Outside-in control –Does plant cell wall integrity regulate cell cycle progression?

Nora Gigli-Bisceglia and Thorsten Hamann*

Department of Biology, Høgskoleringen 5, Realfagbygget, Norwegian University of Science and Technology, 7491 Trondheim, Norway.

Correspondence
*Corresponding author,
e.mail: Thorsten.hamann@ntnu.no

During recent years it has become accepted that plant cell walls are not inert objects surrounding all plant cells but are instead highly dynamic, plastic structures. They are involved in a large number of cell biological processes and contribute actively to plant growth, development and interaction with environment. Therefore, it is not surprising that cellular processes can control plant cell wall integrity while, simultaneously, cell wall integrity can influence cellular processes. In yeast and animal cells such a bi-directional relationship also exists between the yeast/animal extra-cellular matrices and the cell cycle. In yeast, the cell wall integrity maintenance mechanism and a dedicated plasmamembrane integrity checkpoint are mediating this relationship. Recent research has yielded insights into the mechanism controlling plant cell wall metabolism during cytokinesis. However, knowledge regarding putative regulatory pathways controlling adaptive modifications in plant cell cycle activity in response to changes in the state of the plant cell wall are not yet identified. In this review, we summarize similarities and differences in regulatory mechanisms coordinating extra cellular matrices and cell cycle activity in animal and yeast cells, discuss the available evidence supporting the existence of such a mechanism in plants and suggest that the plant cell wall integrity maintenance mechanism might also control cell cycle activity in plant cells.

AHKs Arabidopsis Histidine Kinases
ATM ATAXIA TELANGIECTASIA-MUTATED
ATR ATAXIA TELANGIECTASIA-MUTATED AND RAD3-RELATED
BAK1 BRI1-ASSOCIATED RECEPTOR KINASE
BRI1 BRASSIONSTEROID INSENSITIVE 1
CBI Cellulose Biosynthesis Inhibitor
CCS52A2 CELL CYCLE SWITCH PROTEIN 52 A2
CCH1 CALCIUM CHANNEL 1
CDK CYCLIN DEPENDENT KINASE
CDC CELL DIVISION CYCLE
CESA CELLULOSE SYNTHASE A
Cr *Catharanthus roseus*
CSLD5 CELLULOSE SYNTHASE LIKE D 5
CSL1 CALLOSE SYNTHASE 1
CWD cell wall damage
CWI cell wall integrity
CYCD3 CYCLIN D 3
DEK1 DEFECTIVE KERNEL 1
ECM Extracellular matrix
EFR EF-TU RECEPTOR
ERF115 ETHYLENE RESPONSE FACTOR 115
FER FERONIA
GSL8 GLUCAN SYNTHASE 8
HOG1 HIGH OSMOLARITY GLYCEROL 1
MCA1 MID1-COMPLEMENTING ACTIVITY 1
MID1 MATING PHEROMONE INDUCED DEATH 1
M-phase Mitosis
MscS Mechanosensitive channel of small conductance
MSL MscS-Like
OSCA1 REDUCED HYPEROSMOLALITY, INDUCED CA2+ INCREASE 1
PKC PROTEIN KINASE C
RB RETINOBLASTOMA
RBR1 RB-RELATED PROTEIN 1
RHO GEF RHO GUANINE NUCELOTIDE EXCHANGE FACTOR
RLK receptor like kinase
ROS reactive oxygen species
SBF SCB binding factor
SLN1 SYNTHETIC LETHAL OF N-END RULE 1
SPCH SPEECHLESS
S-phase Synthesis-phase
SWI Switch
THE1 THESEUS 1
WSC wall stress component

Introduction

The ability of organisms to grow is dependent on complex and finely regulated processes involving coordination between cell division and expansion. In multicellular organisms, generally composed of highly organized structures consisting of large numbers of highly specialized cells, daughter cells can differ from mother cells in terms of morphology, identity and functions. The process of differentiation can be dependent on the position of the cell in the tissue, be responsive to external/environmental stimuli and leads to tissue patterning (Masucci et al. 1996, Whyte et al. 2012). In plants, two primary meristems known as Root and Shoot Apical Meristems are ultimately responsible for production of all post-embryonic organs and cells (Shishkova et al. 2007, Gaillochet and Lohmann 2015). Despite the mechanisms controlling cell divisions in plant meristems having been subject of extensive studies in the last decades, their mode of action enabling them to control this central-hub of cell division is still not fully understood. An important aspect of the regulatory mechanisms is formed by the stimuli responsible for fine-tuning the process of cell division and adapting it to a changing environment. The stimuli can originate both from within the organism or can be generated during interactions with the environment. Control of cell division and differentiation by stimuli originating within the organism, is exemplified by mobile signals (such as transcription factors, proteins or phytohormones) released from neighbouring cells, which modify developmental fate and cell division rate of individual cells in the root meristem (Wu and Gallagher 2014, Drisch and Stahl 2015). The plant cell wall ie. the plant extracellular matrix (ECM) forms the interface between the plant and the environment, making the wall also an intrinsic component of most interactions with the environment and processes giving rise to stimuli regulating plant growth and development. The ability to modify growth and cell expansion in response to these stimuli is of particular importance for plants since their growth has to be highly adaptive to environmental change (Osakabe et al. 2013). Despite this importance, knowledge regarding the initial steps translating stimuli into signals regulating cell division and growth is still limited in plants.

In yeast and animals, signals regulating growth and division can also derive from the yeast cell wall or the ECM. Recently, research carried out in yeast has provided mechanistic insights into the processes adapting both cell wall metabolism and composition to cell cycle progression (inside-out control) as well as cell cycle progression to cell wall damage (CWD) impairing cell wall integrity (CWI) (outside-in) (Kono and Ikui 2017). In animals, similar knowledge exists with respect to interactions between ECM and cell cycle progression (Murthy et al. 2017), while in plants evidence regarding both inside-out and outside-in control is very limited.

In this review we summarize first (briefly) similarities and differences of the cell cycle regulatory machinery found in yeast, animals and plants. There will be a particular focus on evolutionary-conserved regulators to provide a foundation for the discussion of how ECM-derived signals can control cell cycle progression. Next, we summarize how cell walls are formed de novo during cell division in plant cells, to illustrate regulatory mechanisms controlling cell wall metabolism in response to cell cycle progression (inside-out). In the last part we examine the mechanisms controlling

cell cycle progression in response to CWD in yeast and ECM impairment in animal cells. There will be a particular focus on how CWD in yeast cells leads to inhibition of cell cycle progression via the CWI maintenance mechanism since its mode of action is fairly well understood and similarities seem to exist with the CWI maintenance mechanism in plants. The similarities between the CWI signalling pathways in yeasts and plants will be used as basis to hypothesize how cell cycle activity could be also controlled in plant cells in response to plant CWD (outside-in control) by the CWI maintenance mechanism.

The mechanism controlling cell cycle progression throughout kingdoms

The ability of organisms to grow, differentiate and reproduce, depends on successful repetition of the cell cycle. This consists normally of 4 stages including 2 gap phases (G1, G2), a synthesis phase (S) in which genetic material is reproduced and mitosis (M-phase) where genetic material is partitioned and the cell divides. The decision to initiate cell division occurs in the G1 phase and is influenced by the presence of different stimuli [including: nutrients, mating factors (in yeast cells), growth factors (in animal cells), hormones and stresses (in plants and animals)] (Harashima et al. 2013). Selected examples for these stimuli and when they influence cell cycle progression are highlighted in Figure 1A-C. An evolutionarily conserved core group of cell cycle regulators has been identified throughout the kingdoms (Table 1). Among those regulators, cyclins and their partners, the cyclin-dependent kinases (CDKs), together form the cyclin-dependent kinase complexes (CDKCs). They are responsible for phosphorylation of different substrates, which control G1/S and/or G2/M stage transitions (Cross et al. 2011). In yeast cells, only a single CDK (CDK1 or CELL DIVISION CYCLE 28, CDC28) was identified, which was activated by multiple cyclins whereas multiple CDKs have been isolated in animal cells. However, it was found that only CDK1 is essential to complete all cell cycle phases (Santamaría et al. 2007). Interestingly the yeast-derived CDK1 was also sufficient to drive cell cycle progression in animal cells indicating the level of functional conservation between yeast and animal cells (Bloom and Cross 2007, Nowack et al. 2012). In *Arabidopsis thaliana*, 80 genes have been identified, which form both conserved and plant-specific core cell cycle regulators (Menges et al. 2005). Amongst these genes, two CDK classes (containing 12 genes) designated as A- and B-type, have been shown to regulate G1/S or G2/M transitions (Gutierrez 2009).

Analysis of the molecular mechanisms regulating the transitions between cell cycle phases shows that in the different kingdoms homologous/analogous proteins drive the cell into the next stage of the cell cycle. Here, we will focus on the transition between G1/S phase. In budding yeast the progression from G1 to S phase is mediated by a complex consisting of CDK1 (CDC28) and CYCLIN3, which phosphorylates the inhibitor WHISKEY5 (Cooper 2006). This in turn enables the SCB binding factor (SBF) complex (consisting of the transcription factors SWITCH4/SWITCH6) to activate expression of genes required for G1/S phase transition (Cooper et al 2006). In animal cells CDK4, highly similar to CDC28, phosphorylates, together with CYCLIN D1, the RETINOBLASTOMA (RB) protein, which releases E2F transcription factors from RB-mediated inhibition. Activation of E2F, induces expression of the cell cycle genes, allowing the G1/S-transition (Lim and Kaldis 2013). The Arabidopsis

CDK1 homolog CDKA1 complements a yeast *cdc2*/*cdc28* loss-of-function strain suggesting that protein activities are conserved (Nowack et al. 2012). In Arabidopsis CDKA1 is required together with D-type cyclins for phosphorylation of the plant RB-RELATED PROTEIN (RBR1). Activity of certain D-type cyclins is also regulated by phytohormones, exemplified by the regulation of CYCLIND3 through cytokinins, which indicates another level of control (Schaller et al. 2014). Phosphorylation leads then to the release of a complex consisting of E2F/DP proteins, allowing transition and expression of S-phase specific genes (Vandepoele et al. 2002).

When cells are committed to enter S phase, they elongate and DNA replication occurs. After the S phase cells enter the G2 phase, where a DNA replication and damage control checkpoint has been described (Maréchal and Zou 2013). In animals, if DNA damage is detected, the ATAXIA TELANGIECTASIA-MUTATED (ATM) and ATAXIA TELANGIECTASIA-MUTATED AND RAD3-RELATED (ATR) -dependent signalling cascades are activated to initiate DNA repairs and arrest cell cycle progression (Maréchal and Zou 2013). In Arabidopsis and yeast, orthologs for both ATM and ATR kinases have been also identified (Carballo et al. 2013), highlighting that sensing and repairing possible DNA damages DNA are also necessary requirements in these organisms.

In all the organisms considered here, once DNA integrity is confirmed cells are able to enter G2 phase. In addition to inherent cell cycle checkpoints, such as the DNA damage and the spindle checkpoint present in all eukaryotic cells (Fig. 1) (Barnum and O'Connell 2014), studies have shown that the extracellular environment can also influence cell cycle progression. Animal cells can sense changes in osmolarity and initiate the p38MAPK pathway (Fig. 1A) (Brocker et al. 2012). In budding yeast the HIGH OSMOLARITY GLYCEROL1 (HOG1) pathway is activated by hyperosmotic stress, which in turn triggers downstream responses including arrest of cell cycle progression either at the G1/S or G2/M transition (Fig. 1B) (Clotet et al. 2006). Similarly in Arabidopsis, perception of mild hyper-osmotic stress activates an ethylene-mediated signalling pathway, which controls CDKA1 activity and stops cell cycle progression at the G2/M transition (Fig. 1C) (Skirycz et al. 2011). Finally, if all checkpoints have been successfully passed and G2 phase has been concluded, cells enter M phase, which terminates with cytokinesis.

Plant cytokinesis: how the plant cell cycle controls cell wall synthesis.

Due to the presence of a rigid carbohydrate-based cell wall, cytokinesis in plants differs markedly from other organisms. Moreover, yeast and animal cells are characterized by the presence of a contractile actomyosin filamentous ring (not present in plant cells) that actively contributes to formation of daughter cells. In plants, cell wall deposition and metabolism are important processes during the final steps of cell division (Mendes Pinto et al. 2013). Plant cytokinesis requires inside-out processes, ie. the cell cycle controls vesicle trafficking and cell wall metabolism tightly to allow de novo formation of a cell wall, which grows towards the already existing cell walls (Müller and Jürgens 2016). The transition from cell plate to newly formed cell wall, with a particular focus on cellulose production and deposition, has been described thoroughly by Chen et al. (2018) in this special issue and will

therefore not covered here again.

In plants, cytokinesis has been divided into four distinct stages namely fusion of Golgi-derived vesicles, formation of tubulo-vesicular network, tubular network and planar fenestrated sheet (Müller and Jürgens 2016). Cytokinesis begins with formation of the pre-prophase band, which is composed of a dense ring of microtubules and actin filaments (Yoshinobu Mineyuki 1999). It marks the future cortical division zone and coordinates the fusion of the newly formed membrane, separating the daughter cell with the already existing ones. The regulatory processes responsible for targeting of Golgi-derived vesicles to the cell plate and the mechanism required for their fusion have been reviewed in depth recently and will therefore not be discussed here (Müller and Jürgens 2016). The vesicles deliver biosynthetic enzymes as well as cell wall precursors required to form the newly synthetized cell walls while their fusion in the cell plate gives rise to the plasma membrane, which will separate the two future daughter cells.

Newly synthetized cell walls, similarly to the primary cell walls, are mainly built of pectins, xyloglucans, cellulose, glycoproteins and callose (Drakakaki 2015). Callose, consisting of β (1→3) linked glucose units, has been detected at two different places during cytokinesis. During the tubulo-vesicular network stage, callose is formed on the outside of the separating membranes (not in the middle close to the future middle-lamella). Later on, callose has been also detected at the site where the newly forming cell wall is connected to the existing cell walls (Samuels et al. 1995). However, callose is being removed soon after cytokinesis has terminated, possibly because the load-bearing cellulose network is in place and provides the necessary structural support. Callose synthases require high Ca^{2+} concentrations to produce callose (Him et al. 2001). This requirement is used in parallel to control activity of callose synthases by tightly regulating local Ca^{2+} distribution. In Arabidopsis, the callose synthase family has 12 members with CALLOSE SYNTHASE1 (CSL1)/ GLUCANSYNTHASE-LIKE6 (GSL6) and GSL8 being implicated in formation of the new cell wall based on localization studies (GSL6) and mutant phenotypes (GSL8) (Thiele et al. 2008, 2009).

Cellulose, consisting of β (1→4) linked glucose units, also forms a component of the developing cell wall, with cellulose synthases (CESAs) (located at the nascent plasma membrane) depositing cellulose already detectable during the tubulo-vesicular membrane network stage (Miart et al. 2014, Chen et al. 2018). It is interesting to note that the CESAs remain preferentially localized in the proximity of the expanding cell plate, where the cellulose microfibrils they produce could form a framework allowing deposition of other cell wall components (Miart et al. 2014). Mutations in cellulose synthases and inhibitor treatments result in abortion and/or arrest of cell division highlighting the importance of cellulose production in this process and cell morphogenesis in general (Somerville 2006). This close relationship between cellulose production and cell cycle progression is further supported by the results of recent screen for inhibitors of cytokinesis, which led actually to the isolation of C17, a novel cellulose biosynthesis inhibitor (CBI) (Hu et al. 2016). While the mechanism responsible for regulation of cell wall deposition during cell division remains to be elucidated, hormones (such as brassinosteroids) together with transcriptional regulation have been implicated in controlling cellulose production during

primary cell wall formation (Sánchez-Rodríguez et al. 2017, Verbančič et al. 2017).

Pectic polysaccharides including homogalacturonan, rhamnogalacturonan I and rhamnogalacturonan II are produced in a methyl-esterified form in the Golgi (Chebli and Geitmann 2017). In the apoplast they are de-esterified to allow crosslinking and formation of a matrix in which existing structures (such as cellulose microfibrils) can be embedded. Studies using the JIM7 antibody (recognizing partially methyl-esterified homogalacturonan) have detected methyl-esterified homogalacturonan in the cell plate, suggesting that pectic polysaccharides are also part of the newly forming cell wall (Clausen et al. 2003). While the presence of pectins at the cell plate and their involvement in formation of the new cell wall has been demonstrated, the mechanism controlling their deposition remains to be elucidated.

Hemicelluloses (xyloglucans, glucomannans, xylans, and mixed-linkage glucans) form another group of cell wall polysaccharides found at the cell plate (Moore and Staehelin 1988). During cell division, hemicelluloses are also produced in the Golgi and their delivery to the cell plate is mediated by the phragmoplast (Chevalier et al. 2010). Together with pectins they form part of the matrix in which cellulose microfibrils are embedded in the forming cell walls. CELLULOSE SYNTHASE LIKE D5 (CSLD5) has been implicated previously in production of xylan, homogalacturonan or mannan polysaccharides with the specific activity remaining to be determined (Bernal et al. 2007, Verhertbruggen et al. 2011, Yin et al. 2011). Recent evidence has shown that the cell wall components produced by CSLD5 are required during cytokinesis (Gu et al. 2016). CSLD5 accumulates preferentially in dividing plant cells and participates in construction of newly forming cell walls. *CSLD5* expression is directly regulated by the transcription factor SPEECHLESS (SPCH), while CSLD5 turnover seems to be mediated by the proteasome. Interestingly it was also shown that degradation of CSLD5 might be controlled by a component of the anaphase-promoting complex, the CELL CYCLE SWITCH PROTEIN 52 A2 (CCS52A2) (Gu et al. 2016). This is of particular importance since the activity of CCS52A2 in turn is regulated by ETHYLENE RESPONSE FACTOR115 (ERF115), a transcription factor required for the Brassinosteroid-mediated regulation of the root stem cell niche division activity (Heyman et al. 2013). In maize, lack of CSLD1 also disrupts cytokinesis and organ development, suggesting CSLD-mediated processes are required in land plants during cytokinesis (Hunter et al. 2012). This overview illustrates how cell wall metabolism can be regulated by the cell cycle machinery, which in turn is controlled by BR, a phytohormone responsible for coordination of cell division with other growth processes and stress responses.

Regulation of cell cycle progression by the extracellular matrix in yeast and animal cells

ECMs with different structures and compositions surround yeast, plant and animal cells. Despite the differences between them, the main function of the ECMs is to provide protection against physical stress. In yeasts and plants, the cell walls (plant ECMs) also allow generation of high levels of turgor pressure on the inside, which is a prerequisite for cell expansion (Hamant and Haswell 2017). Yeast and plant cell walls are composed mainly of polysaccharides with yeast cell walls consisting mainly of

glucan and chitin while plant cell walls exhibit more chemical diversity (supposedly reflecting the more diverse biological functions the walls have to perform) (Höfte and Voxeur 2017). All three ECMs contain proteins, which can have structural and signalling or regulatory functions.

In animal cells, proteins like integrins and PIEZO channels are residing in the plasmamembrane and can perceive mechanical stimuli originating in the ECM and translate these into chemical signals, regulating intracellular processes (including the cell cycle) (Eyckmans et al. 2011; Murthy et al. 2017) (Table 1). Integrins, acting as mechano-sensors, regulate the transition from G1- to S-phase by controlling activation of CYCLIN D1 through the extra-cellular signal regulated kinases pathway (Moreno-Layseca and Streuli 2014). Simultaneously, growth factors also influence the activity of CYCLIN D1 suggesting that CYCLIN D1 integrates physical (mechanical) signals from the ECM with temporal control provided by the release of growth factors. Interestingly, it has also been shown that changes in ECM stiffness and the degree of elasticity, which primarily depend on changes in collagen and elastin concentration, lead to uncontrolled cell proliferation and cancer (Fig. 1A) (Dimitrijevic-Bussod et al. 1999, Cox and Erler 2011). These examples suggest that changes in the mechanical characteristics of the ECMs surrounding animal cells can be sensed and act as regulator for cell cycle progression.

Cell cycle progression in yeast is controlled by several regulatory mechanisms, amongst them processes monitoring CWI and a dedicated plasmamembrane/cell wall integrity checkpoint (Levin 2011, Kono et al. 2016). In *Saccharomyces cerevisiae* three different signalling cascades have been implicated in monitoring the functional integrity of the cell wall and initiating compensatory responses in response to CWI impairment. The compensatory responses include reorganization of the cytoskeleton as well as changes in cell wall metabolism and slow down of cell cycle progression. The first signalling cascade involves plasmamembrane-localized proteins (named WSCs) with cytoplasmic interaction and highly glycosylated extracellular domains acting as nanosprings, which in response to distortion of the cell wall and alternatively displacement of cell wall versus plasmamembrane undergo conformational change (Heinisch et al. 2010). This conformational change leads to activation of a MAP kinase cascade via RHO GUANINE NUCELOTIDE EXCHANGE FACTOR (RHO GEF) and PROTEIN KINASE C (PKC) targeting the SBF complex (Levin 2011). While, as described before, the SBF complex was originally implicated in control of G1/S transition it seems also responsible for regulating expression of cell wall metabolism genes upon CWI impairment (Levin 2011). In addition to the CWI sensors, both a stretch-activated calcium channel complex consisting of MID1 and CCH1 and components of the HOG1 turgor monitoring mechanism can activate the CWI maintenance responses and regulate cell cycle progression through a Ca^{2+} mediated signalling cascade (Fig. 1A) (Levin 2011, Kono and Ikui 2017). More recently it was also shown that a dedicated cell cycle checkpoint exists at the G1/S transition, which in response to plasmamembrane and/or CWD inhibits cell cycle progression until the damage has been repaired (Fig. 1A) (Kono et al. 2016).

Regulation of plant cell cycle activity in response to the state of the cell wall

While our knowledge regarding changes in plant cell cycle activity in response to plant cell wall status is very limited, evidence has accumulated that plants also have a dedicated CWI maintenance mechanism where both osmo- and mechano-perception contribute to detection of and response to CWD. Moreover, despite the CWI pathway having been primarily studied in Arabidopsis, homologs of Arabidopsis genes implicated in mechano- and osmo-perception as well as CWI maintenance have been identified in other plant species suggesting that the mechanism is conserved across the plant kingdom (Galindo-Trigo et al. 2016, Honkanen et al. 2016, Hamant and Haswell 2017, Rosa et al. 2017).

In Arabidopsis, manipulation of the most abundant cell wall polysaccharide (cellulose) through cellulose biosynthesis inhibitors or mutations in the CESA genes, activates a complex set of CWD responses, which are apparently involved in CWI maintenance in plants (Tateno et al. 2015; Hamann 2015). These responses include epidermal cell bulging, reactive oxygen species (ROS) accumulation, increased jasmonic and salicylic acid production, changes in cell wall composition (including deposition of lignin) and growth inhibition (Ellis et al. 2002, Cano-Delgado et al. 2003, Manfield et al. 2004, Tsang et al. 2011, Denness et al. 2011). A recent study involving the cellulose biosynthesis inhibitor isoxaben has described slowdown of cell cycle progression in Arabidopsis seedling roots based on growth studies and reductions in *CYCD3;1* and *CYCB1,1* transcript levels (Gigli-Bisceglia et al. 2018). Interestingly many CBI-induced CWD responses in plants (incl. cell cycle inhibition) are osmo-sensitive and can be suppressed by co-treatments with osmotica at low hyper-osmotic concentrations similar to previous observations in yeast (Hamann et al. 2009, Levin 2011, Gigli-Bisceglia et al. 2018). These data suggest that CWD alone is not the sole indicator of CWI impairment in plant cells and that displacement of cell wall versus plasmamembrane, plasmamembrane stretch and/or changes in the surface tension of the wall, could act as individual or combined stimuli leading to activation of highly specific CWI maintenance responses. This would also be very similar to the situation in yeast cells where a combination of dedicated cell wall- (like the plasmamembrane-localized sensor WSC1), turgor- (like the osmosensor SLN1) and mechano-sensors (MID1, CCH1) provides a high-resolution network controlling simultaneously a large number of downstream responses including cell wall metabolism and cell cycle progression (Levin 2011, Kock et al. 2015).

A large number of proteins have been implicated in CWI maintenance in plants during recent years with receptor like kinases (RLKs) having received particular attention. The *Catharanthus roseus* RLKs (*Cr*RLK)-like family, which has 17 members in Arabidopsis is named particularly often (Franck et al. 2018). These proteins have extracellular domains with pronounced homologies to animal malectin protein motifs (capable of binding small sugar molecules), suggesting that they might be able to bind cell wall components or wall-derived ligands (Schallus et al. 2008). THESEUS1 (THE1), probably one of the most prominent family member, was identified through its ability to suppress the short hypocotyl and ectopic lignification phenotype in a *cesa6 (procuste)* loss-of-function allele (Hematy et al. 2007). Studies involving *THE1* loss-of-function alleles and cellulose biosynthesis inhibitors showed that THE1 is required for several isoxaben-induced CWD responses, implying an important role for THE1 in plant CWI maintenance (Hematy et al. 2007, Denness et al. 2011). However, in the context of CWI controlling

cell cycle progression THE1-dependent processes seem not essential since in *THE1* loss-of-function alleles, cell cycle inhibition upon treatment with isoxaben is still detectable (Gigli-Bisceglia et al. 2018). Like THE1, FERONIA (FER), also belongs to the CrRLK1-family, and seems to be required for Ca^{2+} signalling during mechano-perception and capable of binding to pectin (Shih et al. 2014, Feng et al. 2018). Recently FER was also shown to interact with and stabilize a complex consisting of the flagellin receptor FLAGELLIN-SENSITIVE 2, EF-TU RECEPTOR (EFR) and its co-receptor BRI1-ASSOCIATED RECEPTOR KINASE (BAK1), suggesting it could integrate mechano-sensing with pattern-triggered immunity signalling by acting as a scaffold for different components involved in both processes (Stegmann et al. 2017). This could form an example for how plants integrate mechano- with immune signalling leading to the previously described reduction in growth upon immune system activation.

Both ion channels and Arabidopsis histidine kinases (AHKs) have been implicated in osmotic stress and mechano-perception in plants (Hamant and Haswell 2017). Amongst the ion channels the putatively stretch-activated, plasma membrane localized, mechano-sensitive Ca^{2+}-channel MID1-COMPLEMENTING ACTIVITY1 (MCA1) was shown to be required for activation of CWD responses (Denness et al. 2011). Intriguingly, MCA1 was originally isolated through its ability to complement a yeast strain deficient for the MID1 CCH1 complex, which is contributing to yeast CWI maintenance through a Ca^{2+}-based signalling cascade (Nakagawa et al. 2007). However, in *MCA1* loss-of-function seedlings, isoxaben treatment still leads to inhibition of cell cycle progression and reductions in *CYCB1;1* and *CYCD3;1* transcript levels suggesting that MCA1 is not essentially required in this process (Gigli-Bisceglia et al. 2018). Similarly the Arabidopsis DEFECTIVE KERNEL1 (DEK1) protein could also play a role in CWI maintenance, since it functions as a plasmamembrane localized, mechano-sensitive Ca^{2+}-channel, where loss-of-function leads to embryo lethality, highlighting the importance of mechano-perception during growth and development (Galletti et al. 2015, Tran et al. 2017). Two members of the MscS-like (MSL) family of ion-channels, located in the chloroplasts, were shown to be required for (mechano- and) hypo-osmotic stress perception making them also candidates for detection of CWI impairment (Haswell et al. 2008). Tests with MSL2/3 loss of function seedlings showed that isoxaben treatment still leads to reductions in certain cell cycle transcript levels, implying that these MSLs are not essentially required (Gigli-Bisceglia et al. 2018). Hyper-osmotic stress perception seems to involve both ion-channels, exemplified by OSCA1 and AHKs (Reiser et al. 2003, Yuan et al. 2014). AHKs have been originally implicated in hyper-osmotic stress perception because AHK1 to AHK4 could complement a yeast strain deficient in SLN1, a critical component of the HOG1-mechanism responsible for hyper-osmotic stress perception and control of cell cycle progression (Reiser et al. 2003, Tran et al. 2007, Levin 2011). AHKs are also required for perception of cytokinin, a phytohormone controlling cell cycle activity in plants for example through *CYCD3;1* (Higuchi et al. 2004, Stolz et al. 2011, Scofield et al. 2013, Zürcher and Müller 2016). More recently it was shown that cytokinin signalling mediates drought stress responses and manipulation of cytokinin signalling causes enhanced drought stress tolerance (Li et al. 2016, Nguyen et al. 2016). It is intriguing to note that

isoxaben treatment leads to both osmo-sensitive reductions in the levels of certain cytokinins and expression of *CYCD3;1* (Gigli-Bisceglia et al. 2018). Co-treatments with zeatin suppress the isoxaben effects on *CYCD3;1* expression in a concentration-dependent manner while gene expression profiling experiments suggest that isoxaben induces expression of cytokinin degrading enzymes. These results imply that CWD caused by cellulose biosynthesis inhibition induces changes in cell cycle activity through a cytokinin-mediated mechanism. This could form an "outside-in" mechanism controlling changes in cell cycle activity upon CWI impairment and could complement the previously described "inside-out" mechanism active during cytokinesis.

Conclusions and perspectives

Although plant, yeast and animal cells are structurally diverse, the molecular mechanisms regulating the cell cycle are surprisingly conserved. We used here examples from the animal and yeast field to illustrate the extent of the conservation and how cell cycle progression is altered through dedicated mechanisms in response to signals originating in the ECMs surrounding animal cells or the yeast cell wall. In yeast, these signals are generated by three mechanisms sensing either secondary effects of CWD like changes in surface tension, plasmamembrane stretch and/or osmotic stress, with all three mechanisms contributing to CWI maintenance by activating downstream responses including changes in cell cycle progression. In addition to these mechanisms a dedicated plasmamembrane and CWD checkpoint exists in yeast, which influences G1/S-transition, highlighting the importance of coordinating the state of the plasmamembrane/cell wall with cell cycle progression.

In contrast, our knowledge regarding mechanisms coordinating processes at the plant cell wall with cell cycle activity is very limited. Some of the information available comes from the study of cytokinesis where tight control of cell wall metabolism is essential to ensure correct de novo formation of the cell wall separating the daughter cells. BR-mediated processes could contribute to this inside-out control where cell cycle processes are controlling cell wall metabolism. An analysis of seedlings exposed to CWD generated through cellulose biosynthesis revealed osmo-sensitive effects on root growth and transcript levels of *CYCD3;1*. A genetic analysis suggested that THESEUS1- and MCA1-mediated CWI maintenance processes are not required for these effects. However, follow up studies detected isoxaben-induced, osmo-sensitive changes in the levels of certain cytokinins and suggested isoxaben-induced cytokinin degradation could be responsible for "outside-in" regulation of cell cycle activity. These results provide the knowledge for a targeted analysis of the regulatory mechanisms while the availability of highly specific tools to impair CWI as well as plasmamembrane integrity in combination with tools to study cell cycle activity will enable us in the near future to dissect the mechanism(s) responsible for regulation of cell cycle activity in response to CWI impairment.

Acknowledgments – The authors would like to thank Lauri Vaahtera, Timo Engelsdorf and Camilla Øvstebø for critical reading of and comments on the manuscript. Financial and/or technical support from the EEA grant 7F14155 CYTOWALL (N.G.B./T.H.) and Ministry of Education, Youth and Sports of

the Czech Republic (National Program for Sustainability I, grant no. LO1204) is gratefully acknowledged.

References

Alcaino C, Farrugia G, Beyder A (2017) Mechanosensitive Piezo Channels in the Gastrointestinal Tract. Curr Top Membr 79: 219–244

Andrews BJ, Moore LA (1992) Interaction of the yeast Swi4 and Swi6 cell cycle regulatory proteins in vitro. Proc Natl Acad Sci USA 89: 11852–6

Barnum KJ, O'Connell MJ (2014) Cell cycle regulation by checkpoints. Methods Mol Biol 1170: 29–40

Bernal AJ, Jensen JK, Harholt J, et al (2007) Disruption of *ATCSLD5* results in reduced growth, reduced xylan and homogalacturonan synthase activity and altered xylan occurrence in Arabidopsis. Plant J 52: 791–802

Bloom J, Cross FR (2007) Multiple levels of cyclin specificity in cell-cycle control. Nat Rev Mol Cell Biol 8: 149–160

Brocker C, Thompson DC, Vasiliou V (2012) The role of hyperosmotic stress in inflammation and disease. Biomol Concepts 3: 345–364

Cano-Delgado A, Penfield S, Smith C, et al (2003) Reduced cellulose synthesis invokes lignification and defense responses in Arabidopsis thaliana. Plant J 34: 351–362

Carballo JA, Panizza S, Serrentino ME, et al (2013) Budding Yeast ATM/ATR Control Meiotic Double-Strand Break (DSB) Levels by Down-Regulating Rec114, an Essential Component of the DSB-machinery. PLoS Genet 9: e1003545

Chebli Y, Geitmann A (2017) Cellular growth in plants requires regulation of cell wall biochemistry. Curr Opin Cell Biol 44: 28–35

Chen H-W, Persson S, Grebe M, McFarlane HE (2018) Cellulose synthesis during cell plate assembly. Physiol Plant. doi: 10.1111/ppl.12703

Chevalier L, Bernard S, Ramdani Y, et al (2010) Subcompartment localization of the side chain xyloglucan-synthesizing enzymes within Golgi stacks of tobacco suspension-cultured cells. Plant J 64: 977–89

Clausen MH, Willats WGT, Knox JP (2003) Synthetic methyl hexagalacturonate hapten inhibitors of anti-homogalacturonan monoclonal antibodies LM7, JIM5 and JIM7. Carbohydr Res 338: 1797–800

Clotet J, Escoté X, Adrover MA, et al (2006) Phosphorylation of Hsl1 by Hog1 leads to a G2 arrest essential for cell survival at high osmolarity. EMBO J 25: 2338–46

Cooper K (2006) Rb, whi it's not just for metazoans anymore. Oncogene 25:5228–5232.

Cox TR, Erler JT (2011) Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. Dis Model Mech 4: 165–78

Cross FR, Buchler NE, Skotheim JM (2011) Evolution of networks and sequences in eukaryotic cell

cycle control. Philos Trans R Soc Lond B Biol Sci 366: 3532–44

Culligan KM, Robertson CE, Foreman J, et al (2006) ATR and ATM play both distinct and additive roles in response to ionizing radiation. Plant J 48: 947–61

Denness L, McKenna JF, Segonzac C, et al (2011) Cell wall damage-induced lignin biosynthesis is regulated by a reactive oxygen species- and jasmonic acid-dependent process in Arabidopsis. Plant Physiol 156: 1364–74

Dimitrijevic-Bussod M, Balzaretti-Maggi VS, Gadbois DM (1999) Extracellular Matrix and Radiation G1 Cell Cycle Arrest in Human Fibroblasts. Cancer Res 59: 4843–4847

Drakakaki G (2015) Polysaccharide deposition during cytokinesis: Challenges and future perspectives. Plant Sci 236: 177–184

Drisch RC, Stahl Y (2015) Function and regulation of transcription factors involved in root apical meristem and stem cell maintenance. Front Plant Sci 6: 505

Du Z, Tong X, Ye X (2013) Cyclin D1 promotes cell cycle progression through enhancing NDR1/2 kinase activity independent of cyclin-dependent kinase 4. J Biol Chem 288: 26678–87

Duch A, de Nadal E, Posas F (2012) The p38 and Hog1 SAPKs control cell cycle progression in response to environmental stresses. FEBS Lett 586: 2925–31

Ellis C, Karafyllidis I, Wasternack C, Turner JG (2002) The Arabidopsis Mutant cev1 Links Cell Wall Signaling to Jasmonate and Ethylene Responses. Plant Cell 14: 1557–1566

Eyckmans J, Boudou T, Yu X, Chen CS (2011) A Hitchhiker's Guide to Mechanobiology. Dev Cell 21: 35–47

Feng W, Kita D, Peaucelle A, et al (2018) The FERONIA Receptor Kinase Maintains Cell-Wall Integrity during Salt Stress through Ca 2+ Signaling. Curr Biol 28: 666-675

Franck CM, Westermann J, Boisson-Dernier A (2018) Plant Malectin-Like Receptor Kinases: From Cell Wall Integrity to Immunity and Beyond. Annu Rev Plant Biol 69:annurev-arplant-042817-040557. doi: 10.1146/annurev-arplant-042817-040557

Gaillochet C, Lohmann JU (2015) The never-ending story: from pluripotency to plant developmental plasticity. Development 142: 2237–49

Galindo-Trigo S, Gray JE, Smith LM (2016) Conserved Roles of CrRLK1L Receptor-Like Kinases in Cell Expansion and Reproduction from Algae to Angiosperms. Front Plant Sci 7: 1269

Galletti R, Johnson KL, Scofield S, et al (2015) DEFECTIVE KERNEL 1 promotes and maintains plant epidermal differentiation. Development 142: 1978–1983

García R, Bravo E, Diez-Muñiz S, et al (2017) A novel connection between the Cell Wall Integrity and the PKA pathways regulates cell wall stress response in yeast. Sci Rep 7: 5703

Gigli-Bisceglia N, Engelsdorf T, Strnad M, et al (2018) Cellulose biosynthesis inhibition reduces cell cycle activity in a nitrate reductase- and cytokinin-dependent manner. bioRxiv. doi: https://doi.org/10.1101/286161

Gu F, Bringmann M, Combs J, et al (2016) The Arabidopsis CSLD5 functions in cell plate formation in a cell cycle dependent manner. Plant Cell 28: 1722-37

Gutierrez C (2009) The Arabidopsis cell division cycle. Arab B 7: e0120 . doi: 10.1199/tab.0120

Hamann T (2015) The plant cell wall integrity maintenance mechanism-concepts for organization and mode of action. Plant Cell Physiol 56: 215–23

Hamann T, Bennett M, Mansfield J, Somerville C (2009) Identification of cell-wall stress as a hexose-dependent and osmosensitive regulator of plant responses. Plant J 57: 1015–1026

Hamant O, Haswell ES (2017) Life behind the wall: sensing mechanical cues in plants. BMC Biol 15: 59

Harashima H, Dissmeyer N, Schnittger A (2013) Cell cycle control across the eukaryotic kingdom. Trends Cell Biol 23: 345–56

Haswell ES, Peyronnet R, Barbier-Brygoo H, et al (2008) Two MscS homologs provide mechanosensitive channel activities in the Arabidopsis root. Curr Biol 18: 730–4

Heinisch JJ, Dupres V, Alsteens D, Dufrene YF (2010) Measurement of the mechanical behavior of yeast membrane sensors using single-molecule atomic force microscopy. Nat Protoc 5: 670–677

Hematy K, Sado PE, Van Tuinen A, et al (2007) A receptor-like kinase mediates the response of Arabidopsis cells to the inhibition of cellulose synthesis. Curr Biol 17: 922–931

Heyman J, Cools T, Vandenbussche F, et al (2013) ERF115 Controls Root Quiescent Center Cell Division and Stem Cell Replenishment. Science 342: 860–863

Higuchi M, Pischke MS, Mahonen AP, et al (2004) In planta functions of the Arabidopsis cytokinin receptor family. Proc Natl Acad Sci U S A 101: 8821–8826

Him JL, Pelosi L, Chanzy H, et al (2001) Biosynthesis of (1, 3)-beta-D-glucan (callose) by detergent extracts of a microsomal fraction from Arabidopsis thaliana. Eur J Biochem 268: 4628–38

Höfte H, Voxeur A (2017) Plant cell walls. Curr Biol 27: R865–R870

Honkanen S, Jones VAS, Morieri G, et al (2016) The Mechanism Forming the Cell Surface of Tip-Growing Rooting Cells Is Conserved among Land Plants. Curr Biol 26: 3238–3244

Hu Z, Vanderhaeghen R, Cools T, et al (2016) Mitochondrial Defects Confer Tolerance against Cellulose Deficiency. Plant Cell 28: 2276-2290

Hunter CT, Kirienko DH, Sylvester AW, et al (2012) Cellulose Synthase-Like D1 is integral to normal cell division, expansion, and leaf development in maize. Plant Physiol 158: 708–24

Kock C, Dufr?ne YF, Heinisch JJ (2015) Up against the Wall: Is Yeast Cell Wall Integrity Ensured by Mechanosensing in Plasma Membrane Microdomains? Appl Environ Microbiol 81: 806–811

Kono K, Al-Zain A, Schroeder L, et al (2016) Plasma membrane/cell wall perturbation activates a novel cell cycle checkpoint during G1 in *Saccharomyces cerevisiae*. Proc Natl Acad Sci 113: 6910–6915

Kono K, Ikui AE (2017) A new cell cycle checkpoint that senses plasma membrane/cell wall damage in budding yeast. BioEssays 39: 1–7

Levin DE (2011) Regulation of cell wall biogenesis in Saccharomyces cerevisiae: the cell wall integrity signaling pathway. Genetics 189: 1145–75

Li W, Herrera-Estrella L, Tran LSP (2016) The Yin-Yang of Cytokinin Homeostasis and Drought

Acclimation/Adaptation. Trends Plant Sci 21: 548–550

Lim S, Kaldis P (2013) Cdks, cyclins and CKIs: roles beyond cell cycle regulation. Development 140: 3079–3093

Manfield IW, Orfila C, McCartney L, et al (2004) Novel cell wall architecture of isoxaben-habituated Arabidopsis suspension-cultured cells: global transcript profiling and cellular analysis. Plant J 40: 260–275

Maréchal A, Zou L (2013) DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol 5

Masucci JD, Rerie WG, Foreman DR, et al (1996) The homeobox gene GLABRA2 is required for position-dependent cell differentiation in the root epidermis of Arabidopsis thaliana. Development 122: 1253–60

Mendes Pinto I, Rubinstein B, Li R (2013) Force to divide: structural and mechanical requirements for actomyosin ring contraction. Biophys J 105: 547–54

Menges M, De Jager SM, Gruissem W, Murray JAH (2005) Global analysis of the core cell cycle regulators of Arabidopsis identifies novel genes, reveals multiple and highly specific profiles of expression and provides a coherent model for plant cell cycle control. Plant J 41: 546–566

Miart F, Desprez T, Biot E, et al (2014) Spatio-temporal analysis of cellulose synthesis during cell plate formation in Arabidopsis. Plant J 77: 71–84

Moore PJ, Staehelin LA (1988) Immunogold localization of the cell-wall-matrix polysaccharides rhamnogalacturonan I and xyloglucan during cell expansion and cytokinesis inTrifolium pratense L.; implication for secretory pathways. Planta 174: 433–45

Moreno-Layseca P, Streuli CH (2014) Signalling pathways linking integrins with cell cycle progression. Matrix Biol 34: 144–153

Müller S, Jürgens G (2016) Plant cytokinesis-No ring, No constriction but centrifugal construction of the partitioning membrane. Semin Cell Dev Biol 53: 10–18

Murthy SE, Dubin AE, Patapoutian A (2017) Piezos thrive under pressure: mechanically activated ion channels in health and disease. Nat Rev Mol Cell Biol. 18: 771-783

Nakagawa Y, Katagiri T, Shinozaki K, et al (2007) Arabidopsis plasma membrane protein crucial for Ca2+ influx and touch sensing in roots. Proc Natl Acad Sci U S A 104: 3639–3644

Nguyen KH, Ha C Van, Nishiyama R, et al (2016) *Arabidopsis* type B cytokinin response regulators ARR1, ARR10, and ARR12 negatively regulate plant responses to drought. Proc Natl Acad Sci 113: 3090-5

Nowack MK, Harashima H, Dissmeyer N, et al (2012) Genetic Framework of Cyclin-Dependent Kinase Function in Arabidopsis. Dev Cell 22: 1030–1040

Osakabe Y, Yamaguchi-Shinozaki K, Shinozaki K, Tran L-SP (2013) Sensing the environment: key roles of membrane-localized kinases in plant perception and response to abiotic stress. J Exp Bot 64: 445–58

Reiser V, Raitt DC, Saito H (2003) Yeast osmosensor Sln1 and plant cytokinin receptor Cre1 respond

to changes in turgor pressure. J Cell Biol 161: 1035–1040

Rosa M, Abraham-Juarez MJ, Lewis MW, et al (2017) The Maize MID-COMPLEMENTING ACTIVITY Homolog CELL NUMBER REGULATOR13/NARROW ODD DWARF Coordinates Organ Growth and Tissue Patterning. Plant Cell 29: 474-490

Samuels AL, Giddings Jr. TH, Staehelin LA (1995) Cytokinesis in tobacco BY-2 and root tip cells: a new model of cell plate formation in higher plants. J Cell Biol 130: 1345–1357

Sánchez-rodríguez C, Ketelaar K, Schneider R, et al (2017) BRASSINOSTEROID INSENSITIVE2 negatively regulates cellulose synthesis in Arabidopsis by phosphorylating cellulose synthase 1. Proc Natl Acad Sci 114: 3533-3538

Santamaría D, Barrière C, Cerqueira A, et al (2007) Cdk1 is sufficient to drive the mammalian cell cycle. Nature 448: 811–815

Schaller GE, Street IH, Kieber JJ (2014) Cytokinin and the cell cycle. Curr Opin Plant Biol 21: 7–15

Schallus T, Jaeckh C, Fehér K, et al (2008) Malectin : A Novel Carbohydrate-binding Protein of the Endoplasmic Reticulum and a Candidate Player in the Early Steps of Protein N -Glycosylation. 19: 3404–3414

Scofield S, Dewitte W, Nieuwland J, Murray JAH (2013) The Arabidopsis homeobox gene *SHOOT MERISTEMLESS* has cellular and meristem-organisational roles with differential requirements for cytokinin and CYCD3 activity. Plant J 75: 53–66

Shih HW, Miller N, Dai C, et al (2014) The Receptor-like Kinase FERONIA Is Required for Mechanical Signal Transduction in Arabidopsis Seedlings. Curr Biol 24: 1887–1892

Shishkova S, Rost TL, Dubrovsky JG (2007) Determinate Root Growth and Meristem Maintenance in Angiosperms. Ann Bot 101: 319–340

Skirycz A, Claeys H, De Bodt S, et al (2011) Pause-and-Stop: The Effects of Osmotic Stress on Cell Proliferation during Early Leaf Development in *Arabidopsis* and a Role for Ethylene Signaling in Cell Cycle Arrest. Plant Cell 23: 1876–1888

Somerville C (2006) Cellulose synthesis in higher plants. Annu Rev Cell Dev Biol 22:53–78.

Stegmann M, Monaghan J, Smakowska-Luzan E, et al (2017) The receptor kinase FER is a RALF-regulated scaffold controlling plant immune signaling. Science 355: 287–289

Stolz A, Riefler M, Lomin SN, et al (2011) The specificity of cytokinin signalling in Arabidopsis thaliana is mediated by differing ligand affinities and expression profiles of the receptors. Plant J 67: 157–168

Tateno M, Brabham C, DeBolt S (2015) Cellulose biosynthesis inhibitors - a multifunctional toolbox. J Exp Bot 67: 533–542

Tena G, Asai T, Chiu WL, Sheen J (2001) Plant mitogen-activated protein kinase signaling cascades. Curr Opin Plant Biol 4: 392–400

Thiele K, Wanner G, Kindzierski V, et al (2008) The timely deposition of callose is essential for cytokinesis in Arabidopsis. Plant J. 58: 13-26

Thiele K, Wanner G, Kindzierski V, et al (2009) The timely deposition of callose is essential for

cytokinesis in Arabidopsis. Plant J 58: 13–26

Tran D, Galletti R, Neumann ED, et al (2017) A mechanosensitive Ca2+ channel activity is dependent on the developmental regulator DEK1. Nat Commun 8: 1009

Tran LS, Urao T, Qin F, et al (2007) Functional analysis of AHK1/ATHK1 and cytokinin receptor histidine kinases in response to abscisic acid, drought, and salt stress in Arabidopsis. Proc Natl Acad Sci U S A 104: 20623–20628

Travesa A, Kalashnikova TI, de Bruin RAM, et al (2013) Repression of G1/S Transcription Is Mediated via Interaction of the GTB Motifs of Nrm1 and Whi5 with Swi6. Mol Cell Biol 33: 1476–1486

Tsang DL, Edmond C, Harrington JL, Nuhse TS (2011) Cell Wall Integrity Controls Root Elongation via a General 1-Aminocyclopropane-1-Carboxylic Acid-Dependent, Ethylene-Independent Pathway. Plant Physiol 156: 596–604

Vandepoele K, Raes J, De Veylder L, et al (2002) Genome-wide analysis of core cell cycle genes in Arabidopsis. Plant Cell 14: 903–16

Verbančič J, Lunn JE, Stitt M, Persson S (2017) Carbon supply and the regulation of cell wall synthesis. Mol Plant. 11: 75-94

Verhertbruggen Y, Yin L, Oikawa A, Scheller HV (2011) Mannan synthase activity in the CSLD family. Plant Signal Behav 6: 1620–1623

Whyte WA, Bilodeau S, Orlando DA, et al (2012) Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. Nature 482: 221–5

Wijnen H, Landman A, Futcher B (2002) The G(1) cyclin Cln3 promotes cell cycle entry via the transcription factor Swi6. Mol Cell Biol 22: 4402–18

Wu S, Gallagher KL (2014) The movement of the non-cell-autonomous transcription factor, SHORT-ROOT relies on the endomembrane system. Plant J 80: 396–409

Yang J, Xu Z-P, Huang Y, et al (2004) ATM and ATR: sensing DNA damage. World J Gastroenterol 10: 155-60

Yin L, Verhertbruggen Y, Oikawa A, et al (2011) The Cooperative Activities of CSLD2, CSLD3, and CSLD5 Are Required for Normal Arabidopsis Development. Mol Plant 4: 1024–1037

Yoshinobu Mineyuki (1999) The Preprophase Band of Microtubules: Its Function as a Cytokinetic Apparatus in Higher Plants. Int Rev Cytol 187:1–49

Yuan F, Yang H, Xue Y, et al (2014) OSCA1 mediates osmotic-stress-evoked Ca2+ increases vital for osmosensing in Arabidopsis. Nature 514: 367–71

Zürcher E, Müller B (2016) Cytokinin Synthesis, Signaling, and Function—Advances and New Insights. International review of cell and molecular biology. 324:1-38

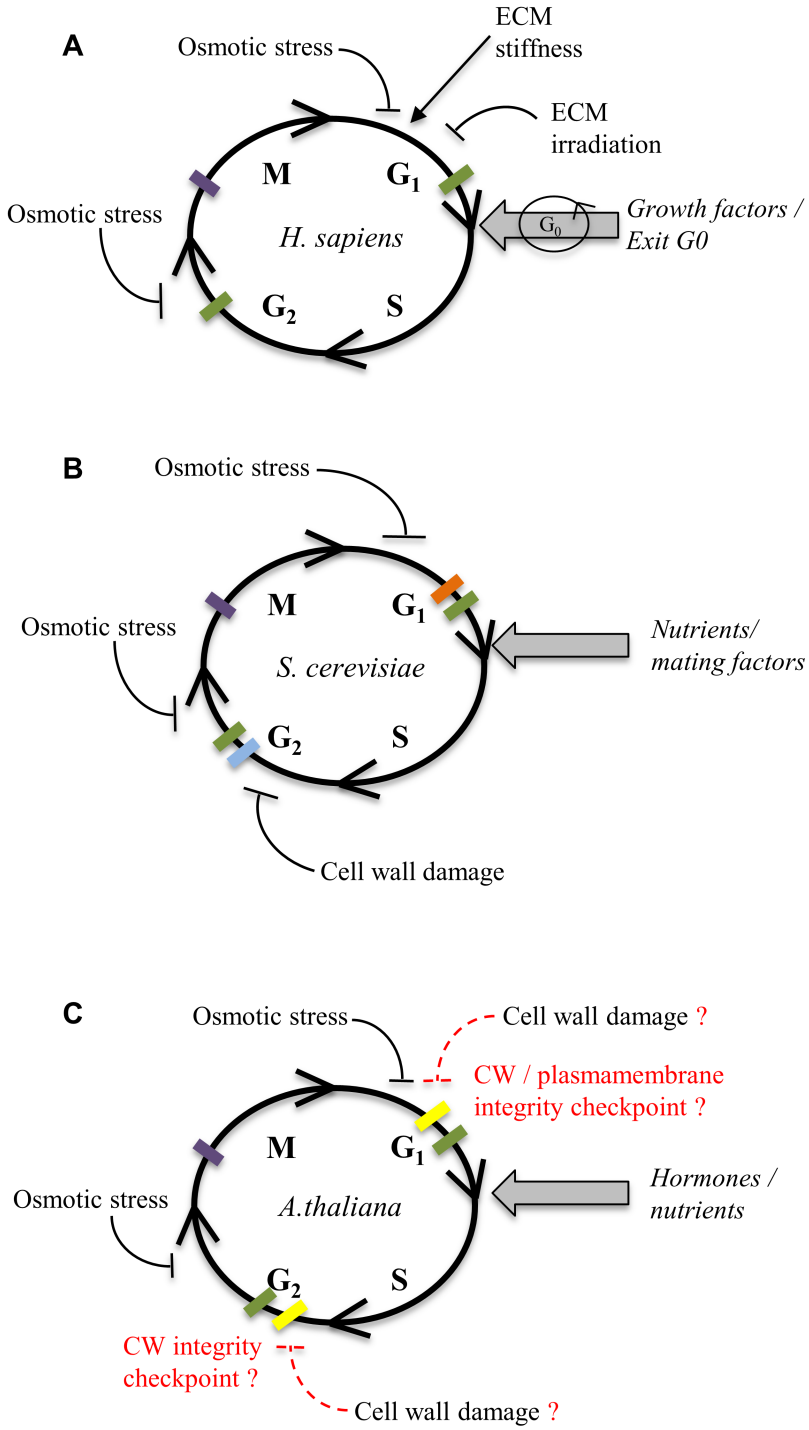

Figure legends

Fig. 1. Schematic representation of cell cycle events in *Homo sapiens* (A), budding yeast *Saccharomyces cerevisiae* (B) and the model plant *Arabidopsis thaliana* (C). Differently colored blocks indicate checkpoints for: DNA damage (green), PM integrity (orange), CWI (blue), spindle checkpoints (violet) and to be characterized (yellow). Bar-head lines and arrows show respectively inhibition or induction of cell cycle progression by external stimuli, as described in the text.