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Protein Phosphatases Drive Mitotic Exit

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1. Introduction

Mitosis is the final stage of the cell cycle that results in the formation of two independent daughter cells with an equal and identical complement of chromosomes (Figure 1). This requires a complex series of events such as nuclear envelope breakdown, spindle formation, equal chromosome segregation, packaging of chromosomes into daughter nuclei and constriction of the plasma membrane at the cell equator, which is subsequently abscised to generate two independent daughter cells. For mitosis to be successful, these events need to occur in a strict order and be spatiotemporally controlled, which is primarily mediated by protein phosphorylation (Dephoure et al., 2008). In human cells more than one thousand proteins show increased phosphorylation during mitosis (Dephoure et al., 2008). These phosphorylation events are mediated by mitotic protein kinases such as cyclin-dependent kinases (Cdks), Auroras, Polo-like kinases (Plks), Mps1, Neks and NimA (Ma and Poon, 2011). In mammalian cells, the majority of phosphorylation events and thus mitotic progression is driven by the activity of Cdk1, which is the main subtype of Cdks (Dephoure et al., 2008). Its activity during mitosis is due to binding cyclin B1 and phosphorylation of a residue in the T-loop.

Mitotic exit involves two stages: (1) membrane ingression, which begins during anaphase following chromosome segregation and involves the breakdown of mitotic structures including the mitotic spindle. It also involves the physical constriction of the cell membrane between segregating chromosomes at the cell equator to generate a thin intracellular bridge between nascent daughter cells. This is followed by (2) membrane abscission at a specific location along the intracellular bridge to generate two independent daughter cells (Figure 1). During mitotic exit, cells also decondense their chromosomes and re-assemble interphase structures such as the nuclear envelope and endoplasmic reticulum. Again, these events need to occur in a strict ordered sequence and requires the reversal of Cdk1-mediated phosphorylation events. Cdk1 is inactivated upon anaphase and is largely dependent on proteasomal-mediated degradation of cyclin B1 by the anaphase promoting complex/cyclosome (APC^{Cdc20}) (Peters, 2006). However, downregulation of Cdk is not sufficient for mitotic exit in human cells. Thus, mitotic phosphatases are also thought to contribute to both the inactivation of Cdk1 at the onset of anaphase and to the mitotic exit process in higher eukaryotes. Consistent with this idea, in the early stages of mitotic exit, Cdk1 is transiently inhibited by phosphorylation prior to the degradation of cyclin B1 (D'Angiolella et al., 2007). It is possible that the transient phosphorylation of Cdk1 is also due to inhibition of the Cdc25C phosphatase by the PP2A phosphatase, which is the same

phosphatase that keeps Cdc25C inactive during interphase (Forester et al., 2007). However, recent evidence indicates that the Cdc14B phosphatase dephosphorylates Cdc25C resulting in its inhibition and consequent phosphorylation of Cdk1 (Tumurbaatar et al., 2011). Moreover, Cdk substrates are dephosphorylated in an ordered sequence from anaphase to cytokinesis (Bouchoux and Uhlmann, 2011). Thus, mitotic exit further depends on the activation of protein phosphatase(s). Indeed, mitotic exit is blocked in cells lacking Cdk1 activity when protein phosphatase activity is suppressed (Skoufias et al., 2007).

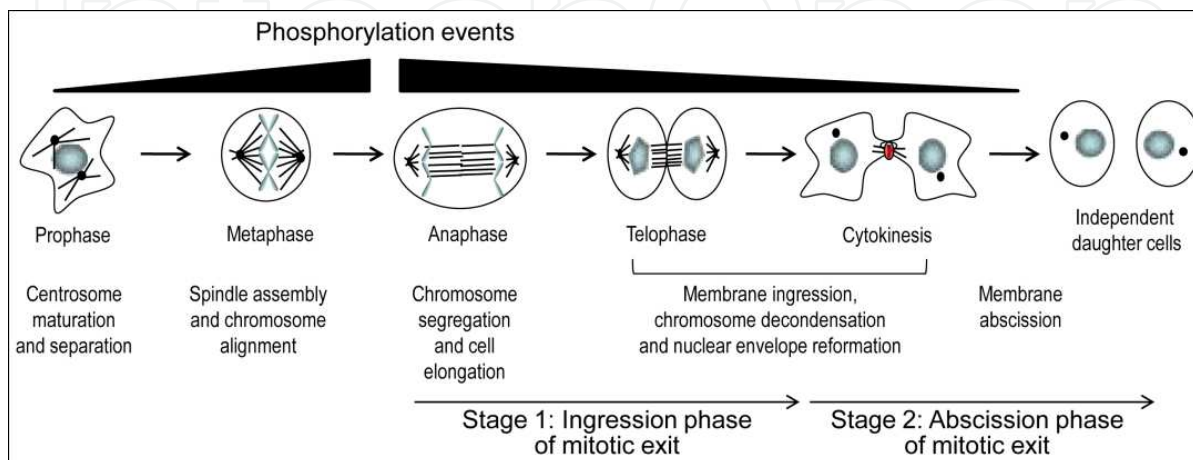


Fig. 1. Schematic illustration of the stages of mitosis. The relative abundance of phosphorylation events is shown above each mitotic stage and the major cellular events occurring at each stage are shown below. These events are known to be regulated by phosphorylation/dephosphorylation. Mitotic exit begins during anaphase and involves two sequential stages: (1) membrane ingression that generates a cleavage furrow followed by (2) membrane abscission of the intracellular bridge that connects the two nascent daughter cells. Chromosomes/nuclei shown in blue. Midbody shown in red.

Although there is a large body of knowledge about the phosphoproteins and protein kinases involved in mitosis and how they are regulated, the specific dephosphorylation events and the involvement of specific phosphatases in mitosis has only recently become appreciated. Studies are now revealing how the timely execution of mitotic events depends on the delicate interplay between protein kinases and phosphatases. To date, most reviews have focused on the role of protein dephosphorylation at the mitotic spindle and specifically how it regulates chromosome alignment (metaphase) and segregation (anaphase) (Bollen et al., 2009, De et al., 2009). This chapter will focus on providing an updated overview of the protein dephosphorylation events that occur during the later stages of mitosis (anaphase – cytokinesis) that contribute to driving mitotic exit and the generation of two independent daughter cells. More specifically, this chapter will provide insights into the protein phosphatases responsible for these dephosphorylation events and how they are regulated in mammalian cells.

2. Mitotic phosphatases in mammalian cells

In *Saccharomyces cerevisiae* (Shou et al., 1999, Visintin et al., 1999) and *Schizosaccharomyces pombe* (Cueille et al., 2001, Trautmann et al., 2001), mitotic exit and co-ordination of the final stage of mitosis, cytokinesis, are driven by the dual serine-threonine and tyrosine-protein

phosphatase, Cdc14. Thus the action of Cdc14 is, in part, to counteract Cdk activity by dephosphorylating Cdk substrates (Visintin et al., 1998). Cdc14 is tightly regulated both spatially and temporally (Stegmeier and Amon, 2004, Queralt and Uhlmann, 2008) as well as being a part of several feedback loops that contribute to a rapid metaphase-anaphase transition (Holt et al., 2008). We have gained a detailed molecular picture of the way that the Cdc14 phosphatase orchestrates mitotic exit in yeast (reviewed in (Stegmeier and Amon, 2004, Queralt and Uhlmann, 2008)). However, much less is known about the protein dephosphorylation events and the responsible phosphatases that reverse Cdk phosphorylation and thus drive mitotic exit in eukaryotes. Homologues of Cdc14 exist in most if not all eukaryotes, but they do not seem to have the same central function in late mitosis as in budding yeast (Trautmann and McCollum, 2002). In *Caenorhabditis elegans*, depletion of CeCDC-14 by RNAi causes defects in cytokinesis; however, this is most likely due to failure to form an intact central spindle (Gruneberg et al., 2002). The human genome encodes two Cdc14 homologues, Cdc14A and Cdc14B and both can rescue Cdc14 yeast phenotypes (Queralt and Uhlmann, 2008), suggesting functional conservation. However, neither Cdc14A nor Cdc14B are required for mitotic exit in higher eukaryotes (Berdougo et al., 2008) although they do seem to be required to generally dephosphorylate Cdk targets (Mocciaro and Schiebel, 2010). This indicates that they have overlapping functions or that additional mitotic exit phosphatases are required. Instead, recent reports suggest that Cdc14s might act by reversing the activating phosphorylations on Cdc25 phosphatases, thereby indirectly contributing to the regulation of Cdk activity in human cells (Krasinska et al., 2007, Vazquez-Novelle et al., 2010, Tumurbaatar et al., 2011). A survey of phosphatase contribution to cell cycle progression in *Drosophila* failed to identify a specific candidate for a mitotic exit phosphatase (Chen et al., 2007), suggesting that more than one phosphatase may act redundantly, or that its involvement in mitotic exit is not the only function of the phosphatase. Recent efforts into identifying phosphatases other than Cdc14 that drive mitotic exit have revealed the serine-threonine calcium- and calmodulin-activated phosphatase, calcineurin (CaN or PP2B) (Chircop et al., 2010a), the protein tyrosine phosphatase containing domain 1 (Ptpcd-1) (Zineldeen et al., 2009), PP1 (Wu et al., 2009), PP2A (Mochida et al., 2009, Schmitz et al., 2010) and oculocerebrorenal syndrome of Lowe 1 (OCRL1) (Ben El et al., 2011) as being required for mitotic exit in mammalian cells (Table 1).

2.1 Cdc14A and Cdc14B

Although the roles of human Cdc14A and Cdc14B are poorly understood, Cdc14A has been linked to centrosome separation and cytokinesis (Kaiser et al., 2002, Yuan et al., 2007), while Cdc14B participates in centrosome duplication and microtubule stabilization (Cho et al., 2005).

2.1.1 Cdc14A

The role of Cdc14A in cytokinesis has been linked to the membrane abscission stage. Ectopically expressed *Xenopus* Cdc14A localizes to the midbody of cytokinetic cells. *Xenopus* oocytes overexpressing wild-type or phosphatase-dead Cdc14A arrests cells in late stage cytokinesis, whereby the nascent daughter cells are connected by a thin intracellular bridge. Neither central spindle formation, nor the re-localization of passenger proteins and centralspindlin complexes to the midbody are affected. Instead targeting of the essential

midbody abscission components, exocyst and SNARE complexes to the midbody, are disrupted in these cells (Krasinska et al., 2007), indicating that Cdc14 midbody localization and more specifically its phosphatase activity is required for abscission.

Phosphatase	Substrates	Function(s)	References
Cdc14A	Unidentified Cdk substrates Cdc25	Centrosome separation, chromosome segregation and cytokinesis Inhibition of Cdk1	(Kaiser et al., 2002, Mailand et al., 2002, Yuan et al., 2007) (Krasinska et al., 2007)
Cdc14B	N.D. SIRT2	Stabilisation and bundling of MTs Downregulation of SIRT2 deacetylase activity by promoting its degradation	(Cho et al., 2005) (Dryden et al., 2003)
Ptpcd-1	Unidentified Cdk substrates	Cytokinesis	(Zineldeen et al., 2009)
PP1	I2 Moesin AIB1 PNUTS B-type lamins Histone H3	Chromosome segregation Cell shape changes for anaphase elongation Relocate AIB1 to chromatin for transcription Chromosome decondensation Targeting ER to chromatin and nuclear envelope reformation Chromosomal reorganisation and nuclear envelope reformation	(Wu et al., 2009) (Kunda et al., 2011) (Ferrero et al., 2011) (Landsverk et al., 2005) (Steen et al., 2000, Ito et al., 2007) (Vagnarelli et al., 2011)
PP2A	Unidentified Cdk substrates	Mitotic exit	(Schmitz et al., 2010, Burgess et al., 2010)
CaN (PP2B)	Dynamin II	Membrane abscission	(Chircop et al., 2010a, Chircop et al., 2010b)
OCRL	PI(4,5)P2	Cleavage furrow formation and membrane ingression	(Ben El et al., 2011)

Table 1. The substrates and function of mitotic phosphatases required for mitotic exit in mammalian cells. N.D. not determined.

Biochemical studies in human HeLa cells suggests that Plk1 regulates the phosphatase activity of Cdc14A during mitosis (Yuan et al., 2007). Plk1 interacts with and phosphorylates Cdc14A resulting in release of Cdc14 auto-inhibited phosphatase activity *in vitro*. This is likely to occur during anaphase. Indeed, overexpression of a phospho-mimetic mutant of Cdc14A in HeLa cells results in aberrant chromosome alignment with delay in prometaphase (Yuan et al., 2007). This suggests that Cdc14A activity is associated with metaphase-anaphase progression and chromosome segregation.

2.1.2 Cdc14B

Although Cdc14B is not required for mitotic exit in mammalian cells, it does appear to play a role in mitosis during the latter stages. The SIRT2 protein is a NAD-dependent deacetylase (NDAC) that is a member of the SIR2 gene family with roles in chromatin structure, transcriptional silencing, DNA repair, and control of cellular life span. SIRT2 abundance and phosphorylation status increase upon mitotic entry. During late stages of mitosis, Cdc14B, but not Cdc14A, mediates SIRT2 dephosphorylation, which in turn targets it for degradation by the 26S proteasome (Dryden et al., 2003). Cells stably overexpressing wildtype SIRT2 but not missense mutants lacking NDAC activity have a prolonged mitotic phase (Dryden et al., 2003). Thus, Cdc14B may contribute to chromatin changes during mitotic exit such as chromosome decondensation by targeting SIRT2 for destruction.

2.2 Ptpcd-1

Of all the phosphatases implicated in mammalian cell mitotic exit to date, the dual-specificity phosphatase, Ptpcd-1, is structurally the most related to Cdc14 (Zineldeen et al., 2009). It is suggested to be a functional isozyme of mammalian Cdc14A (Zineldeen et al., 2009). Like Cdc14A, Ptpcd-1 associates with and co-localises with Plk1 at the midbody of cells in cytokinesis. Both overexpression of Ptpcd-1 and Plk1 cause cytokinesis failure and multinucleate cell formation. No Ptpcd-1 substrates have yet been identified, however like Cdc14B its function is most likely regulated by Plk1. Ptpcd-1 possesses four Plk1 consensus phosphorylation sites and its overexpression could not rescue cytokinesis failure induced by Plk1 depletion (Zineldeen et al., 2009), suggesting that it lies downstream of Plk1. In support of this idea, the yeast homolog of Plk1, Cdc5, regulates Cdc14 phosphorylation and its subcellular localization for mitotic exit (Visintin et al., 2003, Visintin et al., 2008). Based on their midbody co-localization, it is possible that this Plk1/Ptpcd-1 signalling pathway contributes to membrane abscission.

2.3 PP1 and PP2A

The phosphatase inhibitor, okadaic acid, can induce mitotic entry in interphase cells (Yamashita et al., 1990) and this mitotic state can be maintained if Cdk1 activity is inhibited (Skoufias et al., 2007). Okadaic acid inhibits the activity of the protein phosphatase (PP)1 and PP2A. Consequently, both phosphatases have been implicated in reversing mitotic phosphorylation events in *Xenopus* egg extracts (Wu et al., 2009, Mochida et al., 2009). Not surprisingly, both phosphatases are inactivated during mitosis and their reactivation is important for mitotic exit (Wu et al., 2009, Mochida et al., 2009). However, both phosphatases have distinct substrates and are regulated via different mechanisms, which is in line with these enzymes being structurally diverse (Virshup and Shenolikar, 2009).

2.3.1 PP1

PP1 is activated at the metaphase-anaphase transition by a mechanism involving both inactivation of Cdk1 and proteasome-dependent degradation of an unknown protein (Mochida and Hunt, 2007, Skoufias et al., 2007). During early stages of mitosis, PP1 activity is suppressed and this suppression is maintained through dual inhibition by Cdk1 phosphorylation and the binding of inhibitor-1 (I1) (Wu et al., 2009). Protein kinase A phosphorylates I1, mediating its binding to PP1. Partial PP1 activation is achieved during anaphase following a drop in Cdk1 levels due to cyclin B degradation. This shifts the Cdk1/PP1 ratio in favour of PP1 allowing auto-dephosphorylation of PP1 at its Cdk1-mediated phosphorylation site. PP1 subsequently mediates the dephosphorylation of I2 at the I2 activating site, resulting in dissociation of the PP1-I2 inhibitor complex. This results in full activation of PP1 and initiation of mitotic exit. During anaphase, when the outer kinetochore is dis-assembled, I2 levels drop and this may also contribute to the up-regulation of PP1 (Li et al., 2007, Wang et al., 2008). PP1 itself participates in outer kinetochore dis-assembly and chromosome segregation and this may be due to its ability to dephosphorylate Aurora B substrates (Emanuele et al., 2008). Thus, several feedback loops exist and involve protein kinases to initiate and maintain PP1 activity for mitotic exit.

PP1 plays roles in several mitotic events that need to occur in a sequential order and include cell elongation, chromosome segregation, chromosome decondensation and nuclear envelope re-formation. At the onset of mitosis, the cell rounds up and forms a stiff, rounded metaphase cortex. Moesin, the sole *Drosophila* Ezrin-Radixin-Moesin (ERM)-family protein which functions to regulate actin dynamics and cytoskeleton organization (Fehon et al., 2010), plays a critical role in this process and is dependent on the phospho-form of moesin (Kunda and Baum, 2009, Roch et al., 2010, Roubinet et al., 2011). Consequently, dephosphorylation of moesin at the cell poles is required to dismantle this rigid cortex to allow for anaphase elongation and cytokinesis. An RNAi screen for phosphatases involved in the temporal and spatial control of moesin identified PP1 as the responsible phosphatase (Kunda et al., 2011). Overexpression of phosphomimetic-moesin and PP1 depletion blocks proper anaphase elongation of the cell (Kunda et al., 2011).

PP1 is involved in the first step of nuclear envelope re-formation by stimulating the targeting of endoplasmic reticulum to chromatin (Ito et al., 2007). The assembly of the nuclear lamina depends on the dephosphorylation of B-type lamins, which is catalyzed by a PP1/AKAP149 complex that is associated with the nuclear envelope (Steen et al., 2000).

The role of PP1 in chromosome decondensation involves its association with Repo-Man and the PP1 nuclear targeting subunit (PNUTS). During anaphase, a Repo-Man/PP1 complex forms following Repo-Man dephosphorylation. Repo-Man targets the complex to chromosomes to allow PP1 to mediate the dephosphorylation of histone H3 (Vagnarelli et al., 2011). This contributes to the loss of chromosome architecture (Vagnarelli et al., 2006, Trinkle-Mulcahy and Lamond, 2006, Trinkle-Mulcahy et al., 2006). During telophase, PP1 targets PNUTS to the reforming nuclei following the assembly of nuclear membranes concomitant with chromatin decondensation. Here, PNUTS enhances *in vitro* chromosome decondensation in a PP1-dependent manner (Landsverk et al., 2005). Thus, targeting of PNUTS to the reforming nuclei in telophase may be part of a signalling event promoting chromatin decondensation as cells re-enter interphase.

Finally, PP1 appears to play a role in the initiation of transcription upon entry into the next cell cycle, as it is responsible for reversing the inhibitory Cdk1-mediated phosphorylation events of the transcription factor, AIB1 (Ferrero et al., 2011). AIB1 phosphorylation does not appear to affect its transcriptional activity but instead excludes it from condensed chromatin during mitosis to prevent its access to the promoters of AIB1-dependent genes. Its dephosphorylation by PP1 would presumably allow AIB1 to relocate to decondensed chromatin upon entry into the next cell cycle to re-initiate gene transcription.

2.3.2 PP2A

PP2A forms a complex with B-type regulatory subunits and these subunits contribute to PP2A localisation and substrate specificity. As such, PP2A-B55 α and PP2A-B55 δ were considered strong mitotic exit phosphatase candidates since these B55 regulatory subunits are substrate specifiers for Cdk substrates (Janssens et al., 2008). Indeed, both have been shown to be regulators of mitotic exit in human cells (Mochida et al., 2009, Schmitz et al., 2010). In *Xenopus* egg extracts, PP2A-B55 δ is negatively regulated by the kinase greatwall (MASTL in humans) during early mitotic stages to allow the accumulation of mitotically phosphorylated proteins. This is achieved by greatwall-mediated phosphorylation of the small protein ARPP-19, which converts it into a potent PP2A inhibitor (Burgess et al., 2010). PP2A activation induced by MASTL knockdown leads to premature mitotic exit in human cells (Burgess et al., 2010). How PP2A is reactivated once Cdk1 activity decreases to drive mitotic exit remains unclear. Presumably greatwall needs to be inactivated and this is likely to involve an as yet unidentified phosphatase. Alternatively or in addition to this, PP2A may be activated via auto-phosphorylation in a similar manner to PP1 (Wu et al., 2009). Moreover, the identification of PP2A substrates and the role of PP2A for mitotic exit remain key questions for future investigation.

2.4 CaN (PP2B)

Endocytosis is thought to shut down during mitosis then resume during the final stage, cytokinesis (Schweitzer et al., 2005). Endocytosis is required for cytokinesis (Feng et al., 2002) and thought to contribute to the pool of recycling endosomes that are eventually delivered to the site of abscission. Here, they are proposed to (i) provide extra total cell surface area, an increase of at least 25% is required to complete division (Boucrot and Kirchhausen, 2007), (ii) deliver critical cytokinetic proteins to the abscission site (Low et al., 2003), and/or (iii) be directly involved in compound fusion, whereby numerous vesicles fuse with the plasma membrane during abscission to separate the daughter cells (Low et al., 2003, Gromley et al., 2005, Goss and Toomre, 2008, Prekeris and Gould, 2008).

The calcium- and calmodulin-dependent phosphatase, calcineurin (CaN) is an excellent candidate phosphatase for restarting endocytosis during cytokinesis, since it initiates endocytosis in neurons (Liu et al., 1994). In support of this idea, the fission yeast CaN gene is required for cytokinesis and the CaN inhibitors cyclosporin A (CsA) and FK506 block yeast cytokinesis (Yoshida et al., 1994). CaN is required for calcium-induced mitotic exit in cytotstatic factor-arrested *Xenopus* oocytes (Mochida and Hunt, 2007, Nishiyama et al., 2007). CaN is upregulated in *Xenopus* oocytes from metaphase of meiosis II. An increase in cytoplasmic calcium upon fertilisation triggers meiosis II exit in these oocytes, which involves calmodulin-activating kinase-dependent activation of the APC. APC-mediated

inactivation of Cdk is not sufficient to drive Cdk substrate dephosphorylation and meiotic exit in these oocytes and thus activation of CaN is likely to occur in parallel to drive this process. A recent report has indicated that CaN is also required for completion of abscission in human cells (Chircop et al., 2010a). During cytokinesis CaN localizes to two 1.1 μm diameter flanking midbody rings (FMRs) that reside on either side of the 1.6 μm diameter γ -tubulin midbody ring (MR) within the centre of the intracellular bridge. The endocytic protein, dynamin II (dynII), is mitotically phosphorylated by Cdk1/cyclin B1 upon mitotic entry and co-localises with CaN at the FMRs during cytokinesis (Chircop et al., 2010a, Chircop et al., 2010b). CaN inhibition by CsA, dynII depletion, phospho-mimetic dynII phosphopeptides and small molecule dynamin inhibitors lead to aborted cytokinesis and multinucleation (Joshi et al., 2010, Chircop et al., 2010a, Chircop et al., 2010b, Chircop et al., 2011). At the FMRs, a calcium influx activates CaN resulting in dephosphorylation of dynII. This is one of the last molecular events known to occur prior to abscission. Thus, it is possible that CaN-mediated dynII dephosphorylation may be the trigger for cellular abscission to complete cytokinesis.

In the brain, for clathrin-mediated endocytosis (CME) and activity-dependent bulk endocytosis (ADBE), CaN not only targets dynI but also α -adaptin, epsin and eps15 (Cousin and Robinson, 2001). Like dynII, epsin and α -adaptin are mitotically phosphorylated (Chen et al., 1999, Kariya et al., 2000, Dephoure et al., 2008). Thus, they represent additional potential CaN substrates during cytokinesis. Once dephosphorylated they may contribute to the recruitment of the dephosphorylated form of dynII to the abscission site or directly in CME within the intracellular bridge.

2.5 Oculocerebrorenal syndrome of Lowe 1 (OCRL), an inositol 5-phosphatase

Generation of the cleavage furrow during the membrane ingression stage of cytokinesis involves an actin-myosin II contractile ring. At the cleavage furrow, the phosphoinositide phosphatidylinositol 4,5-bisphosphate (PI(4,5)P₂) plays an important role in this process by recruiting and regulating essential proteins of the cytokinesis machinery (Janetopoulos and Devreotes, 2006). PI(4,5)P₂ mis-regulation blocks cleavage furrow formation leading to generation of a multinucleated cell (Emoto et al., 2005, Field et al., 2005, Wong et al., 2005). In *Drosophila*, the localization of PI(4,5)P₂ is restricted at the cleavage furrow by the *Drosophila* ortholog of human oculocerebrorenal syndrome of Lowe 1 (OCRL1) (Ben El et al., 2011), an inositol 5-phosphatase mutated in the X-linked disorder oculocerebrorenal Lowe syndrome. Depletion of this phosphatase results in cytokinesis failure due to mis-localization of several essential cleavage furrow components to giant cytoplasmic vacuoles that are rich in PI(4,5)P₂ and endocytic markers (Ben El et al., 2011). dOCRL is associated with endosomes and mediates PI(4,5)P₂ dephosphorylation on internal membranes to restrict this phosphoinositide at the plasma membrane and thereby regulate cleavage furrow formation and ingression.

3. Conclusion

Here, the role of Cdc14A and Cdc14B, PP1, PP2A-B55, CaN, Ptpcd-1 and OCRL in regulating and driving mitotic exit in mammalian cells was reviewed. It is clear that we have only scraped the surface in our investigations into understanding the role and regulation of

protein phosphatases in mitosis. The identification of all protein phosphatases involved in driving mitotic exit in mammalian cells, their relevant substrates and function as well as how their action is spatio- and temporal regulated *in vivo* remain key questions for future investigation.

Understanding how protein dephosphorylation regulates mitotic exit and how the responsible protein phosphatases are regulated will provide an improved understanding to how two independent daughter cells are generated. Mitotic exit failure results in aneuploidy, which leads to genomic instability and thus contributes to the initiation and progression of tumourigenesis. Thus, an understanding of the molecular pathways that drive mitotic exit may highlight molecular targets for the development of new anti-cancer chemotherapeutic agents. In line with this idea, a recent publication has identified the CaN substrate, dynII, as a molecular target for the treatment of cancer (Chircop et al., 2010a, Chircop et al., 2010b). Inhibitors of dynII possess anti-cancer properties due to their ability to cause cytokinesis failure and subsequent cell growth arrest or apoptotic cell death (Joshi et al., 2010). It will be interesting to pursue the development of other targeted inhibitors to determine if they also possess anti-cancer properties as well as being useful molecular tools to unravel the signalling pathways required for mitotic exit in mammalian cells.

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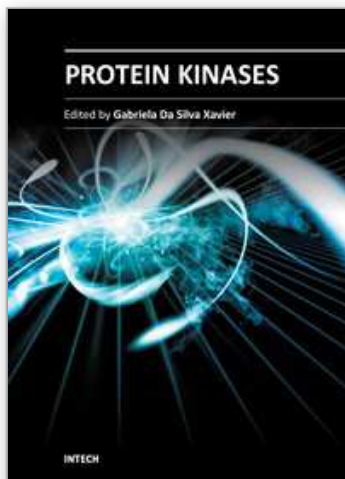
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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

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