. The other model assumes an unaltered binding between CLAVATA3 and the mutated CLAVATA1 but with a loss of propagated signal into the cell. We optimize the models using data from wild type and four single receptor mutant experiments and use data from two receptor double mutant experiments in a validation step. Both models are able to explain all seven phenotypes and in addition

qualitatively predict CLAVATA3 perturbations. The two models for the clavata1-1 mutant differ in the direct mechanism of the mutant, but they also predict other differences in the dynamics of the stem cell regulating network. We show that the interference hypothesis leads to an abundance of receptors, while the loss-of-signal hypothesis leads to sequestration of CLAVATA3 and relies on degradation or internalization of the bound CLAVATA1 receptor. CONCLUSIONS: Using computational modeling, we show that an interference hypothesis and a more parsimonious loss-of-signal hypothesis for a clavata1 non-null mutant both lead to behaviors predicting wild type and six receptor mutant experiments. Although the two models have identical implementations of the unperturbed feedback network for stem cell regulation, we can point out model-predicted differences that may be resolved in future experiments.

Scofield, S. and J. A. Murray (2006). "KNOX gene function in plant stem cell niches." Plant Mol Biol **60**(6): 929-946.

Homeobox genes encode transcriptional regulators that control development in multicellular eukaryotes. In plants, post-embryonic shoot growth relies on the activity of indeterminate cell populations termed shoot meristems, within which members of the class-1 KNOX sub-family of homeobox genes are expressed. KNOX genes are differentially required for meristem development and function to inhibit cell expansion and differentiation associated with organogenesis. Mechanisms must therefore be employed to prevent KNOX gene expression in developing lateral organs such as leaves. This review focuses on the expression patterns, meristematic functions and regulation of KNOX genes, and how the activities of these genes are integrated within the framework of pathways that control plant development.

Shahid, M., et al. (2019). "Comprehensive Analyses of Nitric Oxide-Induced Plant Stem Cell-Related Genes in Arabidopsis thaliana." Genes (Basel) **10**(2).

Plant stem cells are pluripotent cells that have diverse applications in regenerative biology and medicine. However, their roles in plant growth and disease resistance are often overlooked. Using high-throughput RNA-seq data, we identified approximately 20 stem cell-related differentially expressed genes (DEGs) that were responsive to the nitric oxide (NO) donor S-nitrosocysteine (CySNO) after six hours of infiltration. Among these DEGs, the highest number of positive correlations (R >/= 0.8) was observed for CLAVATA3/EMBRYO SURROUNDING REGION-RELATED (CLE) 12. Gene ontology (GO) terms for molecular function showed DEGs associated with signal transduction and receptor activity. A promoter study of these DEGs showed the presence of cis-acting elements that are involved in growth as well as the regulation of abiotic and biotic stress. Phylogenetic analysis of the Arabidopsis stem cell-related genes and their common orthologs in rice, soybean, poplar, and tomato suggested that most soybean stem cell-related genes were grouped with the Arabidopsis CLE type of stem cell genes, while the rice stem cell-related genes were grouped with the Arabidopsis receptor-like proteins. The functional genomic-based characterization of the role of stem cell DEGs showed that under control conditions, the clv1 mutant showed a similar phenotype to that of the wild-type (WT) plants; however, under CySNO-mediated nitrosative stress, clv1 showed increased shoot and root length compared to WT. Furthermore, the inoculation of clv1 with virulent Pst DC3000 showed a resistant phenotype with fewer pathogens growing at early time points. The qRT-PCR validation and correlation with the RNA-seq data showed a Pearson correlation coefficient of >0.8, indicating the significantly high reliability of the RNA-seq analysis.

Stahl, Y. and R. Simon (2005). "Plant stem cell niches." Int J Dev Biol **49**(5-6): 479-489.

Stem cells are required to support the indeterminate growth style of plants. Meristems are a plants stem cell niches that foster stem cell survival and the production of descendants destined for differentiation. In shoot meristems, stem cell fate is decided at the populational level. The size of the stem cell domain at the meristem tip depends on signals that are exchanged with cells of the organizing centre underneath. In root meristems, individual stem cells are controlled by direct interaction with cells of the quiescent centre that lie in the immediate neighbourhood. Analysis of the interactions and signaling processes in the stem cell niches has delivered some insights into the molecules that are involved and revealed that the two major niches for plant stem cells are more similar than anticipated.

Sun, B., et al. (2014). "Timing mechanism dependent on cell division is invoked by Polycomb eviction in plant stem cells." Science **343**(6170): 1248559.

Plant floral stem cells divide a limited number of times before they stop and terminally differentiate, but the mechanisms that control this timing remain unclear. The precise temporal induction of the Arabidopsis zinc finger

repressor KNUCKLES (KNU) is essential for the coordinated growth and differentiation of floral stem cells. We identify an epigenetic mechanism in which the floral homeotic protein AGAMOUS (AG) induces KNU at ~2 days of delay. AG binding sites colocalize with a Polycomb response element in the KNU upstream region. AG binding to the KNU promoter causes the eviction of the Polycomb group proteins from the locus, leading to cell division-dependent induction. These analyses demonstrate that floral stem cells measure developmental timing by a division-dependent epigenetic timer triggered by Polycomb eviction.

Tucker, M. R. and T. Laux (2007). "Connecting the paths in plant stem cell regulation." Trends Cell Biol **17**(8): 403-410.

Stem cell niches are specialized microenvironments where pluripotent cells are maintained to provide undifferentiated cells for the formation of new tissues and organs. The balance between stem cell maintenance within the niche and differentiation of cells that exit it is regulated by local cell-cell communication, together with external cues. Recent findings have shown connections between key developmental pathways and added significant insights into the central principles of stem cell maintenance in plant meristems. These insights include the convergence of important stem cell transcriptional regulators with cytokinin signaling in the shoot meristem, the biochemical dissection of peptide signaling in the shoot niche and the identification of conserved regulators in shoot and root niches.

Vernoux, T. and P. N. Benfey (2005). "Signals that regulate stem cell activity during plant development." Curr Opin Genet Dev **15**(4): 388-394.

Plant stem cells are used continuously to generate new structures during the entire life-span of the organism. In the adult plant, stem cells are found in specialized structures called meristems. The meristems contain the stem cell niche together with rapidly dividing daughter cells that will ultimately differentiate into specific cell types. Some of the master genes that orchestrate the establishment and maintenance of the stem cell niche have now been identified in both the root and the shoot. Recent results show that these genes also determine the fate of the stem cells and that feedback signals from differentiated cells are involved in stem cell specification. These advances have provided a framework to understand how short-range and long-range signals are integrated to specify and position the stem cell niche in the meristems, and how the differentiation potential of plant stem cells is controlled.

Vilarrasa-Blasi, J., et al. (2014). "Regulation of plant stem cell quiescence by a brassinosteroid signaling module." Dev Cell **30**(1): 36-47.

The quiescent center (QC) maintains the activity of the surrounding stem cells within the root stem cell niche, yet specific molecular players sustaining the low rate of QC cell division remain poorly understood. Here, we identified a R2R3-MYB transcription factor, BRAVO (BRASSINOSTEROIDS AT VASCULAR AND ORGANIZING CENTER), acting as a cell-specific repressor of QC divisions in the primary root of Arabidopsis. Ectopic BRAVO expression restricts overall root growth and ceases root regeneration upon damage of the stem cells, demonstrating the role of BRAVO in counteracting Brassinosteroid (BR)-mediated cell division in the QC cells. Interestingly, BR-regulated transcription factor BES1 (BRI1-EMS SUPRESSOR 1) directly represses and physically interacts with BRAVO in vivo, creating a switch that modulates QC divisions at the root stem cell niche. Together, our results define a mechanism for BR-mediated regulation of stem cell quiescence in plants.

Xu, Y. Y. and K. Chong (2005). "[Progress in research on plant stem cell organizer gene WUSCHEL]." Zhi Wu Sheng Li Yu Fen Zi Sheng Wu Xue Xue Bao **31**(5): 461-468.

The WUS (WUSCHEL) gene encodes a transcription factor that specifies the adjacent cells to be stem cell. The WUS dependent signal systems have been found in different tissues recent years. The feedback loop between the CLV and WUS genes maintains the stem cell self-renewal and apical dominance in shoot apical meristem. In the embryonic meristem, the expression of CLV3 depends on WUS only. During post-embryo development, both WUS and STM are needed for CLV3 expression and the triggering of organogenesis. The expression of AG in floral meristem is activated by co-existence of WUS and LFY, AG acts as a negative regulator of WUS expression to downregulate the WUS level. The signal system established by WUS is also involved in ovule development. The somatic embryogenesis can be promoted efficiently by WUS, especially in the presence of auxin. The results of prevoius works indicated that cell competence to WUS activity is related to microenvironment and the combination of WUS signal with different environmental factors could activate different downstream genes.

Yadav, R. K., et al. (2013). "Plant stem cell maintenance involves direct transcriptional repression of differentiation program." Mol Syst Biol **9**: 654.

In animal systems, master regulatory transcription factors (TFs) mediate stem cell maintenance through a direct transcriptional repression of differentiation promoting TFs. Whether similar mechanisms operate in plants is not known. In plants, shoot apical meristems serve as reservoirs of stem cells that provide cells for all above ground organs. WUSCHEL, a homeodomain TF produced in cells of the niche, migrates into adjacent cells where it specifies stem cells. Through high-resolution genomic analysis, we show that WUSCHEL represses a large number of genes that are expressed in differentiating cells including a group of differentiation promoting TFs involved in leaf development. We show that WUS directly binds to the regulatory regions of differentiation promoting TFs; KANADI1, KANADI2, ASYMMETRICLEAVES2 and YABBY3 to repress their expression. Predictions from a computational model, supported by live imaging, reveal that WUS-mediated repression prevents premature differentiation of stem cell progenitors, being part of a minimal regulatory network for meristem maintenance. Our work shows that direct transcriptional repression of differentiation promoting TFs is an evolutionarily conserved logic for stem cell regulation.

Yang, S., et al. (2018). "ROS: The Fine-Tuner of Plant Stem Cell Fate." Trends Plant Sci **23**(10): 850-853.

Reactive oxygen species (ROS) are initially considered to be toxic by-products of aerobic metabolism. However, accumulating evidence has shown that ROS also act as key regulators for the progression of several basic biological processes. Recent studies highlight the key role of ROS in root and shoot stem cell niche maintenance.

Yang, W., et al. (2017). "Cell Cycle Control by Nuclear Sequestration of CDC20 and CDH1 mRNA in Plant Stem Cells." Mol Cell **68**(6): 1108-1119 e1103.

In eukaryotes, most RNA molecules are exported into the cytoplasm after transcription. Long noncoding RNAs (lncRNAs) reside and function primarily inside the nucleus, but nuclear localization of mRNAs has been considered rare in both animals and plants. Here we show that Arabidopsis anaphase-promoting complex/cyclosome (APC/C) coactivator genes CDC20 and CCS52B (CDH1 ortholog) are co-expressed with their target cyclin B genes (CYCBs) during mitosis. CYCB transcripts can be exported and translated; however, CDC20 and CCS52B mRNAs are confined to the nucleus at prophase, and the cognate proteins are not translated until the redistribution of the mRNAs to the cytoplasm after nuclear envelope breakdown (NEBD) at prometaphase. The 5' untranslated region (UTR) plays dual roles in CDC20 mRNA nuclear localization and translation. Mitotic accumulation of CDC20 and CCS52B transcripts enables the timely and rapid activation of APC/C, while the nuclear sequestration of these transcripts at prophase appears to protect cyclins from precocious degradation.

Yoshida, S., et al. (2011). "Stem cell activation by light guides plant organogenesis." Genes Dev **25**(13): 1439-1450.

Leaves originate from stem cells located at the shoot apical meristem. The meristem is shielded from the environment by older leaves, and leaf initiation is considered to be an autonomous process that does not depend on environmental cues. Here we show that light acts as a morphogenic signal that controls leaf initiation and stabilizes leaf positioning. Leaf initiation in tomato shoot apices ceases in the dark but resumes in the light, an effect that is mediated through the plant hormone cytokinin. Dark treatment also affects the subcellular localization of the auxin transporter PIN1 and the concomitant formation of auxin maxima. We propose that cytokinin is required for meristem propagation, and that auxin redirects cytokinin-inducible meristem growth toward organ formation. In contrast to common wisdom over the last 150 years, the light environment controls the initiation of lateral organs by regulating two key hormones: auxin and cytokinin.

Zeng, J., et al. (2017). "Redox regulation of plant stem cell fate." EMBO J **36**(19): 2844-2855.

Despite the importance of stem cells in plant and animal development, the common mechanisms of stem cell maintenance in both systems have remained elusive. Recently, the importance of hydrogen peroxide (H2O2) signaling in priming stem cell differentiation has been extensively studied in animals. Here, we show that different forms of reactive oxygen species (ROS) have antagonistic roles in plant stem cell regulation, which were established by distinct spatiotemporal patterns of ROS-metabolizing enzymes. The superoxide anion (O2.-) is markedly enriched in stem cells to activate WUSCHEL and maintain stemness, whereas H2O2 is more abundant in the differentiating peripheral zone to promote stem cell differentiation. Moreover, H2O2 negatively regulates O2.- biosynthesis in stem cells, and increasing H2O2 levels or scavenging O2.- leads to the termination of stem cells. Our results provide a mechanistic framework for ROS-mediated control of plant stem cell fate and demonstrate that the balance between O2.- and H2O2 is key to stem cell maintenance and differentiation.

Zermiani, M., et al. (2015). "Identification of the Arabidopsis RAM/MOR signalling network: adding new regulatory players in plant stem cell maintenance and cell polarization." Ann Bot **116**(1): 69-89.

BACKGROUND AND AIMS: The RAM/MOR signalling network of eukaryotes is a conserved regulatory module involved in co-ordination of stem cell maintenance, cell differentiation and polarity establishment. To date, no such signalling network has been identified in plants. METHODS: Genes encoding the bona fide core components of the RAM/MOR pathway were identified in Arabidopsis thaliana (arabidopsis) by sequence similarity searches conducted with the known components from other species. The transcriptional network(s) of the arabidopsis RAM/MOR signalling pathway were identified by running in-depth in silico analyses for genes co-regulated with the core components. In situ hybridization was used to confirm tissue-specific expression of selected RAM/MOR genes. KEY RESULTS: Co-expression data suggested that the arabidopsis RAM/MOR pathway may include genes involved in floral transition, by co-operating with chromatin remodelling and mRNA processing/post-transcriptional gene silencing factors, and genes involved in the regulation of pollen tube polar growth. The RAM/MOR pathway may act upstream of the ROP1 machinery, affecting pollen tube polar growth, based on the co-expression of its components with ROP-GEFs. In silico tissue-specific co-expression data and in situ hybridization experiments suggest that different components of the arabidopsis RAM/MOR are expressed in the shoot apical meristem and inflorescence meristem and may be involved in the fine-tuning of stem cell maintenance and cell differentiation. CONCLUSIONS: The arabidopsis RAM/MOR pathway may be part of the signalling cascade that converges in pollen tube polarized growth and in fine-tuning stem cell maintenance, differentiation and organ polarity.

Zhang, X. (2014). "Plant science. Delayed gratification--waiting to terminate stem cell identity." Science **343**(6170): 498-499.

Zhang, Y., et al. (2017). "Two-Step Functional Innovation of the Stem-Cell Factors WUS/WOX5 during Plant Evolution." Mol Biol Evol **34**(3): 640-653.

WUS and WOX5, which are expressed, respectively, in the organizing center (OC) and the quiescent center (QC), are essential for shoot/root apical stem-cell maintenance in flowering plants. However, little is known about how these stem-cell factors evolved their functions in flowering plants. Here, we show that the WUS/WOX5 proteins acquired two distinct capabilities by a two-step functional innovation process in the course of plant evolution. The first-step is the apical stem-cell maintenance activity of WUS/WOX5, which originated in the common ancestor of ferns and seed plants, as evidenced by the interspecies complementation experiments, showing that ectopic expression of fern Ceratopteris richardii WUS-like (CrWUL) surrounding OC/QC, or exclusive OC-/QC-expressed gymnosperms/angiosperms WUS/WOX5 in Arabidopsis wus-1 and wox5-1 mutants, could rescue their phenotypes. The second-step is the intercellular mobility that emerged in the common ancestor of seed plants after divergence from the ferns. Evidence for this includes confocal imaging of GFP fusion proteins, showing that WUS/WOX5 from seed plants, rather than from the fern CrWUL, can migrate into cells adjacent to the OC/QC. Evolutionary analysis showed that the WUS-like gene was duplicated into two copies prior to the divergence of gymnosperms/angiosperms. Then the two gene copies (WUS and WOX5) have undergone similar levels of purifying selection, which is consistent with their conserved functions in angiosperm shoot/root stem-cell maintenance and floral organ formation. Our results highlight the critical roles and the essential prerequisites that the two-step functional innovation of these genes performs and represents in the origin of flowering plants.

Zheng, Y. and X. Liu (2019). "Review: Chromatin organization in plant and animal stem cell maintenance." Plant Sci **281**: 173-179.

Stem cells have self-renewal capacity and can differentiate into specialized cell types. Although the origin, form and differentiated destinations of stem cells differ between animals and plants, they are regulated by similar epigenetic mechanisms during differentiation. There is increasing evidence that the three-dimensional (3D) genome organization plays important roles in gene expression regulation during stem cell differentiation. In plant cells, however, studies related to chromatin interaction in gene expression regulation are just beginning and will be a hot topic in the future. In this review, we summarized the similarities of plant and animal stem cell niches and their function in stem cell maintenance, the roles of chromatin conformation changes in regulating gene expression and recent findings about chromatin organization in plant cells at genome-wide and loci-specific levels.

Zhou, Y., et al. (2015). "Control of plant stem cell function by conserved interacting transcriptional regulators." Nature **517**(7534): 377-380.

Plant stem cells in the shoot apical meristem (SAM) and root apical meristem are necessary for postembryonic development of aboveground tissues and roots, respectively, while secondary vascular stem cells sustain vascular development. WUSCHEL (WUS), a homeodomain transcription factor expressed in the rib meristem of the Arabidopsis SAM, is a key regulatory factor controlling SAM stem cell populations, and is thought to establish the shoot stem cell niche through a feedback circuit involving the CLAVATA3 (CLV3) peptide signalling pathway. WUSCHEL-RELATED HOMEOBOX 5 (WOX5), which is specifically expressed in the root quiescent centre, defines quiescent centre identity and functions interchangeably with WUS in the control of shoot and root stem cell niches. WOX4, expressed in Arabidopsis procambial cells, defines the vascular stem cell niche. WUS/WOX family proteins are evolutionarily and functionally conserved throughout the plant kingdom and emerge as key actors in the specification and maintenance of stem cells within all meristems. However, the nature of the genetic regime in stem cell niches that centre on WOX gene function has been elusive, and molecular links underlying conserved WUS/WOX function in stem cell niches remain unknown. Here we demonstrate that the Arabidopsis HAIRY MERISTEM (HAM) family of transcription regulators act as conserved interacting cofactors with WUS/WOX proteins. HAM and WUS share common targets in vivo and their physical interaction is important in driving downstream transcriptional programs and in promoting shoot stem cell proliferation. Differences in the overlapping expression patterns of WOX and HAM family members underlie the formation of diverse stem cell niche locations, and the HAM family is essential for all of these stem cell niches. These findings establish a new framework for the control of stem cell production during plant development.

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