Review

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The diverging role of CDC14B: from mitotic exit in yeast to cell fate control in humans

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Abstract

CDC14, originally identified as crucial mediator of mitotic exit in budding yeast, belongs to the family of dual-specificity phosphatases (DUSPs) that are present in most eukaryotes. Contradicting data have sparked a contentious discussion whether a cell cycle role is conserved in the human paralogs CDC14A and CDC14B but possibly masked due to redundancy. Subsequent studies on *CDC14A* and *CDC14B* double knockouts in human and mouse demonstrated that CDC14 activity is dispensable for mitotic progression in higher eukaryotes and instead suggested functional specialization. In this review, we provide a comprehensive overview of our current understanding of how faithful cell division is linked to phosphorylation and dephosphorylation and compare functional similarities and divergences between the mitotic phosphatases CDC14, PP2A, and PP1 from yeast and higher eukaryotes. Furthermore, we review the latest discoveries on CDC14B, which identify this nuclear phosphatase as a key regulator of gene expression and reveal its role in neuronal development. Finally, we discuss CDC14B functions in meiosis and possible implications in other developmental processes.

Keywords CDC14; cell cycle; gene expression; PP2A; protein phosphorylation
Subject Categories Cell Cycle; Post-translational Modifications & Proteolysis
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See the Glossary for abbreviations used in this article.

Introduction

In 1974, the *CDC14* gene was identified in the model organism *Saccharomyces cerevisiae* (budding yeast) by future Nobel laureate Lee Hartwell in his screen for regulators of the cell division cycle (CDC) (Hartwell *et al*, 1973). Later work demonstrated that budding yeast *CDC14* encodes a protein phosphatase that counteracts mitotic CDK1 (cyclin-dependent kinase 1) activity, thereby facilitating mitotic exit and cytokinesis (Wan *et al*, 1992; Visintin *et al*, 1998; Miller *et al*, 2015; Fig 1). CDC14 dephosphorylates substrates that preferentially adhere to the CDK1 consensus target sequence, (S/T)Px(K/R), with a clear preference for serine over threonine residues (Gray *et al*, 2003). In early anaphase, the FEAR (for: CDC fourteen early anaphase release) pathway is activated and reliefs the nucleolar, Cfi1/Net1-mediated sequestration of CDC14, leading to the dispersal of CDC14 into the nucleoplasm, where it regulates many aspects of the closed mitosis of budding yeast, such as rDNA segregation, spindle stabilization, and priming of the mitotic exit network (MEN) (Visintin *et al*, 1999; Jaspersen & Morgan, 2000; Pereira & Schiebel, 2003; D'Amours *et al*, 2004; Sullivan *et al*, 2004; Higuchi & Uhlmann, 2005). The MEN in turn promotes further CDC14 release from the nucleolus, and bolsters its retention in the cytoplasm where it reverses CDK1 phosphorylation events (Shou *et al*, 1999). In this respect, one key contribution to CDK1 inactivation is dephosphorylation and activation of the CDK1 inhibitor Sic1 and its transcriptional activator Swi5 (Visintin *et al*, 1998). In addition, CDC14 positively regulates CDH1, an activator of the mitotic ubiquitin ligase APC/C (anaphase-promoting-complex/cyclosome), triggering further cyclin B1 degradation (Jaspersen *et al*, 1999) following an initial wave of cyclin B proteolysis induced by APC/C^{CDC20}. CDC14 was also demonstrated to interact with Iqg1, a member of the IQGAP family of GTPase-activating proteins that recruits actin to the myosin ring. By dephosphorylating CDK1 sites on Iqg1, CDC14 enables actin ring formation for timely cytokinesis (Miller *et al*, 2015).

In vertebrates, evolution gave rise to the paralogs *CDC14A* and *CDC14B*. Human CDC14A is cytoplasmic and associates with the actin cytoskeleton and the centrosome in interphase, as well as with the basal body during ciliogenesis; however, it does not localize to the nucleolus (Mailand *et al*, 2002; Chen *et al*, 2016; Uddin *et al*, 2019). Human CDC14B is nucleolar in interphase, associates with mitotic chromosomes as well as spindle poles, and has the ability to bind to microtubules (Cho *et al*, 2005; Chen *et al*, 2017). During hominoid evolution, *CDC14B* duplicated through retroposition further generated the near-pseudogene *CDC14C* (also referred to as *CDC14Bretro*) that is only expressed in testis and brain (Rosso *et al*, 2008). This intron-less *CDC14C* differs in a few bases from the *CDC14B* coding sequence, resulting in a shift of subcellular protein localization to the cytosolic site of the endoplasmic reticulum (ER) (Rosso *et al*, 2008). These localization and expression changes imply functional diversification, but the possible role(s) of CDC14C at the ER in the brain and testis remain unclear.

Studies based on siRNA-induced knockdown and overexpression experiments initially allocated a critical role in cell division to the

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Glossary

APC/C	Anaphase-promoting complex/cyclosome
CDC14	Cell division cycle 14
CDK	Cyclin-dependent kinase
CTD	C-terminal domain
DUSP	Dual-specificity (Ser/Thr/Tyr) phosphatase
ESCs	Embryonic stem cells
FEAR	Cdc14 early-anaphase release
MEN	Mitotic exit network
MPF	Maturation-promoting factor
PP2A	Protein phosphatase 2A
PPP	Phosphoprotein phosphatase
SAC	Spindle assembly checkpoint

human paralogs CDC14A and CDC14B. It was suggested that CDC14A is important for chromosome segregation and cytokinesis, whereas CDC14B was linked to spindle assembly and mitotic exit (Mailand *et al*, 2002; Dryden *et al*, 2003; Cho *et al*, 2005). However, single knockout studies in avian and human cell lines did not confirm defects in the cell cycle, but instead identified roles in DNA repair, actin rearrangement, and ciliogenesis (Berdougo *et al*, 2008; Mocciaro *et al*, 2010; Chen *et al*, 2017; Uddin *et al*, 2019). The possibility that redundant functions of the two CDC14 paralogs simply masks their role in cell cycle progression was also excluded, since there were no defects in mitotic kinetics or cell growth in *CDC14A/CDC14B* double-knockout mouse embryonic fibroblasts (MEFs) as well as non-transformed hTERT-RPE1 cells (human telomerase reverse transcriptase-immortalized retinal epithelial cells that do not express *CDC14C*; Partscht *et al*, 2021; Villarroya-Beltri *et al*, 2023). Instead, it appears that the functions of human CDC14 paralogs have diverged through evolution and that it is the predominant threonine-directed phosphatases PP2A and PP1A that perform the key mitotic exit and cytokinesis functions in higher eukaryotes (Schmitz *et al*, 2010; Cundell *et al*, 2013, 2016; Grallert *et al*, 2015).

While CDC14 phosphatases belong to the group of single-subunit DUSPs (dual-specificity protein phosphatases) (Tonks, 2006; Patterson *et al*, 2009), PP2A and PP1 are members of the phosphoprotein phosphatase (PPP) family and operate as multi-subunit holoenzymes (Virshup & Shenolikar, 2009). In this respect, it is important to note that while DUSPs generally have the ability to target tyrosine as well as serine/threonine residues, CDC14 has lost its preference for tyrosine (due to changes in the tyrosine binding pocket, which now provides access to proline) and threonine residues (due to an active-site steric clash), resulting in CDC14's proline-directed phosphoserine specificity (Gray *et al*, 2003; Bremmer *et al*, 2012). Humans PP1 is composed of a catalytic subunit (of which there are four possible isoforms: PP1α, PP1β, PP1γ1 and PP1γ2) and one or multiple regulatory subunits (Terrak *et al*, 2004). The exact number of regulatory subunits that can modulate the specificity and activity of PP1 is not known; however, there are over 150 candidates that potentially associate with PP1 (Egloff *et al*, 1997; Holder *et al*, 2019). PP2A is a heterotrimeric complex consisting of a scaffolding subunit A, a regulatory subunit B, and a catalytic subunit C. Diversity of PP2A phosphatases arises from combinations with two scaffolding A subunits (PR65α, PR65β), twelve regulatory B subunits (classified into the families B55, B56, PR48 and PR93), and two catalytic C subunits (PP2Acα, PP2Acβ). The regulatory subunits B55 and B56 display four and five isoforms, respectively (Xing *et al*, 2006; Xu *et al*, 2006; Seshacharyulu *et al*, 2013).

Here, we compare the contribution of the phosphatases CDC14, PP2A and PP1 to mitotic progression from yeast to human. In addition, we evaluate recent data that propose CDC14B as a key regulator of specialized cell cycle programs. CDC14B has evolved beyond its role in cell division to become a multifunctional, gene expression-regulating

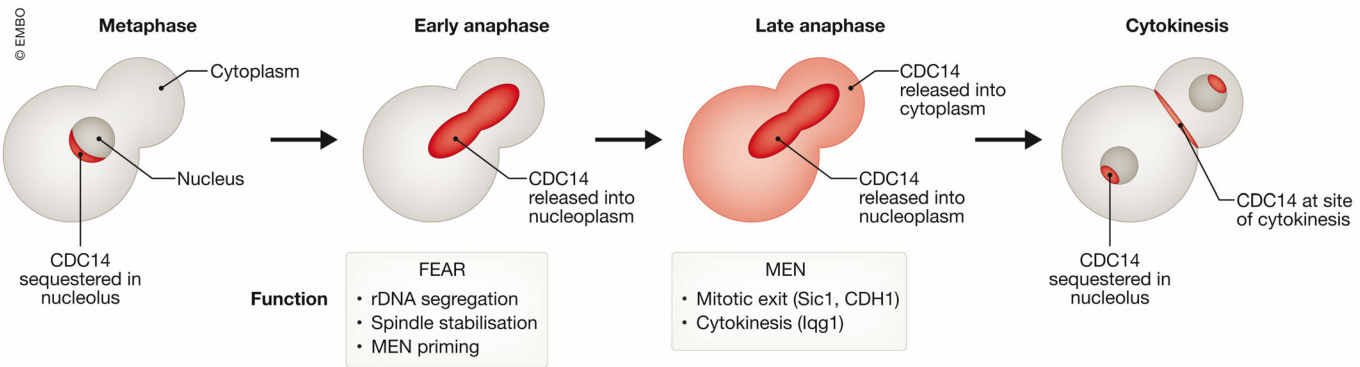

Figure 1. Basic functions of budding yeast CDC14.

In *Saccharomyces cerevisiae* (budding yeast), CDC14 phosphatase counteracts the activity of mitotic CDK1, thereby bringing the cell cycle to completion. CDC14 confined to the nucleolus is released during anaphase in two waves by the FEAR and MEN pathways, respectively. In early anaphase, the FEAR pathway triggers a partial release of CDC14 from the nucleolus into the nucleoplasm, leading to the dephosphorylation of CDK1 substrates that control different aspects of chromosome movement. In addition, CDC14 contributes to the activation of the MEN as part of a positive feedback loop, which enables full liberation of CDC14 from the nucleolus and its retention in the cytoplasm at late anaphase. Budding yeast CDC14 is the key phosphatase to reverse the CDK1-mediated phosphorylations necessary to exit mitosis and also contributes to inactivation of CDK1 through dephosphorylation of CDH1 and Sic1 that results in cyclin B1 degradation and CDK1 inhibition, respectively. CDC14 also transiently localizes to the site of cytokinesis, where it dephosphorylates the CDK1 substrate Iqg1, thereby promoting actin ring formation.

protein involved in neuronal development, mitotic survival, and sustainability of the spindle assembly checkpoint (SAC). Lastly, we review the involvement of CDC14B in meiosis and explore its potential contribution to other developmental processes.

Unraveling the mysteries of mitosis

Eukaryotic cells have evolved the process of mitosis, that is, the segregation of the duplicated chromosomes by the mitotic spindle, followed by cytokinesis and the formation of two identical daughter cells. Entry and exit from mitosis are tightly controlled by a coordinated series of phosphorylation and dephosphorylation events that are achieved through the organized activation and inactivation of mitotic kinases and phosphatases, respectively. Sequential proteolysis combined with positive and negative feedback loops create unique and unidirectional regulatory states with distinct activation levels of the mitotic kinases and phosphatases. The main kinase active during mitosis is CDK1. During the G2 phase, CDK1 activity gradually increases until a critical threshold is reached that triggers the G2/M transition. This threshold comprises 30% of its maximum activation and promotes a switch-like boost of further CDK1 activation that is promoted by feedback loops and inactivation of counteracting phosphatases (Lindqvist *et al*, 2007). CDK1 activity reaches its maximum at metaphase, and satisfaction of the SAC eventually triggers its inactivation via APC/C-dependent cyclin B degradation, thereby initiating exit from mitosis. The activation of CDK1-counteracting phosphatases is crucial for complete CDK1 inactivation and the reversal of its mitotic phosphorylation events.

In budding yeast, the CDC14 phosphatase plays an essential role in controlling mitotic exit. In higher eukaryotes, mitotic exit and cytokinesis appear to rely mainly on the phosphatase $PP2A^{B55}$. In the section below, we will provide an overview of our current understanding of mitosis with an emphasis on the mitotic phosphatases, their regulatory modules, and how they contribute to faithful cell division in yeast compared to higher eukaryotes. For a complementary understanding of the important interplay between the phosphoprotein phosphatases PP1 and PP2A and the Polo and Aurora kinases during mitosis in higher eukaryotes, we recommend the excellent review by Holder *et al* (2019).

Mitotic entry—the rise of CDK1

In human cells, the initiation of mitosis is facilitated by the activation of CDK1 in complex with either mitotic cyclin A or cyclin B. This leads to the phosphorylation of hundreds of substrates, which drives mitotic key events including nuclear envelope breakdown, kinetochore assembly, chromosome condensation, spindle formation, and disassembly of the nucleus, while inhibiting regulators of anaphase spindle elongation and cytokinesis. The sharp increase of mitotic CDK1 activity involves multiple events and positive feedback loops. A conserved regulatory module during the mitotic entry comprises the Greatwall kinase (Gwl; MASTL in mammals, Rim15 in budding yeast, Ppk18 in fission yeast) that phosphorylates the endosulfines ENSA and ARPP19 (Igo1/Igo2 in budding yeast, Cek1/Igo1 in fission yeast). Phosphorylated endosulfines bind and inhibit the CDK1-counteracting phosphatase $PP2A^{B55}$ ($PP2A^{Cdc55}$ in budding yeast; $PP2A^{Pab1}$ in fission yeast), thereby facilitating phosphorylation of proteins by CDK1 (Gharbi-Ayachi *et al*, 2010; Mochida *et al*, 2010; Cundell *et al*, 2013). In higher eukaryotes, the inactivation of PP2A allows for complete CDK1-mediated activation of the phosphatase CDC25 (Mih1 in budding yeast) and inactivation of the kinase Wee1 (Swe1 in budding yeast; Clarke *et al*, 1993; Mueller *et al*, 1995), and thereby contributes to the removal of the conserved inhibitory phosphorylation on CDK1-Y15 targeted by both of these enzymes. The activity of Greatwall kinase is positively regulated by CDK1-mediated phosphorylation in metazoans (Blake-Hodek *et al*, 2012). In addition to Greatwall-mediated inhibition of $PP2A^{B55}$, another layer of $PP2A^{B55}$ temporal regulation at the G2/M transition was added by the recent finding of CDK1 directly phosphorylating PP2A at threonine 304, thereby disrupting the binding to the regulatory subunit B55 (Nasa *et al*, 2020). In fission yeast, however, the equivalent Greatwall-endosulfine pathway is negatively regulated by nutrient availability through the action of the TORC1 kinase (target of rapamycin complex 1; Chica *et al*, 2016). Hence, in the presence of adequate amount of nutrients, TORC1 phosphorylates and inhibits the fission yeast Greatwall kinase Ppk18, thereby promoting $PP2A^{Pab1}$ activity and delaying mitotic entry. This prolongs G2 phase and enhances cell growth before the cell enters mitosis. Conversely, under nutrient-poor conditions, TORC1 activity drops and Ppk18 promotes $PP2A^{Pab1}$ inactivation allowing fast completion of the cell cycle and entry into quiescence in G1 (Chica *et al*, 2016). Recently, it has been demonstrated that the Greatwall-ENSA pathway is coupled with nutritional conditions and cell growth in higher eukaryotes as well (Sanz-Castillo *et al*, 2023). In fact, during periods of nutrient abundance, mammalian Greatwall kinase is directly activated through phosphorylation by mTORC1. This mitosis-independent activation prevents the activity of $PP2A^{B55}$ toward downstream targets of mTORC1, thereby contributing to a negative feedback loop in the PI3K/AKT/mTOR pathway (Sanz-Castillo *et al*, 2023). Interestingly, in temperature-stressed budding yeast, the endosulfines were suggested to promote mitotic entry through positive rather than negative regulation of $PP2A^{Cdc55}$, possibly by controlling its nucleo-cytoplasmic distribution (Juanes *et al*, 2013). Under unstressed conditions, the impact of the budding yeast Rim15-Igo1/2 (MASTL-endosulfines) module on PP2A inhibition in early mitosis appears to be relatively minor compared to the contribution of the fungi-specific Zds protein family (Rossio *et al*, 2014; Thai *et al*, 2017). Zds1 and Zds2 complex with Cdc55 and sequester it in the cytoplasm, thereby promoting cytoplasmic $PP2A^{Cdc55}$ functions at the expense of nuclear ones (Rossio & Yoshida, 2011). Cytoplasmic $PP2A^{Cdc55}$ then dephosphorylates Mih1. While in vertebrate cells, CDC25 is hyperphosphorylated at the onset of mitosis (Wicky *et al*, 2010), its budding yeast counterpart Mih1 is hypophosphorylated as cells enter mitosis (Pal *et al*, 2008; Lucena *et al*, 2017). The conserved CDK1-activating phosphorylation of Mih1 precedes $PP2A^{Cdc55}$-mediated dephosphorylation of Mih1, but the exact functional significance of this dephosphorylation at the G2/M transition is not yet clear (Izumi *et al*, 1992; Kumagai & Dunphy, 1992; Pal *et al*, 2008). Interestingly, initial CDK1-mediated phosphorylations activate the budding yeast CDK1 inhibitor kinase Swe1 before further phosphorylation events inactivate Swe1. $PP2A^{Cdc55}$ regulates mitotic entry by counteracting these early CDK1-mediated phosphorylations on Swe1. This limits the initial negative feedback loop on CDK1 and permits bypassing

the inhibitory activity of Swe1 in early mitosis (Harvey *et al*, 2011). Activation of Wee1 by CDK1 phosphorylations appears to be conserved in vertebrates (Deibler & Kirschner, 2010).

Another important phosphatase during mitotic entry is PP1 (Glc7 in budding yeast). As CDK1 and PLK1-mediated activating phosphorylations on CDC25 occur, PP1 promotes mitotic entry in *Xenopus laevis* by removing an inhibitory CDC25 phosphorylation at S287 (S216 in human) that is mediated by DNA-responsive checkpoint kinases (Peng *et al*, 1997; Margolis *et al*, 2003). Removal of the scaffold protein 14-3-3 from CDC25 was suggested as prerequisite for its PP1-mediated activation (Margolis *et al*, 2003). Xenopus $PP2A^{B56}$ dephosphorylates critical threonine residues in CDC25 (T138; T130 in humans), which maintain 14-3-3 binding and so prevent CDC25 activation by PP1 (Margolis *et al*, 2006). $PP2A^{B56}$ in turn is activated by checkpoint kinases that phosphorylate B56 at S37. Once the checkpoint kinases are inactivated, PP2A autodephosphorylation leads to the activation of CDC25 (Margolis *et al*, 2006). Little is known about the potential role of the budding yeast homolog Glc7 and $PP2A^{Rts1}$ during the G2/M transition (Hisamoto *et al*, 1994). The subsequent sharp increase in CDK1 activity globally represses PP1 through inhibitory phosphorylations.

In contrast to $PP2A^{B55}$ and PP1, the activity of $PP2A^{B56}$ has not yet been shown to be directly affected by CDK1 activity; still, the bulk activity of all three phosphatases is inhibited at mitotic commitment as shown in fission yeast (Grallert *et al*, 2015). However, a local pool of $PP2A^{B56}$/$PP2A^{Rts1}$/$PP2A^{Par1}$ remains active in mitosis, since active $PP2A^{B56}$ is needed at kinetochores to maintain centromeric sister chromatid cohesion (Riedel *et al*, 2006; Tang *et al*, 2006; Yahya *et al*, 2020; Ueki *et al*, 2021).

While budding yeast CDC14 is sequestered in the nucleolus by Net1 and is not dispersed before anaphase onset, fission yeast Clp1 and human CDC14B are released from the nucleolus already at the onset of mitosis (Kaiser *et al*, 2002; Mailand *et al*, 2002). Clp1 is important for faithful mitotic entry, since its deletion leads to precociously transition into mitosis (Trautmann *et al*, 2001; Esteban *et al*, 2004; Wolfe & Gould, 2004). In fact, Clp1 delays mitotic commitment by counteracting the promoting CDK1 sites on CDC25 (Esteban *et al*, 2004; Wolfe & Gould, 2004). In addition, SPB-anchored signaling events emanating from the scaffold molecules Sid4, a SIN (septation initiation network; similar to MEN in budding yeast) component, and Cut12 were previously thought to function independently in controlling Clp1 activity at late mitosis and CDK1 activity at the G1/M transition, respectively. However, recently it has been discovered that they cooperate to expel Clp1 from the SPB thereby supporting mitotic commitment (Chan *et al*, 2017). Interestingly, CDC14B was previously suggested to dephosphorylate and inactivate CDC25; however, cells genetically depleted for both CDC14A and CDC14B did not show altered mitotic entry or delayed mitotic exit kinetics (Tumurbaatar *et al*, 2011; Partscht *et al*, 2021; Villarroya-Beltri *et al*, 2023).

Mitotic exit—return of the phosphatases

Cells commit to exit from mitosis at the metaphase-to-anaphase transition via a tightly regulated process that involves the coordinated activity of multiple pathways, eventually leading to chromosome segregation, cytokinesis, and the formation of two daughter cells. A hallmark of the mitotic exit program comprises downregulation of the CDK1-cyclin B1 activity, which is accompanied by an increase in the activity of its counteracting phosphatase. One of the first events of mitotic exit is activation of the E3 ubiquitin ligase APC/C^{CDC20} upon satisfaction of the SAC. APC/C^{CDC20} mediates proteasomal degradation of cyclin B1, thereby initiating downregulation of CDK1 activity, and of securin/Pds1, an inhibitor of the protease separase/Esp1, thus allowing separase cleavage of cohesin rings and subsequent separation of sister chromatids. In budding yeast, Net1 phosphorylation by CDK1 with the mitotic cyclin Clb2 and by polo-like kinase Cdc5 initiates CDC14 release from the nucleolus in early anaphase, in a manner counteracted by $PP2A^{Cdc55}$. $PP2A^{Cdc55}$ inactivation itself leads to dephosphorylation of CDC14 on serine 429, a phospho-site thought to inhibit CDC14 phosphatase activity (Li *et al*, 2014; Touati *et al*, 2019). Hence, the early activation of CDC14 requires downregulation of $PP2A^{Cdc55}$, and this is mediated by separase in concert with Zds1/2 as part of the FEAR pathway (Queralt & Uhlmann, 2008). In fact, separase and Zds1/Zds2 facilitate CDK1-Clb2-mediated phosphorylation of Cdc55, altering the dynamic interaction between Net1 and $PP2A^{Cdc55}$ (Játiva *et al*, 2019). Furthermore, inhibition of nuclear $PP2A^{Cdc55}$ is needed for full APC/C^{CDC20} activation to foster Clb2 degradation and subsequent CDK1 inactivation (Rossio *et al*, 2013). In this way, budding yeast CDC14 takes center stage in the efficient inactivation of CDK1 activity at late anaphase, through dephosphorylation and activation of the CDK1-inhibitor Sic1, its transcription factor Swi5, and the APC/C-activator CDH1/Hct1 (Visintin *et al*, 1998; Jaspersen *et al*, 1999). The switch from APC/C^{CDC20} to $APC/C^{CDH1/Hct1}$ initiates a second wave of Clb2 degradation at the end of anaphase and expands the substrate spectrum toward additional mitotic regulators such as Polo-like kinases and Aurora kinases (Ipl1 in budding yeast) in order to enable mitotic exit. Since budding yeast CDC14 is the key phosphatase inactivating CDK1, strains expressing temperature-sensitive *CDC14* alleles arrest with high levels of mitotic Clb2 and persistent CDK1 activity in late anaphase when shifted to the restrictive temperature. Still, CDC14 is not the only phosphatase acting on mitotic phosphoproteins during mitotic exit in budding yeast. In fact, time-resolved phosphoproteome analysis has revealed that serine-directed CDC14 cooperates with threonine-directed $PP2A^{Cdc55}$ and $PP2A^{Rts1}$ phosphatases to modulate the sequential and ordered removal of specific phosphorylations (Touati *et al*, 2019).

Substrate dephosphorylation during budding yeast mitotic exit can be further dissected via a degron-tagged CDC14 that allows incomplete depletion, circumventing the mitotic exit failure associated with the complete inactivation of CDC14 and the subsequent persistence of substrate phosphorylation. Unexpectedly, this has shown additional phosphorylation events to occur during mitotic exit despite the decreases in CDK1, Plk1 (Cdc5), and Aurora kinase activity (Touati *et al*, 2018)—likely via activation of late mitotic kinases such as Mob1-Dbf2 and Mob2-Cbk1, which belong to the NDR (nuclear Dbf2-related) kinase family. These kinases facilitate chromosome segregation and cytokinesis. Interfering with the activity of CDC14, $PP2A^{CDC55}$ and $PP2A^{Rts1}$ does not only delay the overall protein dephosphorylation program during mitotic exit, but also restrains these concurrent late-mitotic phosphorylations, indicating that these phosphatases also participate in late mitotic kinase activation (Touati *et al*, 2019). $PP2A^{Rts1}$ may play a special role by positively regulating late Ipl1 (Aurora kinase) and NDR kinase activity

during mitotic exit, while $PP2A^{Cdc55}$ is particularly important for facilitating transient phosphorylation and dephosphorylation events. These include the above-mentioned temporary phosphorylation of Net1 by CDK1 and Cdc5 in response to the anaphase-specific attenuation of the Net1-$PP2A^{Cdc55}$ interaction, allowing activation of CDC14 through phosphorylation.

Budding yeast CDC14 has a key role in regulating the order of dephosphorylation events. Overall, serine-directed phospho-sites are dephosphorylated earlier than threonine-directed phospho-sites-in the budding yeast mitotic exit program, and partially depleting CDC14 disturbs this order, reflecting the preference of CDC14 of serine over threonine resides (Touati *et al*, 2018, 2019). On the other hand, even complete loss of $PP2A^{Cdc55}$ or $PP2A^{Rts1}$ activity only marginally alters the order of global dephosphorylation during mitotic exit. The fact that interfering with both CDC14 and $PP2A^{Cdc55}$ or CDC14 and $PP2A^{Rts1}$, respectively, enhances the mitotic exit delay compared to inhibiting each phosphatase individually, emphasizes that each of them makes unique contributions despite the high overlap of phospho-sites they target. This underscores the complexity of the budding yeast phosphatase network and the need to consider their combined effects for a more comprehensive understanding of mitotic regulation.

In fission yeast and higher eukaryotes, re-activation of the phosphatase PP2A is initiated as CDK1 activity drops due to the APC/C^{CDC20}-mediated degradation of cyclin B1. Henceforth, upon mitotic exit, PP1 can autocatalytically remove its inhibitory phosphorylations due to its stoichiometric advantage in relation to CDK1-mediated re-phosphorylation events (Grallert *et al*, 2015; Heim *et al*, 2015; Ma *et al*, 2016). Recovery of PP1 activity results in reversion of MASTL kinase autophosphorylation, which in turn triggers $PP2A^{B55}$ activation that subsequently completes MASTL dephosphorylation and inactivation as part of a positive feedback loop. The fast rate of TP site and slow rate of SP site dephosphorylation, reflecting the sequence preference of PP2A phosphatases, constitutes an essential regulatory element during mitotic exit in human cells, including the timely activation of the APC/C activators CDC20 and CDH1 (Fujimitsu *et al*, 2016; Qiao *et al*, 2016; Zhang *et al*, 2016; Hein *et al*, 2017). In particular, conserved inhibitory phosphorylations on CDC20 occur on threonines and are removed rapidly during mitotic exit, while CDH1 is inactivated by relatively long-lasting serine phosphorylations, ensuring its activation only in late mitosis (Hein *et al*, 2017).

In conclusion, yeast CDC14 is essential for CDK1 inactivation and cooperates with PP2A phosphatases to convey timely mitotic exit in budding yeast. On the other hand, although similar mitotic functions of the human paralogs CDC14A and CDC14B have been proposed, strong evidences instead suggest major roles of the phosphatases $PP2A^{B55}$, $PP2A^{B56}$, and PP1 in late mitotic events. Initial studies implicated human CDC14A in correct chromosome segregation and cytokinesis, while CDC14B was thought to be vital for mitotic exit (Mailand *et al*, 2002; Dryden *et al*, 2003). Contrary to these expectations, however, these results could not be confirmed when *CDC14A* or *CDC14B* was knocked out (Berdougo *et al*, 2008; Mocciaro *et al*, 2010). Furthermore, recent *CDC14A/CDC14B* double knockout studies in mice and human cell lines did not reveal any obvious cell division defects either, also ruling out possible cross-compensation of the CDC14 paralogs, and suggesting that PP2A and PP1 phosphatases mainly perform this mitotic exit function in higher eukaryotes (Partscht *et al*, 2021; Villarroya-Beltri *et al*, 2023). In line with this, okadaic acid and microcystins, potent inhibitors of PP1/PP2A but not of CDC14, block mitotic exit in higher eukaryotes (Picard *et al*, 1989; Félix *et al*, 1990; Yamashita *et al*, 1990; Lucocq, 1992; Potapova *et al*, 2011).

CDC14B is a key regulator of gene expression and cell fate

While mitotic exit in higher eukaryotes is mainly driven by PP2A/PP1 phosphatases, CDC14 functions have shifted to more specialized roles—so what particular role has CDC14B adapted to? This year, two independent studies elucidated CDC14B phosphatase substrates by mass-spectrometry, with one analyzing the global phosphoproteome of human somatic cells and the other analyzing mouse embryonic stem cells (ESCs). Both studies showed that CDC14B activity regulates gene expression and organizes chromatin (Partscht *et al*, 2023; Villarroya-Beltri *et al*, 2023). Among the identified CDC14B protein substrates was the key transcription factor MeCP2 that was subsequently verified as CDC14B target during prolonged mitosis in human RPE1 cells. CDC14B was demonstrated to counteract HIPK2 kinase phosphorylation of serine 92 of MeCP2 e1 isoform (corresponding to serine 80 of MeCP2 isoform e2), thereby modulating translation of cyclin B1 and in turn the sustainability of SAC-induced mitotic arrest (Partscht *et al*, 2023; Fig 2A).

A different context emerged for CDC14B-dependent gene regulation in mouse ESCs, where it targets the substrate UTF1 (undifferentiated embryonic transcription factor 1). CDC14B-mediated UTF1 dephosphorylation on serine residues 48 and 54 was shown to induce de-repression of bivalent promoters and exit from stemness (Villarroya-Beltri *et al*, 2023; Fig 2B). Another study identified the deubiquitinase USP9X as CDC14B substrate, thereby controlling

Figure 2. CDC14B as a regulator of gene expression with crucial role in controlling cell fate decisions.

(A) HIPK2 accumulates during prolonged mitosis to phosphorylate Ser92 of MeCP2-e1, thereby stimulating mitotic cyclin B1 translation. CDC14B counteracts this phosphorylation and additionally regulates cyclin B1 on the transcriptional level through a yet unknown mechanism. Cyclin B1 translation partly balances its slow degradation, until cyclin B1 decline rate levels fall below a threshold where there is CDK1-cyclin B1 activity insufficient to maintain the mitotic state. Hence, CDC14B activity decreases mitotic cyclin B1 expression leading to a less sustainable mitotic arrest which in turn accelerates mitotic slippage. (B) CDK1-cyclin A2 and ERK2 kinase activity maintains stemness along the neural lineage through phosphorylation of different epigenetic factors such as UTF1. During neural differentiation, CDC14A and CDC14B are transcriptionally upregulated. CDC14B regulates the stability of UTF1 by dephosphorylating serine residues 48 and 54, leading to its proteasomal degradation. UTF1 destabilization via CDC14B leads to de-repression of bivalent promoters that are crucial for differentiation into neural cells. To exit from stemness, pluripotency genes need to be downregulated in addition to the induction of developmental genes. CDC14B may additionally dephosphorylate other epigenetic regulators to control neural differentiation, and CDC14A phosphatase may play a role in this process as well. (C) CDK1-cyclin B1 and CDC14B control mitotic Ser2563 phosphorylation of USP9X deubiquitinase. Phosphorylated and activated USP9X deubiquitinates and stabilizes Wilms tumor protein 1 (WT1), a transcription factor for the interleukin IL-8. In this way, CDC14B negatively regulates mitotic transcription and secretion of IL-8, which may confer resistance to apoptosis via autocrine and paracrine signaling.

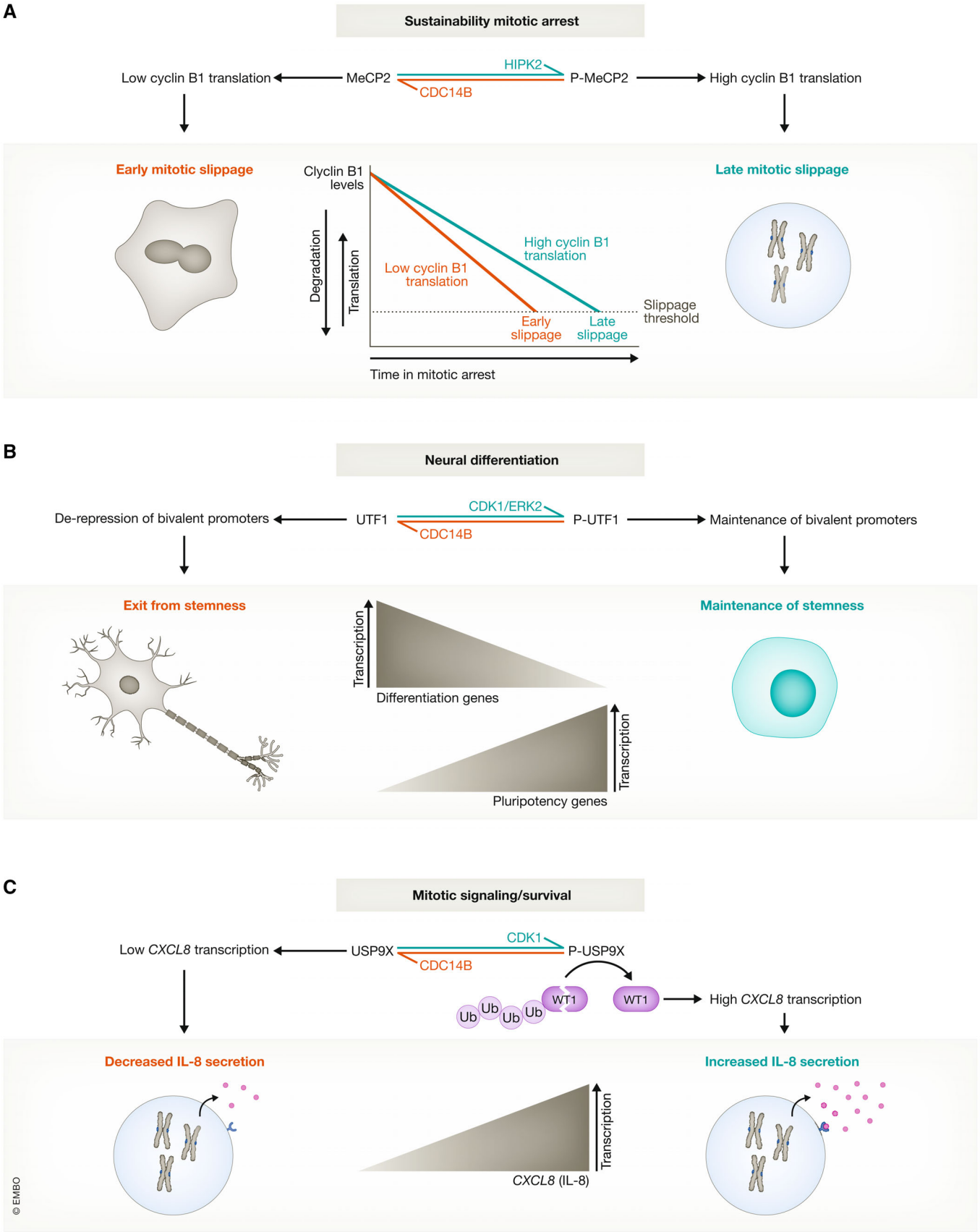

Figure 2.

stabilization of the transcription factor Wilms tumor protein 1 (WT1), which in turn promotes IL-8 expression to convey mitotic survival (Dietachmayr *et al*, 2020; Fig 2C). These new findings implicate CDC14B as crucial regulator of gene expression with a key role in controlling specific cellular processes. In the following sections, we will explore CDC14B functions in the mitotic checkpoint, neural development, and meiosis.

CDC14B reveals the crucial role of cyclin B1 translation for sustained mitotic arrest

The SAC surveys proper attachment of the mitotic spindle to chromosomes, and delays anaphase onset by inhibition of the APC/C E3 ligase until all microtubule fibers are properly attached to kinetochores. This surveillance mechanism halts mitotic progression in the instance of mitotic disturbances and is essential for ensuring that daughter cells receive the correct number of chromosomes. In the event of irresolvable spindle defects, however, the SAC-induced cell division block can no longer be sustained at a specific point in time, resulting either in apoptosis or mitotic slippage (Gascoigne & Taylor, 2008). While in apoptosis, a cell sacrifices itself for the benefit of the cell population, mitotic slippage is a phenomenon where the cell bypasses proper cell division and instead progresses into G1 without chromosome segregation, resulting in tetraploid G1 cells that in turn might promote genomic instability and oncogenesis (Fujiwara *et al*, 2005).

Sustainability of the SAC and its consequences for cell fate depends on progressive accumulation of apoptotic signals (including degradation of anti-apoptotic proteins such as MCL-1), and on the slow decay of the CDK1 activator cyclin B1 (Brito & Rieder, 2006; Gascoigne & Taylor, 2008; Allan *et al*, 2018). If apoptotic signals exceed a certain threshold while cyclin B level remains still above a critical level, the cell triggers apoptosis and undergoes mitotic cell death. Conversely, if cyclin B1 levels (and associated CDK1 activity) declines below the point where it can still maintain the mitotic state, the cell slips out of mitosis without cytokinesis and escapes mitotic cell death. Early investigations showed gradual proteasomal degradation of cyclin B1 as a consequence of APC/C^{CDC20} E3 ligase activity escaping SAC inhibition (Brito & Rieder, 2006). More recently, it was found that checkpoint inhibition of CDC20 during an extended mitotic arrest can be circumvented via translation of shorter CDC20 isoforms (Tsang & Cheeseman, 2023). Furthermore, the E3 ubiquitin ligase $CRL2^{ZYG\text{-}11}$ also initiates cyclin B1 degradation during prolonged mitosis and thereby facilitates mitotic slippage (Balachandran *et al*, 2016). As protein translation was thought to be generally inactive during mitosis, the impact of cyclin B1 synthesis on its turnover during prolonged mitosis was originally neglected; nevertheless, mitotic transcription is not globally inhibited, but continues for certain genes including *CCNB1*, which encodes cyclin B1 (Sciortino *et al*, 2001). Furthermore, other recent results suggest that the primary means of regulating mitotic gene expression may be through translational regulation (Tanenbaum *et al*, 2015).

CDC14B is crucial for determining sustainability of a mitotic arrest. Surprisingly, its activity does not impact a cell's ability to degrade cyclin B1 during arrest, but to synthesize it. In fact, CDC14B negatively regulates cyclin B1 expression on both the transcriptional and the translational level, and lack of its activity impedes mitotic slippage (Guillamot *et al*, 2011; Partscht *et al*, 2023). This finding emphasizes the importance of active translation of mitotic cyclin B1 in order to maintain a prolonged SAC and for delaying mitotic slippage. This previously neglected role of cyclin B1 translation in regulating mitosis may help to explain the substantial inter-cell-line variation among cancer cells in response to anti-mitotic treatment (Gascoigne & Taylor, 2008).

How CDC14B regulates transcription of cyclin B1 remains obscure, but it might involve the complex phosphorylation code on the RNA polymerase II C-terminal domain (CTD) (Guillamot *et al*, 2011). Still, CTD-Ser5 phosphorylation on its own is probably insufficient to modulate cyclin B1 transcription, at least in human RPE1 cells (Partscht *et al*, 2023). Downstream of gene transcription, CDC14B limits cyclin B1 translation by removing the HIPK2-mediated phosphorylation on Ser92 of MeCP2. In RPE1 cells, the normally unstable and stress-induced kinase HIPK2 was found to predominantly accumulate not upon DNA damage induction but during prolonged mitosis (Partscht *et al*, 2023). How cyclin B1 escapes global translation repression during mitosis and how the CDC14B/HIPK2-MeCP2 axis modulates remains to be determined.

CDC14B in neuronal development

The CDC14B substrates UTF1 and MeCP2 are both key transcriptional regulators of gene expression during neuronal development (Laskowski & Knoepfler, 2012; Cheng & Qiu, 2014; Gulmez Karaca *et al*, 2019; Raina *et al*, 2021). UTF1 is expressed during early embryonic development in pluripotent cells and maintains pluripotency by regulating bivalent gene expression. Human CDC14A and CDC14B phosphatases are both transcriptionally upregulated upon neuronal differentiation. As CDC14B becomes dispersed from the nucleolus, it dephosphorylates serine 48 and serine 54 of UTF1, promoting its proteasomal degradation via the SIAH and SPOP E3 ligases. In addition, CDC14 phosphatases downregulate UTF1 transcription by an unknown mechanism. Together, this leads to derepression of bi-valent promoters, allowing expression of genes important for exit from stemness and initiation of differentiation into neural progenitors (Villarroya-Beltri *et al*, 2023). Consequently, mice with deletions in *CDC14A* and *CDC14B* exhibit deficient neural differentiation associated with reduced brain size and structural defects of the cerebellum. The exact contribution of CDC14A to these phenotypes remains to be established. It is conceivable that CDC14A and CDC14B phosphatases dephosphorylate several epigenetic regulators to exit from stemness. This is supported by the observation that, in addition to UTF1, the epigenetic regulators DNMT3L, TET1 and TET2 are hyperphosphorylated in mouse ESCs that lack CDC14A and CDC14B (Villarroya-Beltri *et al*, 2023).

MeCP2 is another CDC14B substrate that is highly expressed in neurons and critical for both brain development and maintenance of mature neuronal networks (Skene *et al*, 2010; Nguyen *et al*, 2012). The importance of the X-linked MeCP2 in human brain maturation is highlighted by its association with Rett syndrome, a neurological disorder that mainly occurs in females and causes intellectual impairment, developmental regression, and motor dysfunction typically appearing after a period of normal development (Amir *et al*, 1999). In fact, Rett syndrome is (after Down syndrome) the leading cause of intellectual disability in females.

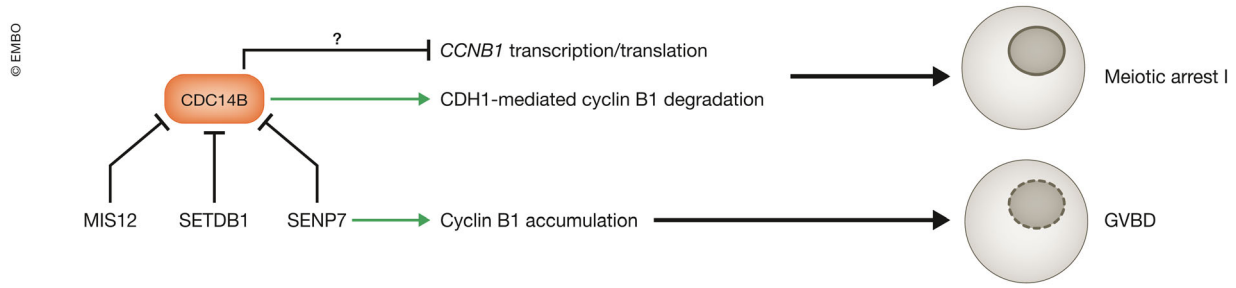

Figure 3. The role of CDC14B in regulating meiotic maturation of oocytes.
Mammalian oocytes undergo a prolonged arrest at the G2/prophase stage of meiosis I. CDC14B activity can dephosphorylate and activate the APC/C activator CDH1 at this stage, hence promoting cyclin B1 degradation and inhibiting germinal vesicle breakdown. Given the ability of CDC14B to regulate cyclin B1 synthesis in somatic cells, it is conceivable that CDC14B additionally negatively regulates cyclin B1 (*CCNB1*) transcription and translation to control meiotic resumption. MIS12 induced by a surge of hormones sequesters and inhibits CDC14B, allowing cyclin B1 accumulation and resumption of meiosis. CDC14B can additionally be repressed through the epigenetic regulators SETDB1 and SENP7. The question mark indicates that the molecular mechanism of transcriptional/translational regulation of *CCNB1* is not understood.

Phosphorylation of MeCP2 serine 80 (isoform e2) or serine 92 (e1 isoform), which is regulated by HIPK2 and CDC14B in mitotic RPE1 cells, is located near the methyl-CpG binding domain (MDB), and its dephosphorylation in mouse cortical neurons is associated with attenuated binding to chromatin (Tao *et al*, 2009). Nevertheless, despite its MDB proximity, Ser80 phosphorylation does not alter the overall MeCP2 binding ability to heterochromatin, but instead fine-tunes MeCP2 binding to a selected subset of promoters. Interestingly, Ser80 dephosphorylation depends on neuronal activity and promotes both transcriptional up- (56 genes) and downregulation (149 genes) of certain genes, including genes involved in synaptic function (Tao *et al*, 2009). In fact, membrane depolarization in response to neuronal excitation triggers phosphorylation of mouse MeCP2 on residues S86, T148, T149, S164, S229, S274, T308, S421 (corresponds to S423 in human) and S424 (corresponds to S426 in human), while S80 instead becomes dephosphorylated, implying MeCP2 phosphorylation as an important functional switch between the resting and firing state of a neuron (Tillotson & Bird, 2020). Since neuronal activity-mediated changes in gene expression are essential for neuronal survival and maturation, they are critical for learning, memory, and normal development. Consistently, knock-in mice expressing non-phosphorylatable MeCP2^{S80A} also display locomotor defects, a phenotype reminiscent of Rett symptoms, thus reflecting the important role of phosphorylation (Tao *et al*, 2009). While the identity of MeCP2 S80/92 kinase and phosphatase in activated neurons is unknown, it will be exciting to test whether it also involves MeCP2 phospho-regulation by HIPK2/CDC14; especially since HIPK2 loss in the midbrain was previously reported to results in increased apoptosis of dopaminergic neurons and behavioral deficits (Zhang *et al*, 2007).

CDC14B as the gatekeeper of meiotic arrest in oocytes

Meiosis is a developmental program in germ cells of sexually-reproducing organisms, which produces gametes, and it represents a survival mechanism in unicellular eukaryotes such as yeast. It involves a single round of DNA replication followed by two rounds of specialized cell divisions, called meiosis I and II. During meiosis I, the homologous chromosomes exchange genetic material through recombination, before they separate and the cells (while still retaining 2C DNA content) become haploid; meiosis II then separates sister chromatids. Most mammalian oocytes remain arrested at the G2/prophase stage of meiosis I for an exceptionally long time, known as the germinal vesicle (GV) because of the large nucleus of the oocyte. This arrest can last for years in mice and for decades in humans. A hormone surge and activation of CDK1-cyclin B1 (in this context originally called MPF or maturation promoting factor) initiates meiosis I resumption (marked by GV breakdown) (Masui & Markert, 1971; Smith & Ecker, 1971). To maintain the meiosis I G2/prophase arrest, CDK1 is kept inactive via inhibitory T14/Y15 phosphorylation by the oocyte-specific Wee1-like kinase Wee1B, as well as by APC/C^{CDH1}-suppressed cyclin B1 accumulation (Holt *et al*, 2011; Adhikari *et al*, 2016). This APC/C^{CDH1} activation during early meiosis I is a notable characteristic of mammalian oocytes that differs from mitosis (Homer *et al*, 2009). CDH1 appears to remain active during meiosis I arrest due to the removal of inhibitory phosphorylation by CDC14B, and because of downregulation of the CDH1 inhibitor EMI1 (Marangos *et al*, 2006; Schindler & Schultz, 2009; Fig 3). In addition, mouse oocytes depleted of the kinetochore protein MIS12 show impaired meiotic I G2/M transition since they fail to accumulate cyclin B1 (Bai *et al*, 2020). Overexpression of cyclin B1 or depletion of CDC14B rescues the MIS12 depletion phenotype, implying a non-canonical function of MIS12 as a negative regulator of CDC14B activity in early meiosis. MIS12 also does not show kinetochore localization in mouse oocytes as in case of somatic cells and therefore is not important for spindle organization and meiotic progression after the G2/M transition. It has been speculated that CDC14B is sequestered and inactivated by cytosolic MIS12, in a manner comparable to Net1-mediated nucleolar sequestration of budding yeast CDC14, but the underlying mechanism has yet to be elucidated (Bai *et al*, 2020). In addition, it will be interesting to see whether the meiotic MIS12-CDC14B axis also regulates cyclin B1 on the level of transcription and translation, as the case in prometaphase arrested somatic cells (Partscht *et al*, 2023).

Apart from the proposed inhibitory MIS12 activity toward CDC14B during germinal vesicle breakdown, meiotic CDC14B expression has also been found to be modulated by SETDB1

and SENP7 activity (Kim *et al*, 2016; Huang *et al*, 2017). The methyltransferase SETDB1 mediates H3K9 trimethylation at the *CDC14B* gene locus, thereby downregulating its transcription and alleviating meiotic I arrest (Kim *et al*, 2016). The deSUMOylase SENP7 can also epigenetically modify histone H3 during oocyte development, but how exactly it affects *CDC14B* expression and whether this is really a direct effect remains to be determined (Huang *et al*, 2017).

In budding yeast, inactivation of CDC14 leads to failure of meiosis and uncoupling of meiotic events, noticeable the occurrence of only a single meiotic division with a mixture of chromosomes segregating reductionally (meiosis-I like) and equationally (meiosis-II like) (Sharon & Simchen, 1990; Marston *et al*, 2003). Interestingly, while the MEN network mainly functions in spore morphogenesis during budding yeast meiosis, the FEAR pathway takes center stage here by controlling CDC14 release and CDK1 inactivation, resulting in reduced CDC14 activation and higher CDK1 activity compared to the exit from mitosis (Kamieniecki *et al*, 2005; Pablo-Hernando *et al*, 2007). This might reflect the fact that after meiotic exit, residual CDK1 activity is necessary to prevent inappropriate S phase initiation between meiosis I and meiosis II. Furthermore, CDC14-mediated activation of the Yen1 resolvase, important for resolving persistent repair intermediates that could otherwise hinder chromosome segregation during budding yeast mitotic exit, has also been implicated in ensuring faithful meiotic recombination and crossover formation (García-Luis *et al*, 2014; Alonso-Ramos *et al*, 2021).

Final remarks and conclusions

In the model organism *S. cerevisiae*, the CDC14 phosphatase is critical for mitotic exit and cytokinesis. In higher eukaryotes, the phosphatases PP2A and PP1 appear to be the major CDK1 counteracting phosphatases that drive mitosis, while the paralogous CDC14 homologs CDC14A and CDC14B have taken over more specialized cell-cycle roles (Berdougo *et al*, 2008; Partscht *et al*, 2021; Villarroya-Beltri *et al*, 2023). This raises the question of how human cells exit mitosis without the involvement of the phosphoserine-specific phosphatases like CDC14. Slow turnover of phosphoserine residues by phosphoprotein phosphatases is probably used to delay dephosphorylation of phosphoserine sites compared to phosphothreonine residues (Holder *et al*, 2019).

CDC14B controls regulators of gene expression and epigenetics, thereby impacting cell fate and development as outlined in Fig 2 (Dietachmayr *et al*, 2020; Partscht *et al*, 2023; Villarroya-Beltri *et al*, 2023). Given the multiple roles of MeCP2 in development and tissue homeostasis, and the requirement of WT1 for kidney and gonads development, it is tempting to speculate that CDC14B also plays a crucial role in processes beyond neural differentiation (Nguyen *et al*, 2012; Bian *et al*, 2013; Hastie, 2017). Recent evidence indicates that HIPK2 phosphorylates MeCP2-e2 on Ser80 when hepatic stellate cells trans-differentiate into myofibroblasts (Moran-Salvador *et al*, 2019). Transdifferentiation of hepatic stellate cells is induced upon liver damage in order to produce extracellular matrix and can lead to fibrosis if hepatic stellate cell activation persists. It will be interesting to see whether CDC14B counteracts MeCP2 phosphorylation also here, as in the case in mitotic RPE1 cells (Partscht *et al*, 2023). Furthermore, considering the ability of CDC14B to impede CDK1-cyclin B1 activity, which can cause unscheduled increase of the cell's ploidy, one might speculate that CDC14B could contribute to programmed polyploidization during specific developmental processes (Guillamot *et al*, 2011; Partscht *et al*, 2023). Polyploidy—such as observed in liver (hepatocytes), bone marrow (megakaryocytes), heart (cardiomyocytes), placenta (trophoblast giant cells), and pancreas (acinar cells)—emerges from various origins and can have different developmental significance (Gjelsvik *et al*, 2019; Donne *et al*, 2020), and in certain cases, reducing CDK1-cyclin B1 activity might be sufficient to increase cellular ploidy (Diril *et al*, 2012; Edgar *et al*, 2014; Øvrebø & Edgar, 2018).

CDC14B regulates meiotic oocyte arrest by controlling the stability of cyclin B1 during the meiotic phase (Bai *et al*, 2020; Subramanian *et al*, 2020), and CDC14B activity is negatively regulated by MIS12, SETDB1 and SENP7 (Fig 3; Kim *et al*, 2016; Huang *et al*, 2017; Bai *et al*, 2020). However, further research is needed to understand how CDC14B is regulated beyond meiosis, into which we currently have little insight. This would help to understand how CDC14B controls specialized cell cycle programs.

In conclusion, the essential cell cycle functions of budding yeast CDC14 have turned out not to be conserved in humans, despite a highly conserved catalytic domain (Bremmer *et al*, 2012). How this divergence of CDC14-involving signaling networks arose is therefore an interesting question to consider. The presence of redundant phosphatases probably helped to diversify CDC14 function. While there may still not be a definitive answer, it is likely that changes in CDC14's regulation and localization pattern led to a change in its substrates and thus function(s). Conversely, it might be that the substrates and interaction partners of CDC14 diverged in their regulation, localization, and function. Further studies are needed to elucidate the evolutionary history and functional variation of this important family of phosphatases.

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Author contributions

Patrick Partscht: Conceptualization; visualization; writing – original draft.
Elmar Schiebel: Conceptualization; funding acquisition; writing – original draft.

Disclosure and competing interests statement

The authors declare that they have no conflict of interest.

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