Critical Reviews in Biochemistry and Molecular Biology

ISSN: 1040-9238 (Print) 1549-7798 (Online) Journal homepage: http://www.tandfonline.com/loi/ibmg20

PP2A as a master regulator of the cell cycle

Nathan Wlodarchak & Yongna Xing

To cite this article: Nathan Wlodarchak & Yongna Xing (2016) PP2A as a master regulator of the cell cycle, Critical Reviews in Biochemistry and Molecular Biology, 51:3, 162-184, DOI: 10.3109/10409238.2016.1143913

To link to this article: http://dx.doi.org/10.3109/10409238.2016.1143913

Critical Reviews in Biochemistry and Molecular Biology

http://informahealthcare.com/bmg
ISSN: 1040-9238 (print), 1549-7798 (electronic)
Editor: Michael M. Cox
Crit Rev Biochem Mol Biol, 2016; 51(3): 162–184
© 2016 Taylor & Francis. DOI: 10.3109/10409238.2016.1143913

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

PP2A as a master regulator of the cell cycle

Nathan Wlodarchak and Yongna Xing

McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, WI, USA

Abstract

Protein phosphatase 2A (PP2A) plays a critical multi-faceted role in the regulation of the cell cycle. It is known to dephosphorylate over 300 substrates involved in the cell cycle, regulating almost all major pathways and cell cycle checkpoints. PP2A is involved in such diverse processes by the formation of structurally distinct families of holoenzymes, which are regulated spatially and temporally by specific regulators. Here, we review the involvement of PP2A in the regulation of three cell signaling pathways: wnt, mTOR and MAP kinase, as well as the G1→S transition, DNA synthesis and mitotic initiation. These processes are all crucial for proper cell survival and proliferation and are often deregulated in cancer and other diseases.

Keywords

Cancer, cell cycle, cell division, mitosis, phosphatase, PP2A

History

Received 30 October 2015
Revised 28 December 2015
Accepted 4 January 2016
Published online 15 February 2016

Introduction

Numerous proteins are involved in regulating the complex processes in cell division, and kinases and phosphatases are the primary regulators. Several kinases and phosphatases are well understood and reviewed in detail (Belle *et al*., 1990; Bononi *et al*., 2011; Fisher *et al*., 2012; Holt, 2012; Hunter, 1995; Mochida & Hunt, 2012). It is clear from early work that the initial focus on cell cycle regulation was kinases, and phosphatases were thought of merely as housekeeping enzymes. More recently, phosphatases are increasingly appreciated for their tight regulation and specific action on key players in the cell cycle (Janssens & Goris, 2001; Virshup & Shenolikar, 2009). One of the most versatile and important phosphatases involved in cell division is protein phosphatase 2A (PP2A). PP2A regulates every stage of the cell cycle in several critical pathways and, not surprisingly, has been widely implicated in tumor suppression (Eichhorn *et al*., 2009). As such, PP2A is being actively investigated as a therapeutic target (Sangodkar *et al*., 2015). This review is an attempt to aggregate the numerous substrates dephosphorylated by PP2A and discuss its regulatory activity in major pathways at each stage of the cell cycle.

Protein phosphatase 2A: a complex and diverse family of phosphatases

Background

Eukaryotic phosphatases can be divided into three super families: the serine/threonine phosphatases (PSPs), the tyrosine phosphatases (PTPs) and the dual specificity phosphatases (DSPs) [reviewed in (Hunter, 1995; Shi, 2009; Virshup & Shenolikar, 2009)]. There are around 100 PTPs, approximately equivalent to the number of tyrosine kinases in the genome. Over 400 serine/threonine kinases are expressed in the human proteome (Manning *et al*., 2002), exceeding that of PSPs by more than 10 fold. Serine/threonine phosphorylation constitutes more than 98% of total protein phosphorylation inside mammalian cells; however, the number of genes encoding PSPs (7) is very small. This controversy is reconciled by the fact that some of the PSPs form a large number of diverse oligomeric complexes. In particular, PP2A forms ∼100 heterotrimeric holoenzymes and protein phosphatase 1 (PP1) forms ∼400 heterodimeric holoenzymes. Some kinases also form oligomeric complexes, such as cell cycle dependent kinases (CDKs) and mTOR, on a scale much smaller than PP2A and PP1 though, underlying that complex and tight control of both kinases and phosphatases are important for cellular processes.

The PSPs are further divided into three families: phosphoprotein phosphatases (PPPs), metal-dependent protein phosphatases (PPMs) and aspartate-based phosphatases (Figure 1). The PPP family is the largest family of phosphatases, and many PPPs are involved in cell cycle regulation, including PP2A (Hunter, 1995; Shi, 2009; Virshup & Shenolikar, 2009). The PPP family phosphatases have a structurally conserved active site configuration. Two catalytic metal ions are coordinated by six conserved residues [two aspartate (D), one asparagine (N) and three histidine (H) residues], and a catalytic water molecule. Phosphate binding is coordinated by one conserved histidine and two arginine (R) residues. The dephosphorylation reaction proceeds via an S_N2 mechanism with the activated water serving as a nucleophile to attack the phosphate group attached to Ser or Thr residues (Shi, 2009). PP2A is one of the most complex members in the PPP family,

Address for correspondence: Yongna Xing, 6451 Wisconsin Institutes for Medical Research II, 1111 Highland Ave, Madison, WI 53705, USA. Tel: +1 608-262-8376. E-mail: xing@oncology.wisc.edu

regulating diverse physiological and cellular processes such as neuronal stabilization, cardiac muscle function and the cell cycle. As such, it is implicated in many human diseases such as Alzheimer's disease, cardiac disease and cancer (Eichhorn *et al*., 2009; Heijman *et al*., 2013; Kotlo *et al*., 2012; Martin *et al*., 2013). PP2A affects such variety of processes due to the formation of diverse heterotrimeric holoenzymes.

Regulation and activation of PP2A

Each PP2A holoenzyme is formed by a combination of three subunits: a common catalytic (C or PP2Ac) subunit containing the active site, a regulatory (B) subunit which confers substrate specificity and a common scaffolding (A) subunit that holds B and C together (Xu *et al*., 2006). There are two isoforms, α and β, for both A and C, and they share high sequence homology. The α isoform for each is expressed at a much higher level and is the predominant isoform studied in PP2A research. In addition to A and B subunits, cellular PP2Ac is also found associated with α4 protein and TOR Signaling Pathway Regulator-like (TIPRL) (Nakashima *et al*., 2013). Extensive efforts on understanding the structural and biochemical basis of PP2A regulation illuminated a linear pathway for the biogenesis of PP2A holoenzymes (Figure 2). The exact function of α4 on PP2Ac has been difficult to unravel. Our recent structural evidence suggests it preferentially binds to the partially folded PP2Ac and stabilizes it for stable latency (Jiang *et al*., 2013). α4 stabilizes PP2Ac in part by protecting it from ubiquitination by Midline 1 (MID1) and preventing its subsequent degradation (Liu *et al*., 2001; Short *et al*., 2002). This provides a pool of latent PP2Ac for the biogenesis of diverse heterotrimeric holoenzymes while simultaneously preventing the unregulated phosphatase activity of free PP2Ac and protecting cells from non-targeted dephosphorylation (Jiang *et al*., 2013).

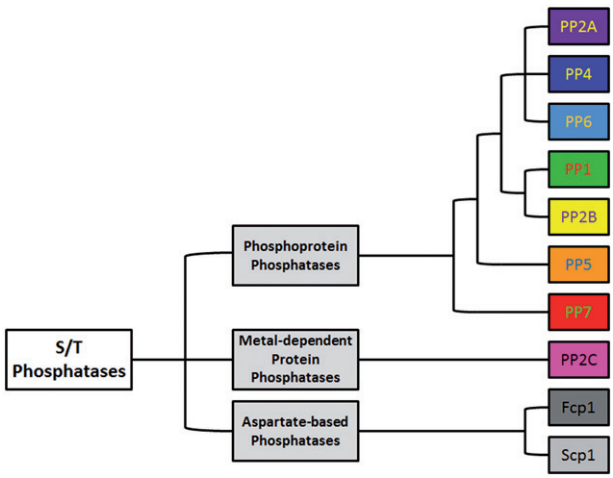

Figure 1. Serine/threonine phosphatases are classified based on biochemical mechanism. They are divided into three families, the aspartate-based phosphatases, the metal-dependent protein phosphatases and the phosphoprotein phosphatases. The phosphoprotein phosphatases have similar active site configurations and require catalytic metal ions in the active site. PP2A is a member of this family. Adapted from Stanevich (2013). (see colour version of this figure at www.informahealthcare.com/bmg).

Consequently, PP2A must be activated before being assembled into active holoenzymes. The phosphotyrosyl phosphatase activator (PTPA), now known as PP2A-specific phosphatase activator, plays a critical role in PP2A activation (Guo *et al*., 2014). PTPA stabilizes an active conformation of the active site and facilitates the loading of catalytic metal ions (Guo *et al*., 2014). PP2A together with PTPA forms a combined ATP-binding pocket, which orients the γ-phosphate of ATP to directly chelate catalytic metal ions. Following activation, the phosphatase active site catalyzes ATP hydrolysis. This is crucial for efficient loading of authentic catalytic metal ions and acquisition of pSer/Thr-specific phosphatase activity (Guo *et al*., 2014). Evidence suggests there is a Zn^{2+} ion in the active site and that ATP is required to load a

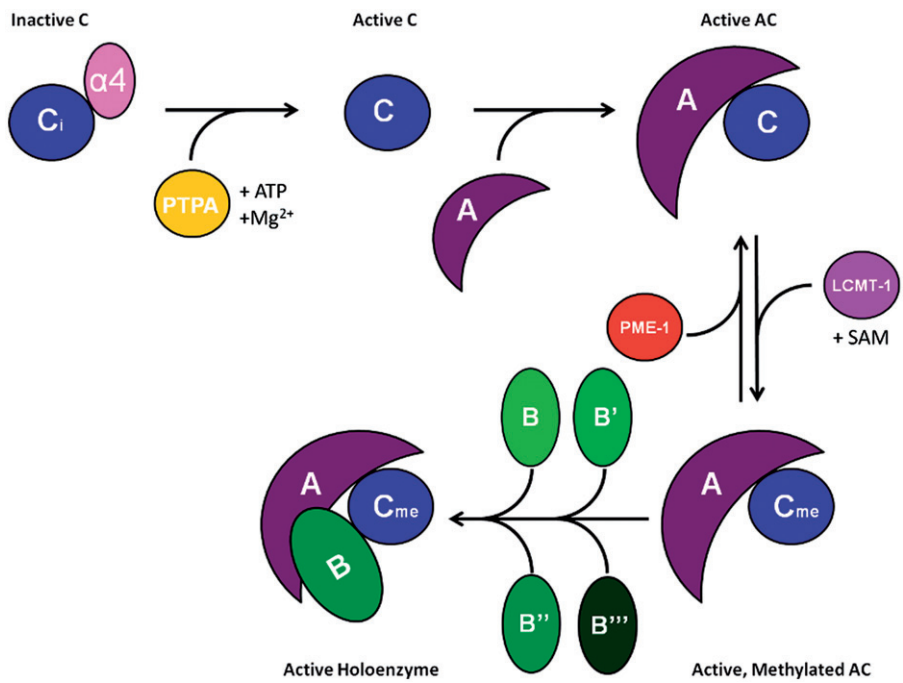

Figure 2. PP2A biogenesis and holoenzyme assembly is regulated by unique factors. α4 protects inactive PP2Ac from ubiquitination by MID1. Activating metal ions are loaded by PTPA, and active PP2Ac binds to the scaffold subunit (A). The C-terminal tail of PP2Ac can be methylated by LCMT-1 and reversed by PME-1. Active, methylated PP2A-AC can then form holoenzymes with one B subunit. These available B subunits are divided into four families: B, B′, B″ and B‴, each with unique characteristics and regulation. (see colour version of this figure at www.informahealthcare.com/bmg).

Mg^{2+} ion into the second position to activate PP2A (Guo *et al*., 2014).

PP2Ac also undergoes post-translational modification on its unstructured carboxy-terminal tail (Janssens *et al*., 2008; Lee & Pallas, 2007); phosphorylation on T304 and Y307 and carboxymethylation on L309 (Low *et al*., 2014). The latter is reversibly controlled by PP2A-specific methyltransferase known as leucine carboxy methyltransferase (LCMT-1), and by PP2A-specific methylesterase 1 (PME-1) (Stanevich *et al*., 2011; Xing *et al*., 2008). PP2A methylation is essential for cellular function, and cells will undergo apoptosis in the absence of LCMT-1 (Lee & Pallas, 2007). Reduction in LCMT-1 expression or over-expression of PME-1 can promote transformation through Akt or S6K pathways (Jackson & Pallas, 2012). Methylation is crucial for the formation of stable heterotrimeric B/PR55 family holoenzymes inside cells (Longin *et al*., 2007), but it is not required for *in vitro* assembly nor is the carboxymethylated PP2Ac tail visible in the PP2A-Bα structure (Xu *et al*., 2008). Carboxymethylation is also not required for *in vitro* assembly of PP2A-B′ holoenzymes, but B′ holoenzyme structures show the carboxymethylated tail is situated in an area between the A–B interface with several negatively charged residues, suggesting a possible role of methylation in charge neutralization (Cho & Xu, 2007; Xu *et al*., 2006). Although PP2Ac carboxymethylation is not strictly required for holoenzyme assembly *in vitro*, it is clearly required for proper *in vivo* holoenzyme assembly (Lee & Pallas, 2007; Mumby, 2001). PP2Ac methylation also fluctuates during the cell cycle, indicating that regulation of PP2Ac methylation and holoenzyme assembly is required for cell cycle regulation (Janssens *et al*., 2008; Yu *et al*., 2001).

Structural diversity of holoenzymes

Protein phosphatase 2A (PP2A) can act on a wide range of substrates via its diverse holoenzymes, each containing a distinct B subunit from four families: the B (PR55), B′ (PR56), B″ (PR72) and B‴ (Striatin) (Shi, 2009). Currently, the identified regulatory subunits are encoded by 15 genes which can be alternatively spliced to yield 26 different B subunits (Eichhorn *et al*., 2009). A summary of subunit nomenclature can be found in Table 1. These subunits share sequence homology within each family, but have little-to-no sequence homology between the families (Eichhorn *et al*., 2009). No specific ‘‘recognition motif’’ has been identified for PP2A substrates, and the recognition is likely due to structural elements inherent to each subunit. The structure of the core dimer of PP2A revealed important insights on how holoenzyme assembly and activity are regulated (Xing *et al*., 2006). The core of PP2Ac contains two central β-sheets flanked by α-helices, with the loops connecting to the β-sheets forming the active site, and the active site loops harbor six conserved residues that chelate catalytic metal ions. The active site loops are highly dynamic (Guo *et al*., 2014; Jiang *et al*., 2013). As such, all holoenzyme (and core enzyme) structures solved to date required potent inhibitors such as microcystin LR (MCLR) or okadaic acid (OA) to stabilize the active site for crystallization (Wlodarchak *et al*., 2013; Xing *et al*., 2006; Xu *et al*., 2006,2008,2009).

The A-subunit consists of 15 Huntington-elongation-A-subunit-TOR (HEAT) repeats arranged in a horseshoe shape. PP2Ac binds to the ridge region of repeats 10–15 and the regulatory subunits bind to the ridge of the N-terminal repeats. The A-subunit can undergo a large degree of conformational changes, explaining how so many structurally diverse B subunits can form active holoenzymes with the same A-C dimer (Wlodarchak *et al*., 2013). The B′γ1 holoenzyme was the first holoenzyme structure solved (Xu *et al*., 2006). Similar to the A-subunit, the B′γ1 subunit is also a HEAT repeat protein. The structure of the Bα holoenzyme demonstrated a much wider conformation for the A-subunit than the B′ holoenzyme, with little interaction between the B and C subunits (Xu *et al*., 2008). The Bα subunit is a 7-bladed β-propeller with a hairpin that extends to interact with the side face of the N-terminal HEAT repeats of the A-subunit (Xu *et al*., 2008). Recently, the high-resolution structure of a B″ holoenzyme associated with PR70 and two structures of B″ family subunits in isolation were finally solved (Dovega *et al*., 2014; Wlodarchak *et al*., 2013). These structures show that the B″ subunits are distinct from other families and consist of a multi-domain arrangement with two prominent calcium binding EF hands and a hydrophobic interacting motif. One of the EF hands directly contacts the top ridge of the scaffold subunit and is important for A–B″ binding (Dovega *et al*., 2014; Wlodarchak *et al*., 2013). The N-terminal hydrophobic motif binds to the N-terminal side surface of the A-subunit while the C-terminal domain interacts with PP2Ac. These tripartite contacts between AC and PR70 force the A-subunit into a tight conformation, and this is required for enhanced substrate-specific dephosphorylation (Wlodarchak *et al*., 2013). These observations suggest that precise orientation of substrates is dependent on subtle structural features and compact conformation of the holoenzymes derived from large conformational changes in the

Table 1. A summary of PP2A subunit nomenclature.

PP2A subunit family	Protein name/isoform	Other names
A	Aα	PR65α
	Aβ	PR65β
B/PR55	Bα	B55α/PR55α
	Bβ1	B55β1/PR55β1
	Bβ2	B55β2/PR55β2
	Bγ	B55γ/PR55γ
	Bδ	B55δ/PR55δ
B′/PR61	Bα	B56α/PR61α
	Bβ	B56β/PR61β
	B′γ1	B56γ1/PR61γ1
	B′γ2	B56γ2/PR61γ2
	B′γ3	B56γ3/PR61γ3
	B′δ	B56δ1/PR61δ
	B′ε	B56ε/PR61ε
B″/PR72	B″α	PR130
	B″α	PR72
	B″β	PR70
	B″γ	G5PR
B‴/Striatin	B‴	Striatin
C	Cα	PP2Acα
	Cβ	PP2Acβ

There is a variety of abbreviations used for protein subunits in the PP2A field. Many regulatory subunits have splicing variants, such as Bβ and B′γ. Note that not all of them are shown. Table adapted from Van Kanegan & Strack (2009).

A-subunit. Future structural and functional studies are required to illuminate these mechanisms in more detail.

Given the diversity of holoenzyme structures, it is no surprise that PP2A has been suggested or confirmed to dephosphorylate over 300 substrates (Table 2). Most of these substrates are involved in cell cycle regulation, and although some of PP2A-mediated dephosphorylation cause positive regulation of proliferation pathways, the majority of PP2A-mediated dephosphorylation events play a negative regulatory role. PP2A is implicated in a wide array of human diseases due to its prominent function in the cell cycle and many other essential cellular processes.

The cell cycle initiation: signaling pathways

The initiation of the cell cycle is controlled by many diverse and complex signaling pathways. There is a large and incredibly detailed body of information on each of these signaling pathways elsewhere. Presented here is a brief review on three critical signaling pathways, Wnt, mTOR and MAPK, with a focus on the role of PP2A in their regulation.

Wnt signaling pathway

The Wnt pathway is involved in the regulation of cell proliferation and polarity as well as embryonic development. It facilitates the initiation of the cell cycle by activating the transcription of critical promoters of cell division such as cyclin D1 and c-Myc (He *et al*., 1998; Rimerman *et al*., 2000). In the absence of Wnt signaling (Figure 3A), the protein β-catenin is degraded by the action of a complex composed of axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1) [reviewed in Clevers & Nusse (2012) and MacDonald *et al*. (2009)]. GSK3β and CK1 phosphorylate β-catenin, targeting it for ubiquitination and proteasomal degradation (Amit *et al*., 2002; van Noort *et al*., 2002). APC and axin have unique domains that bind to CK1 and GSK3β to serve as scaffolds to increase β-catenin phosphorylation, and these scaffolds are often found mutated in cancers (Dajani *et al*., 2003; Kinzler *et al*., 1991; Nishisho *et al*., 1991). Wnt signaling (Figure 3B) is activated when extracellular Wnt binds to the receptor frizzled and co-receptor LRP 5/6. An intracellular complex is then formed with the receptors disheveled, axin, CK1 and GSK3β, which then prevents the phosphorylation and subsequent degradation of β-catenin (Julius *et al*., 2000). β-Catenin can then accumulate in the nucleus and bind to TCF family transcription factors and activate Wnt responsive genes (Behrens *et al*., 1996). These include critical promoters of cell division such as cyclin D1 and c-Myc (He *et al*., 1998; Rimerman *et al*., 2000).

β-Catenin is the central substrate in Wnt signaling, and its regulation is highly dependent on phosphorylation and dephosphorylation. The phosphorylation events are sequential, with CK1 phosphorylating S45 followed by GSK3β phosphorylating T41, S37 and S33 (Amit *et al*., 2002; van Noort *et al*., 2002). Phosphorylation at S37 and S33 allows the ubiquitin ligase β-transducin repeat containing protein (β-TRCP) to bind β-catenin and target it for degradation (Latres *et al*., 1999). In addition to phosphorylating β-catenin, CK1 and GSK3β can phosphorylate APC and axin which increases the affinity of β-catenin for these scaffolds (Ferrarese *et al*., 2007; Ha *et al*., 2004; Jho *et al*., 1999). These phosphorylation events are disrupted when the complex is perturbed by Wnt signaling. β-catenin, APC and axin can be dephosphorylated by phosphatases such as PP2A and PP1, and this event can also increase β-catenin levels. PP1 increases β-catenin levels by dephosphorylating axin which reduces its affinity for GSK3β (Luo *et al*., 2007). Unlike PP1, PP2A has a dual and opposing role in β-catenin regulation (Figure 3). The PP2A-Bα holoenzyme has been shown to directly interact with and dephosphorylate β-catenin to enhance Wnt signaling (Zhang *et al*., 2009). In addition to dephosphorylating the residues relevant to destruction, this holoenzyme can also dephosphorylate residues S552 and S675, the functionality of which has yet to be elucidated (Zhang *et al*., 2009). The B55α holoenzyme can also directly bind axin, likely through a different domain than the one that PP2Ac can bind (Zhang *et al*., 2009). In contrast, the PP2A B′α holoenzyme has been implicated in negative regulation of Wnt signaling (Figure 3). B′α can bind to the destruction complex through APC. Overexpression of B′α results in decreased β-catenin levels and the amino terminus of β-catenin being required for this effect (Seeling *et al*., 1999). In addition to β-catenin regulation, PP2A negatively regulates Wnt signaling through GSK3β both directly and indirectly (Figure 3). GSK3β is inhibited by phosphorylation on S9 by AKT (Leung-Hagesteijn *et al*., 2001). DNAJB6 with Heat Shock Cognate 40 (HSC40) can recruit PP2A to GSK3β where it can directly dephosphorylate S9 and activate GSK3β (Mitra *et al*., 2012), which targets more β-catenin for destruction (Kumar *et al*., 2012). PP2A also inhibits Protein Kinase B (AKT or PKB) (Kumar *et al*., 2012), which indirectly activates GSK3β by downregulating phosphorylation on S9. This pathway also provides an important intersection with the mTOR pathway, another critical cell cycle initiating pathway.

Mechanistic target of rapamycin (mTOR)

The mTOR pathway is involved in many diverse cellular processes. It is stimulated by amino acids, cellular metabolism, and growth factors, and results in increased growth, metabolism and biomolecule synthesis (Laplante & Sabatini, 2012). These are crucial for accumulating enough cellular components required for cell division. Due to the multifaceted role of mTOR in cell regulation, it is an intensely studied pathway with major implications in cancer, heart disease and even some neurological diseases such as autism (Chen *et al*., 2014; Fruman & Rommel, 2014; Laplante & Sabatini, 2012; Sciarretta *et al*., 2014;). Rapamycin was known to have toxic effects on yeast, and the responsible genes (DDR1&2/TOR1&2) were discovered in 1993, with the protein being discovered 1 year later (Brown *et al*., 1994; Cafferkey *et al*., 1993; Kunz *et al*., 1993). Two complexes are formed with the mTOR catalytic protein: mTORC1 and mTORC2 (Shimobayashi & Hall, 2014). Both complexes contain some shared as well as some unique components. The shared components are the tti1 and tel2 scaffolds, deptor and mLST8 (Shimobayashi & Hall, 2014). mTORC1 contains the unique proteins raptor and pras40, whereas mTORC2 contains

Table 2. PP2A-interacting proteins identified by literature and database searches. Reviews, Pubmed and Biogrid (Chatr-Aryamontri *et al*., 2015) results are presented.

Interacting proteins	B subunit	PhosphoSite	Interaction boundary	References
ADCY8	–	–	–	(Crossthwaite *et al*., 2006)
ADRA1A	–	–	–	(Krueger *et al*., 1997)
AKAP9	PR130	–	–	(Takahashi *et al*., 1999)
AKT	Bα	T308	–	(Kuo *et al*., 2008)
APC	B′, B‴	bCatenin, -	302–625, 188–774	(Breitman *et al*., 2008; Galea *et al*., 2001)
AP1M1	Bα	T156	–	(Ricotta *et al*., 2008)
APP	B′γ, B′ε	–	–	(Olah *et al*., 2011)
AR	–	–	–	(Yang *et al*., 2007)
ARL2	Bα	–	–	(Shern *et al*., 2003)
ATM	–	S1981	2427–2841	(Goodarzi *et al*., 2004)
ATR	–	–	–	(Kim *et al*., 1999)
ATXN7L2	PR72	–	–	(Lim *et al*., 2006)
AURKA	–	S51	46–56	(Horn *et al*., 2007)
AXIN1	B′α	–	595–726	(Arnold *et al*., 2009; Yamamoto *et al*., 2001)
BANF1-ANKLE4	Bα	–	59–938	(Asencio *et al*., 2012)
ARRB2	–	–	–	(Beaulieu *et al*., 2005)
BAX	–	S184	–	(Xin & Deng, 2006)
BAZ	B′	S1085	–	(Krahn *et al*., 2009)
BCL2	B′γ	T69, S70, S87	–	(Lin *et al*., 2006)· (Ruvolo *et al*., 2008)
BEST1	–	–	–	(Marmorstein *et al*., 2002)
BLNK	Bγ	–	–	(Oellerich *et al*., 2011)
BRCA1	B′γ	–	–	(Woods *et al*., 2012)
BUBR1	B′	–	630–720	(Xu *et al*., 2013)
CACNA1C	Bα, Bβ, PR70	S1928	1927–2029	(Hall *et al*., 2006)
CACNA1S	Bα	–	–	(Kristensen *et al*., 2012)
CAPN1	–	–	–	(Hall *et al*., 2006)
CAMK4	–	–	–	(Westphal *et al*., 1998)
CAMK2B	–	T253	–	(Hoffmann *et al*., 2005)
CPD	–	–	–	(Varlamov *et al*., 2001)
CAS	–	–	–	(Yokoyama & Miller, 2001)
CASP3	–	–	–	(Alvarado-Kristensson & Andersson, 2005)
CBX1	–	–	–	(Nozawa *et al*., 2010)
CCNG1	B′α	–	–	(Okamoto *et al*., 1996,2002)
CCNG2	B′β, B′γ	–	–	(Bennin *et al*., 2002)
CCT2	Bγ	–	–	(Glatter *et al*., 2009)
CDCA2 (repoman)	B′α	S893	586–595	(Qian *et al*., 2013)
CDC25	B′	T138	–	(Lammer *et al*., 1998; Margolis *et al*., 2003,2006a,b)
CDC6	PR70	S54/S74	49–90	(Davis *et al*., 2008; Petersen *et al*., 1999; Wlodarchak *et al*., 2013)
CDH1 (e-cadherin)	–	–	–	(Gotz *et al*., 2000)
CDK16	Bα	–	–	(Varjosalo *et al*., 2013a)
CDK 4	–	–	–	(Sablina *et al*., 2007)
CDK5R1	B′δ	–	–	(Louis *et al*., 2011)
CDK9	–	–	–	(Ammosova *et al*., 2005)
CFTR	–	–	–	(Vastiau *et al*., 2005)
CHEK1	–	S317 & S345	–	(Leung-Pineda *et al*., 2006)
CIP2A	–	–	–	(Junttila *et al*., 2007)
CFL1	–	–	–	(Samstag & Nebl, 2003)
GJA1	–	–	–	(Kanemitsu *et al*., 1998; Meilleur *et al*., 2007)
CSNK1E	–	–	–	(Varjosalo *et al*., 2013b)
CTLA4	B′α	–	151–159	(Baroja *et al*., 2002)
CTNNB1 (β-Catenin)	B′, Bα	S33, S37, T41, S45, S552, S675	APC, Mult.	(Seeling *et al*., 1999; Zhang *et al*., 2009)
CUL3	B′β	–	315–374	(Bennett *et al*., 2010; Oberg *et al*., 2012)
CXCR2	–	–	–	(Fan *et al*., 2001)
DARPP32	PR72	T75	–	(Ahn *et al*., 2007b)
DLG4	B′δ	–	–	(Arbuckle *et al*., 2010)
DNML1/DRP1	Bβ2	S656	–	(Merrill *et al*., 2013)
E4orf3 [adenovirus]	–	–	–	(Shtrichman *et al*., 1999)
EGFR	PR130, B′ε	–	–	(Foerster *et al*., 2013; Zwaenepoel *et al*., 2010)
EIF1AK2	B′α	–	–	(Xu & Williams, 2000)
EIF4EBP1	Bα	–	–	(Bishop *et al*., 2006)
ELAVL1	B′ε	–	–	(Abdelmohsen *et al*., 2009)
ERAL1	–	S18	–	(Keen *et al*., 2005)
ETF1	–	–	–	(Lechward *et al*., 1999)
ERK1/ERK2	B′β, B′γ	T202/T185	IEK-1	(Letourneux *et al*., 2006)
ESPL1 (separase)	B′α-ε	–	1419–1474	(Holland *et al*., 2007)
FAM107A	Bα	–	–	(Ewing *et al*., 2007)
FBXO43	–	–	319–375	(Wu *et al*., 2007)

(*continued*)

Interacting proteins	B subunit	PhosphoSite	Interaction boundary	References
FMRP	–	–	–	(Narayanan *et al*., 2007)
GNA12	–	–	–	(Zhu *et al*., 2004)
GNB2L1	–	–	138–317	(Kiely *et al*., 2006)
GRIA1	–	–	–	(Mao *et al*., 2005)
GRB2	Bα	–	–	(Bisson *et al*., 2011)
GRIN2A	–	–	–	(Chan & Sucher, 2001)
GRK5	Bα	–	–	(Wu *et al*., 2012)
GSK3B	B′δ	S9	–	(Liu & Eisenman, 2012)
H2AX	–	–	–	(Chowdhury *et al*., 2005)
HAND1	B′δ	–	150–216	(Firulli *et al*., 2003)
HAND2	B′δ	–	–	(Firulli *et al*., 2003)
HCP6	B	–	–	(Yeong *et al*., 2003)
HDAC4	Bα	S298	1–289	(Paroni *et al*., 2008)
HDAC5	Bα	–	–	(Greco *et al*., 2011; Joshi *et al*., 2013)
HDM2	CyG	S166	400–489	(Okamoto *et al*., 2002)
HOX11	–	–	–	(Kawabe *et al*., 1997)
HRX	–	–	–	(Adler *et al*., 1997)
HSF2	–	–	–	(Xing *et al*., 2007)
HTR1A	–	–	–	(Bauman *et al*., 2000)
IER3	–	–	–	(Letourneux *et al*., 2006)
IKBKB	–	S77 &S181	121–179	(Kray *et al*., 2005; Li *et al*., 2006)
IKBKG	–	S68	–	(Fu *et al*., 2003; Palkowitsch *et al*., 2008)
IL6ST	–	S782	–	(Mitsuhashi *et al*., 2005)
IQGAP1	–	–	–	(Takahashi & Suzuki, 2006)
IRAK1	–	–	–	(Dobierzewska *et al*., 2011)
JAK2	–	–	–	(Fuhrer & Yang, 1996)
JNK	–	–	–	(Shanley *et al*., 2001)
KCNQ2	B′γ	–	E12–14	(Borsotto *et al*., 2007)
KRT8	–	–	–	(Tao *et al*., 2006)
KRT18	–	–	–	(Tao *et al*., 2006)
KSR1	Bα	S392	249–320	(Ory *et al*., 2003)
LATS2	Bα	–	–	(Woods *et al*., 2012)
LNX1	–	–	–	(Guo *et al*., 2012)
MAPK14	–	–	–	(Alvarado-Kristensson & Andersson, 2005)
MASTL (greatwall)	Bα	T194	–	(Hegarat *et al*., 2014)
MDM2	B′α/CyG	T216	100–280, 400–489	(Okamoto *et al*., 2002)
MEK3	α4	T193	–	(Prickett & Brautigan, 2007)
MEKK3	Bα, Bδ	S526	–	(Fritz *et al*., 2006)
MET	–	S985	–	(Hashigasako *et al*., 2004)
MID1	–	–	–	(Short *et al*., 2002)
MKK4	–	–	–	(Avdi *et al*., 2002)
MLH1	Bβ&Bδ	–	–	(Cannavo *et al*., 2007)
MTOR	Bα	–	–	(Peterson *et al*., 1999)
MYC (cMYC)	B′α	S62	40–179	(Arnold & Sears, 2006)
NDRG1	Bα	–	–	(Tu *et al*., 2007)
NEK1	B′α	S109	1–267	(Surpili *et al*., 2003)
NHE3	B′δ	–	651–839	(Bobulescu *et al*., 2010)
NKCC1	–	–	–	(Liedtke *et al*., 2005)
NKD1	PR72	–	–	(Creyghton *et al*., 2005,2006)
NM23H2	–	–	–	(Chen *et al*., 2008)
NOD2	B′ε	–	–	(Nimmo *et al*., 2011)
NOTCH1	Bα	–	–	(Yatim *et al*., 2012)
NR3A	–	–	–	(Ma & Sucher, 2004)
NRF1	B′γ	–	–	(Satoh *et al*., 2013)
NTRK1	B′β & B′δ	–	–	(Van Kanegan & Strack, 2009)
OCLN	–	–	–	(Seth *et al*., 2007)
OSBP	–	–	–	(Wang *et al*., 2005)
PACS1	–	S278	–	(Scott *et al*., 2003)
PAK1	–	–	–	(Westphal *et al*., 1999)
PAK3	–	–	–	(Westphal *et al*., 1999)
PDE4D/AKAP1	B′δ	–	2083–2319	(Dodge-Kafka *et al*., 2010)
PER3	–	–	–	(Sathyanarayanan *et al*., 2004)
PIM1	B′β	–	70–139	(Ma *et al*., 2007)
PIN1	B′β	–	–	(Huang *et al*., 2001; Michniewicz *et al*., 2007)
PKR	B′α	B′α	B′α	(Xu & Williams, 2000)
POLA2	–	–	–	(Dehde *et al*., 2001)
PPFIA1	B′δ	–	–	(Rual *et al*., 2005)
PRKAR1A	–	–	–	(Ahn *et al*., 2007a)
PTPN14	–	–	–	(Wang *et al*., 2012)
PTTG1 (Securin)	–	–	–	(Gil-Bernabe *et al*., 2006)

(*continued*)

Table 2. Continued

Interacting proteins	B subunit	PhosphoSite	Interaction boundary	References
PXN (paxillin)	B′γ1/2	–	–	(Ito *et al*., 2000)
RAF1	Bα/δ	S259	–	(Adams *et al*., 2005)
RALA	Aβ	S183, S184	–	(Sablina *et al*., 2007)
RB1	PR70	T826	792–928	(Lees *et al*., 1991; Magenta *et al*., 2008)
RBL1 (p107)	PR59	Mult.	–	(Voorhoeve *et al*., 1999)
REC8	B′-sgo	Mult.	–	(Ishiguro *et al*., 2010)
RELA	A	S536	1–155, 354–551	(Fuhrer & Yang, 1996; Li *et al*., 2006; Yang *et al*., 2001)
REV1	Bα& Bδ	–	–	(Naji *et al*., 2012)
RHEB	–	–	–	(Lee *et al*., 2007)
RHOB	–	–	–	(Lee *et al*., 2007)
RPS6KB1	–	–	–	(Westphal *et al*., 1999)
RRAS	–	–	–	(Lee *et al*., 2007)
RRN3	Bα	S44	–	(Mayer *et al*., 2004)
RSA1 & RSA2	–	–	–	(Schlaitz *et al*., 2007)
RUNX2	–	–	–	(Rajgopal *et al*., 2007)
SET	–	–	–	(Li *et al*., 1996)
SG2NA	–	–	–	(Moreno *et al*., 2000)
SHC	–	Y317	–	(Ugi *et al*., 2002)
SLC6A2	–	–	–	(Sung *et al*., 2005)
SMAD3	–	–	1–232	(Heikkinen *et al*., 2010)
SMAD9	B′ε	–	–	(Colland *et al*., 2004)
SMURF1	Bδ	–	–	(Xie *et al*., 2013)
SOX2	B′γ	–	–	(Cox *et al*., 2013)
SP1	–	T739	–	(Chuang *et al*., 2012)
SPHK1	B′α	S225	451–470	(Pitman *et al*., 2011)
SPRY1	A	S112, S115	50–60	(Lao *et al*., 2007)
SRC	Bγ	S12	–	(Eichhorn *et al*., 2007)
STAT5	–	–	–	(Yokoyama *et al*., 2001)
STE20	–	–	–	(Liedtke *et al*., 2005)
STK24	B‴	T178, T182	–	(Gordon *et al*., 2011)
SUMO1	–	–	–	(Grant, 2010)
TAU	Bα	Mult.	197–259, 265–328	(Xu *et al*., 2008)
TAX	–	–	–	(Fu *et al*., 2003)
TBC1D3	B′γ	S6K	–	(Wainszelbaum *et al*., 2012)
TCEAL1	Bα & Bδ	–	–	(Sowa *et al*., 2009)
TGFBR1	Bα	–	–	(Griswold-Prenner *et al*., 1998)
TH	B′β	S19, S31, S40	R37 & R38	(Saraf *et al*., 2010)
TIP	–	–	–	(McConnell *et al*., 2007)
TOM22	Bβ	–	–	(Dagda *et al*., 2005)
TOP1	Bβ	–	–	(Trzcinska *et al*., 2002)
TP53 (p53)	–, B′γ1/3	S37, T55	–	(Dohoney *et al*., 2004; Li *et al*., 2007)
TRAF2	B′γ	T117	272–501	(Li *et al*., 2006)
TSC2	–	–	–	(Lee *et al*., 2007)
TTP	–	–	–	(Sun *et al*., 2007)
UBD	–	–	–	(Aichem *et al*., 2012)
UBR5	Bγ	–	–	(Chen *et al*., 2013)
UPF1	–	–	–	(Ohnishi *et al*., 2003)
VIM	Bα	–	–	(Turowski *et al*., 1999)
VPU [HIV]	B′ε	–	–	(Jager *et al*., 2012)
ZRANB1	B‴	–	–	(Tran *et al*., 2013)

The first row is the abbreviated interacting protein, the second is B subunit if known, the third is dephosphorylation site if known, the fourth is interacting boundary if known and the last row indicates the reference to the work documenting the interaction. Abbreviations were used based on Biogrid entries using Uniprot naming rules. Historical/common names are given in parenthesis where standard abbreviations are not commonly used or not easily interpretable. All proteins mentioned are human, with the exception of important human viral proteins, which have virus names indicated in [brackets].

rictor, mSin1 and protor1/2 (Laplante & Sabatini, 2012; Shimobayashi & Hall, 2014). Deptor is an inhibitor of both mTOR complexes and suppresses the function of S6 kinase 1 (S6K1), AKT and Serum and Glucocorticoid regulated kinase 1 (SGK1) (Peterson *et al*., 2009). Deptor is highly overexpressed in some multiple myelomas, and this overexpression can induce AKT function due to loss of feedback inhibition of phosphoinositide-3 kinase (PI3K) from mTORC1 (Peterson *et al*., 2009). Raptor and rictor help regulate substrate specificity to mTORC1 and mTORC2, respectively. Raptor binds with mTOR in the mTORC1 complex and is necessary for binding and phosphorylation of S6K1 and 4E-BP1, which in turn induce protein synthesis and proliferation (Kim *et al*., 2002; Nojima *et al*., 2003). GβL (also known as mLST8) is found in both mTORC2 and mTORC1 and is essential in stabilizing the interaction of mTOR with raptor (Kim *et al*., 2003; Laplante & Sabatini, 2012).

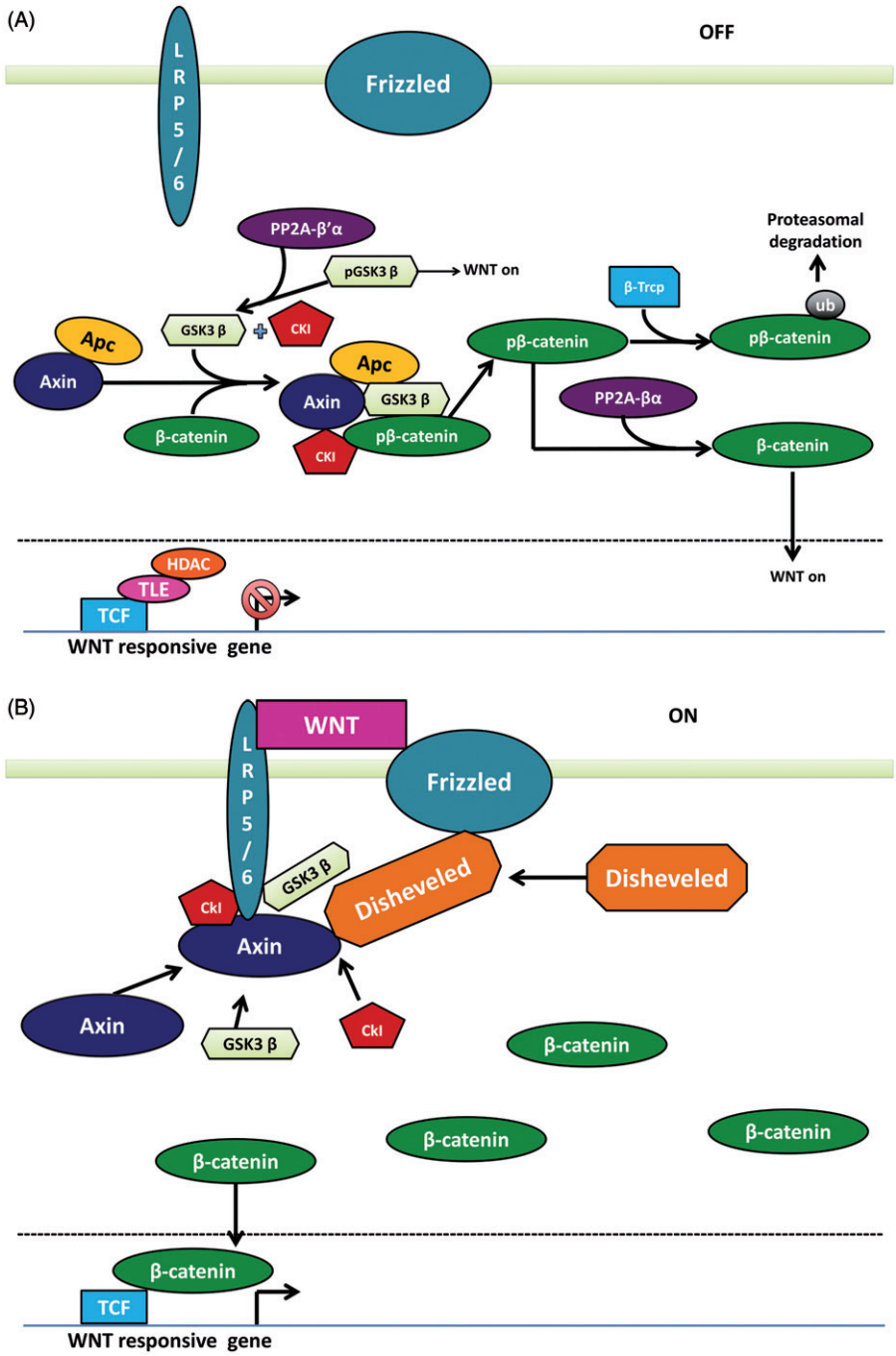

Figure 3. PP2A positively and negatively regulates the Wnt signaling pathway. (A) Wnt OFF. In the absence of Wnt signaling, a complex of Axin, Apc, GSK3β and CK1 phosphorylate β-catenin, targeting it for proteasomal degradation. PP2A-B′α promotes β-catenin degradation by removing an inhibitory phosphorylation on GSK3β. PP2A-Bα can directly dephosphorylate β-catenin, promoting the activation of wnt responsive genes. (B) Wnt signaling ON. In the presence of Wnt ligand, Wnt receptors LRP5/6 and frizzled sequester the Axin, GSK3β and CK1, preventing the phosphorylation of β-catenin. β-Catenin accumulates and translocates to the nucleus, promoting the transcription of Wnt responsive genes. Figure adapted from MacDonald *et al*. (2009). (see colour version of this figure at www.informahealthcare.com/bmg).

Both complexes are regulated by highly diverse processes. Wnt signaling can activate both mTOR complexes, as can stimulation by insulin (Inoki *et al*., 2006; Shimobayashi & Hall, 2014). Wnt can stimulate mTORC2 directly through the GTPase RAC1 and stimulates mTORC1 indirectly by inactivating glycogen synthase kinase 3β, which is necessary to activate an mTORC1 inhibitor, tuberous sclerosis complex 2 (TSC2) (Inoki *et al*., 2006; Shimobayashi & Hall, 2014). Insulin, long known to stimulate protein synthesis, activates mTOR through a central molecule, phosphatydilinositol-3,4,5-triphosphate, produced by PI3K (Hsu *et al*., 2011; Shimobayashi & Hall, 2014). This molecule can directly stimulate mTORC2 and can indirectly stimulate mTORC1 by activation of AKT which inhibits TSC2 (Klippel *et al*., 1997; Shimobayashi & Hall, 2014). Free amino acids activate mTORC1 via binding to RAS-related GTP binding protein (RAG) heterodimers, causing a global conformational change (Sancak *et al*., 2008). The RAG complex associated with amino acids can recruit mTORC1 to the lysosome where it is activated by binding to RAS homolog enriched in brain (RHEB) (Sancak *et al*., 2008; Shimobayashi & Hall, 2014).

Although the mTOR regulation pathways are well established, the downstream substrates of mTOR are not very well characterized. Mass spectrometric studies have identified 93 potential substrates in human embryonic kidney cells and 174 potential substrates in mouse embryonic fibroblasts (Hsu *et al*., 2011). Very few of these substrates have been studied in detail. The best known substrates of mTOR are the ribosomal S6 kinase (S6K) and eIF4e binding protein 1 (4E-BP) (Shimobayashi & Hall,

2014). Many proteins that are involved in growth and proliferation are encoded by mRNAs that have secondary structures in their 5′-UTR (untranslated region) that inhibit scanning by the 40S ribosomal subunit [reviewed in Ma & Blenis (2009)]. Phosphorylation of 4E-BP by mTORC1 can inhibit its binding to eIF4E, which is necessary to recruit the pre-initiation complex (Burnett *et al*., 1998; Ma & Blenis, 2009). An important component of the pre-initiation complex is eIF4B, which upon phosphorylation recruits eIF4A, a family of RNA helicases that facilitate efficient unwinding of secondary mRNA structures. eIF4B phosphorylation is mediated by S6K after phosphorylation and activation by mTORC1 (Burnett *et al*., 1998; Ma & Blenis, 2009). These mTOR substrates both work in concert to translate these structured mRNAs to enhance growth and proliferation. mTOR regulates autophagy by the phosphorylation of Unc 51-like kinase 1 (ULK1). Autophagy is promoted by ULK1 when activated by phosphorylation on S317 and S777 by AMP activated protein kinase (AMPK) (Kim *et al*., 2011). mTOR phosphorylates ULK1 on S757, which prevents AMPK phosphorylation and subsequent activation (Kim *et al*., 2011). Recently, LIPIN1, a protein that helps promote lipid biosynthesis, was identified as a potential mTOR substrate, but more work is needed to further characterize this substrate (Yuan *et al*., 2012).

There is evidence that PP2A can associate and dephosphorylate S6K, and the same report indicated that mTOR can inactivate PP2A, providing two modes of S6K activation (Peterson *et al*., 1999) (Figure 4). PP2A has also been shown to affect mTOR activity by regulating AKT. AKT, which inhibits TSC2, requires phosphorylation on T308 and S473 for activation, and the PP2A B′α holoenzyme has been shown to dephosphorylate AKT on T308, thereby inactivating it (Kuo *et al*., 2008) (Figure 4). Upstream of AKT, driven by insulin signaling, is insulin receptor substrate 1 (IRS1) which is necessary to transduce insulin receptor signaling to PI3K (Carlson *et al*., 2004). PP2A can dephosphorylate IRS1, leading to its stabilization and mTOR can inhibit PP2A activity toward IRS1 potentially directly phosphorylating IRS1 at S307, leading to IRS1 degradation (Carlson *et al*., 2004; Hartley & Cooper, 2002) (Figure 4).

Multiple reports have indicated that mTOR can negatively regulate PP2A activity, and most of this negative regulation supports mTOR activation through insulin signaling and PI3K. In contrast, PP2A can negatively regulate mTOR when amino acids are not present. MAP4K3 can signal to activate mTOR when amino acids are present, and autophosphorylation on S170 is necessary for this activation (Yan *et al*., 2010). When amino acids are withdrawn, PP2A dephosphorylates S170 and prevents mTOR activation by this pathway (Yan *et al*., 2010) (Figure 4).

The role of PP2A in mTOR activation is further regulated by its regulatory proteins. TIPRL can overcome amino acid withdrawal and stimulate mTOR activation by inhibiting PP2A phosphatase activity. However, the yeast homolog, TIP41, has a negative effect on mTOR activation by binding to TAP42 (Nakashima *et al*., 2013). In contrast to observations in yeast, the association between PP2Ac and α4, the mammalian homolog of TAP42, is not dependent on mTOR, indicating that the functions of TIPRL and α4 in mTOR signaling are not conserved and remain to be deciphered (Yoo *et al*., 2008).

The mTOR pathway is a critical pathway to initiate cell growth, and the regulation of this pathway is exceedingly complex, involving many feedback loops and antagonistic partnerships, especially with PP2A. mTOR has been intensely investigated and is frequently targeted for potential treatment of diseases such as cancer. Nevertheless, there are still important gaps in our understanding of mTOR substrates, regulation and crosstalk with other signaling pathways. Further study will deepen our understanding of growth signaling and possibly lead to significant drug development.

Mitogen activated protein kinase signaling pathway

Mitogen-activated protein (MAP) kinase pathways help regulate many cellular functions such as proliferation, differentiation and apoptosis. There are four families of MAP kinases: ERK1/2, ERK5, JNK and p38 [reviewed in Hommes *et al*. (2003), Imajo *et al*. (2006), McCubrey *et al*. (2007), Meloche & Pouyssegur (2007)]. When activated, MAP kinases phosphorylate downstream substrates to induce cellular responses. MAPKs are activated by upstream kinases (MAPK kinases), and those MAPKKs are activated by further upstream kinases, MAPKK kinases (MAPKKKs) (Imajo *et al*., 2006). These kinases are activated by cellular growth signals, cytokines or stress signals. ERK5, JNK and p38 generally have pro-apoptotic functions and are activated by stresses, whereas ERK1/2 promotes proliferation and transformation (Imajo *et al*., 2006; Meloche & Pouyssegur, 2007; Wu, 2007). The ERK1/2 pathway was the first MAPK pathway discovered and is the best studied. Growth factors such as epidermal growth factor (EGF) or fibroblast growth factor (FGF) bind to their respective receptors and recruit a complex of SRC homology-2-containing protein (SHC), growth factor receptor bound protein 2 (GRB2) and son of sevenless (SOS) (Egan *et al*., 1993) (Figure 5). This complex changes Ras conformation, disrupting GDP interaction and promoting GTP association which activates Ras and recruits Raf (MAPKKK) to the membrane bound complex (Freedman *et al*., 2006; Milburn *et al*., 1990), where Raf is activated by dimerization and phosphorylation (Rajakulendran *et al*., 2009). Raf then phosphorylates and activates MEK1, which subsequently phosphorylates and activates ERK1/2 (Crews *et al*., 1992; Wu *et al*., 1996) (Figure 5). ERK1/2 phosphorylates transcription factors Jun and Fos which can then translocate to the nucleus and bind DNA to initiate transcription of genes involved in cell cycle regulation such as AP-1, which in turn can promote cyclin D1 expression (Monje *et al*., 2005; Weber *et al*., 1997). ERK1/2 can also phosphorylate and stabilize c-Myc, which can then enhance its transcriptional activity toward cell cycle promoting genes such as cyclin D1 and CDC25A (Mathiasen *et al*., 2012; Meloche & Pouyssegur, 2007).

The ERK1/2 MAPK pathway and its downstream substrates are also regulated by the action of phosphatases. There are at least 11 MAPK phosphatases (MKPs), which are split into three families based on cellular localization. There is significant cross-activity between the MKPs and all four of

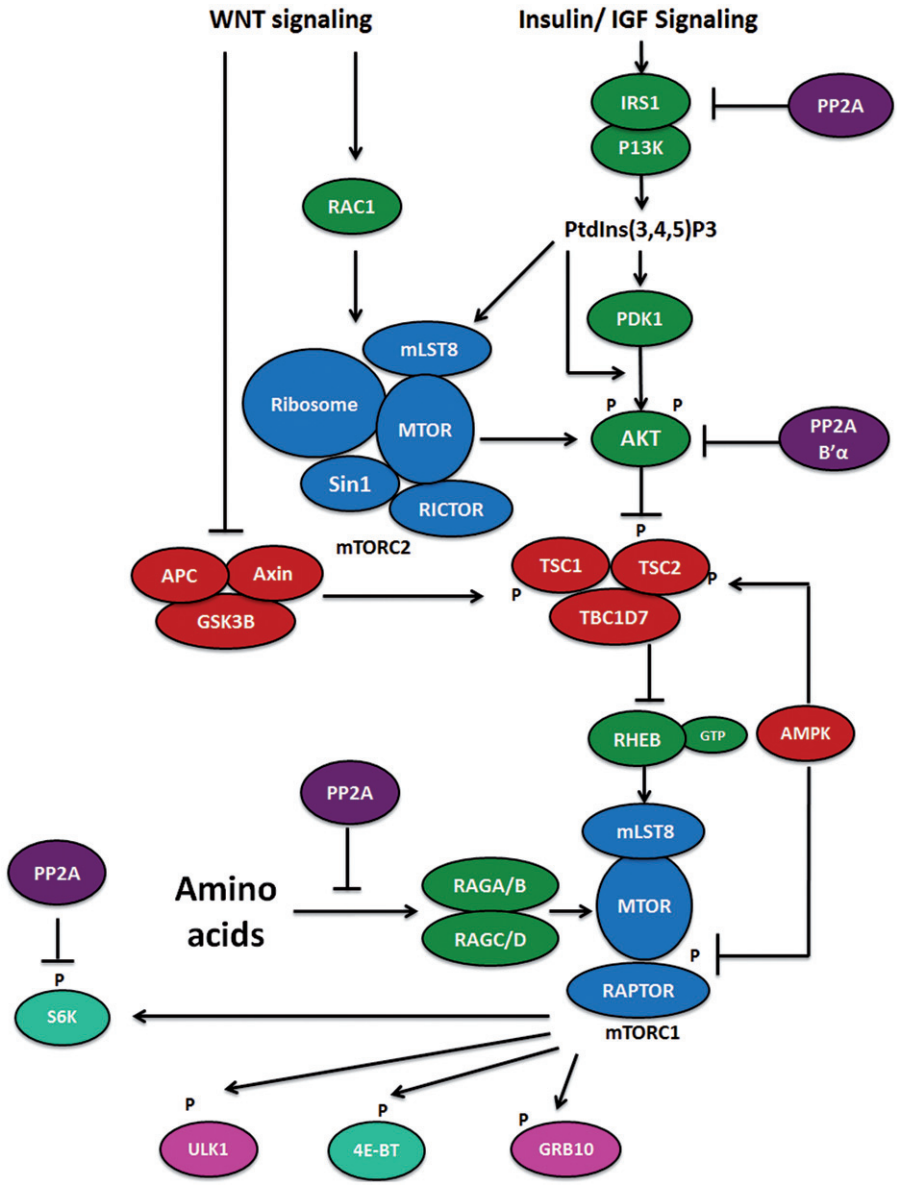

Figure 4. PP2A negatively regulates the mTOR signaling pathway. The mTOR complexes are colored blue. Proteins involved in mTOR inhibition and activation are colored red and green, respectively with PP2A in purple. Downstream factors inhibiting and stimulating growth are colored magenta and teal, respectively. Growth factors stimulate the mTOR pathway via inhibiting the function of the TSC complex that inhibits mTOR activation. Wnt signaling can inhibit the TSC complex or directly stimulate mTORC2. Amino acids can also stimulate mTOR activity. PP2A inhibits the mTOR pathway by inhibiting IRS1 in the insulin signaling pathway or MAP4K3 in the amino acid pathway, or by inhibiting AKT function. PP2A can also reverse mTOR phosphorylation of S6K. Figure adapted from Shimobayshi & Hall (2014). (see colour version of this figure at www.informahealthcare.com/bmg).

the MAPK pathways, and many of the MKPs, such as MKP-1 and MKP-3, have an overall transforming effect and are implicated in many cancers [reviewed in Wu (2007)]. MKP-1 has been the best studied of the MKPs, and is implicated in a variety of cancers. One of the mechanisms implicated in maintaining cell survival is its ability to prevent stress-induced apoptosis by preferentially dephosphorylating p38 and JNK, inactivating two critical stress-induced apoptotic pathways in the cell (Franklin & Kraft, 1997; Franklin *et al*., 1998).

Protein phosphatase 2A (PP2A) appears to have a role primarily in negative regulation of the ERK MAPK pathway (Figure 5). SHC is an important member of the complex that binds growth receptors and activates Ras (Egan *et al*., 1993). PP2A can bind to the phospho-tyrosine binding domain of SHC and negatively regulate Ras activation (Ugi *et al*., 2002). After growth factor stimulation, T317 phosphorylation of SHC can dissociate PP2A and allow downstream activation (Ugi *et al*., 2002). It is currently unknown whether PP2A actively dephosphorylates SHC or which regulatory subunit is responsible for PP2A's inhibitory effect (Ugi *et al*., 2002). PP2A can also directly inactivate ERK by dephosphorylation (Letourneux *et al*., 2006) (Figure 5). This is mediated by the B′β and B′γ subunits, which can also be phosphorylated by ERK if IEX-1 is expressed, thus reversing PP2A mediated inactivation (Letourneux *et al*., 2006). Sprouty2 is an inhibitor of FGF stimulated ERK activation. Sprouty2 is normally phosphorylated and cannot bind Grb2, and phosphorylation on T55 allows c-Cbl to bind and target sprouty2 for degradation by the proteasome (Lao *et al*., 2007). Upon FGF stimulation, sprouty2 is dephosphorylated by PP2A, which exposes the Grb2 binding motif on the C-terminus (Lao *et al*., 2007) (Figure 5). When bound to Grb2, ras is unable to be recruited to the complex and be activated, thus down-regulating ERK activation by FGF (Egan *et al*., 1993). PP2A binds to sprouty2 between residues 50–60, competing with c-Cbl binding and thus activating and protecting sprouty2 (Lao *et al*., 2007).

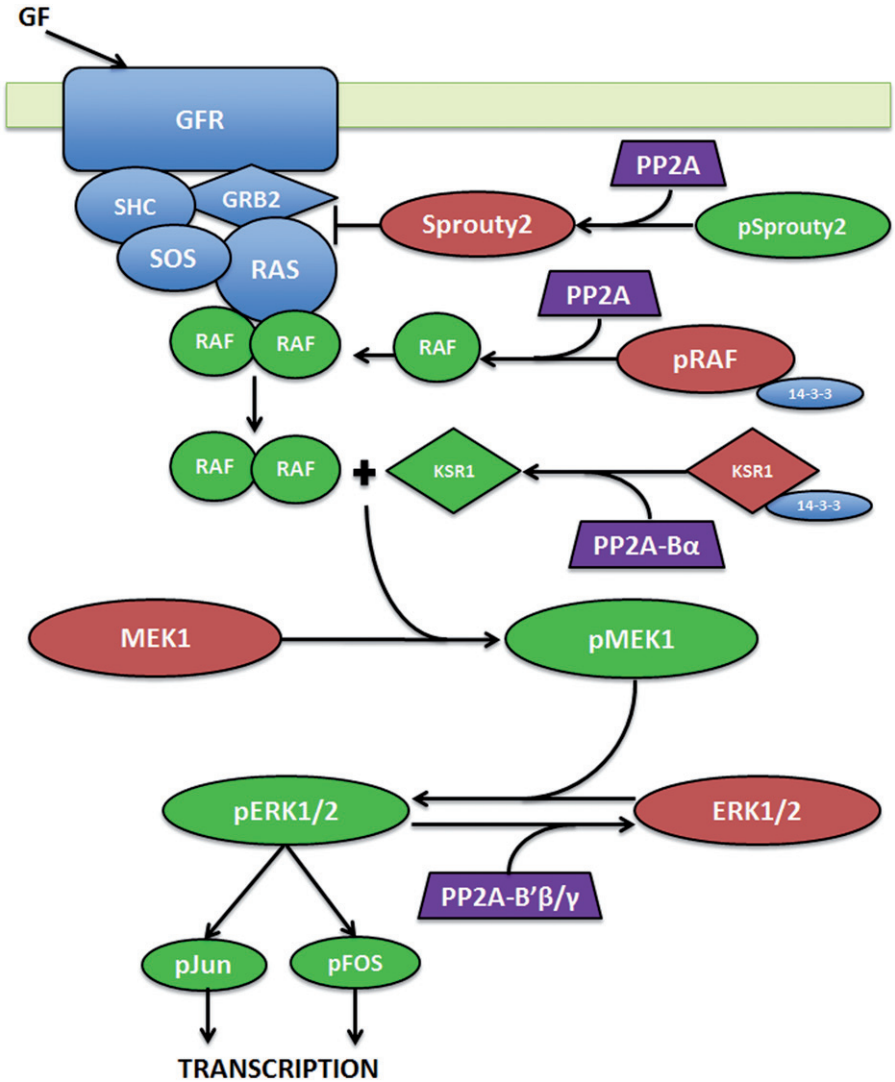

Figure 5. PP2A positively and negatively regulates the MAPK signaling pathway. Growth factors stimulate a complex of proteins: SHC, GRB2 and SOS to assemble on a growth factor receptor. This complex activates Ras which starts a signal cascade from activation of Raf, to activation of MEK, ERK and eventually the transcription factors that activate the transcription of growth related genes. PP2A can activate Raf by dephosphorylating S259 and causing 14–3-3 release. PP2A-Bα dephosphorylates S392 of KSR1, which leads to dissociation of 14–3-3 from KSR1, essential for MEK1 activation. PP2A negatively regulates MAPK upstream by activating Sprouty2, which inhibits GRB2 and subsequent RAS complex formation. PP2A-B′β/B′γ can directly dephosphorylate ERK1/2 downstream of the signaling cascade, thereby inactivating it. Factors promoting cell division are shown in green and those opposing cell division are shown in red. Figure adapted from McCubrey *et al*. (2007). (see colour version of this figure at www.informahealthcare.com/bmg).

PP2A can also positively regulate ERK MAPK signaling. EGF receptors are targeted for ubiquitination and degradation by c-Cbl, which requires phosphorylation on various residues (McCubrey *et al*., 2007). This interaction is disrupted upon recruitment of SRC homology 2 domain containing inositol polyphosphate phosphatase, SHIP2 (Zwaenepoel *et al*., 2010). PR130, a PP2A regulatory subunit from the B″ family, forms a holoenzyme which can form a complex with SHIP2 and is required for SHIP2-mediated stabilization of EGFR (Zwaenepoel *et al*., 2010). Mapping studies indicate that the catalytic domain of SHIP2 interacts with the EF hands of PR130, and mutation in this region disrupts the stabilizing effect of PR130 holoenzyme on EGFR (Zwaenepoel *et al*., 2010). It is currently unknown whether catalytic activity is required for this effect and whether PP2A-PR130 dephosphorylates EGFR, SHIP2 or other associated targets. Downstream of growth factor receptor, the kinase suppressor of ras (KSR1) is a critical positive regulator of ras signaling (Ory *et al*., 2003). It is a necessary scaffold to transduce the activation signal from ras-1 to MEK to ERK. PP2A-Bα holoenzyme is associated with the KSR1 complex and is required for MEK activation (Ory *et al*., 2003). When phosphorylated, S392 of KSR1 associates with 14–3-3 protein and remains cytoplasmic. PP2A-Bα directly dephosphorylates KSR1 at S392 which is then freed from 14–3-3 and can translocate to the membrane, an event required for MEK activation (Ory *et al*., 2003) (Figure 5). Similarly, PP2A and PP1 have been shown to positively regulate Raf-1 activity by dephosphorylating S259, allowing 14–3-3 release from Raf-1 and membrane translocation (Jaumot & Hancock, 2001) (Figure 5). PP2A-B′β and -B′δ can also positively regulate MAPK signaling in neuronal PC12 cells through action on TrkA. PP2A enhances autophosphorylation of TrkA likely by dephosphorylating an inhibitory Ser/Thr, allowing Ras activation by TrkA and sustained MAPK signaling (Van Kanegan & Strack, 2009).

Taken together, the role of PP2A in regulation of MAPK pathway is complex and other as-yet-unidentified regulatory proteins may be involved. Signaling scaffolding proteins, such as KSR1, are crucial for coordinating spatiotemporal control of the function of kinases, phosphatases and other signaling molecules. The role of PP2A in both positive and negative regulation of MAPK are likely crucial for fine-tuning and precise control of this pathway. There is also crosstalk with many of these pathways as well as other cell cycle promoting pathways, highlighting the importance of phosphatases in

regulating the initiation of the cell cycle and the complexity by which they do so.

Cell cycle progression: Rb and the G1-S transition

In G1 phase, cell cycle initiation pathways, such as those mentioned above, initiate growth and transcription of factors, such as cyclin D1, that control cell cycle progression. Before the cell can transition from G1 to synthesis (S) phase, it must pass through a critical cell checkpoint to ensure that the cell is ready for DNA synthesis. The master regulator of this checkpoint, and first discovered tumor suppressor protein, is the retinoblastoma tumor suppressor protein (Rb).

Rb phosphorylation

Retinoblastoma tumor suppressor protein (Rb) is an approximately 105 kDa protein consisting of three functional domains: an N-terminal structured region, a two-part central pocket region and a C-terminal unstructured region (Harbour & Dean, 2000). There are two other proteins structurally and functionally related to Rb: p107 and p130. Together, these proteins make up the pocket protein family and have all been implicated in diverse cellular processes such as cell cycle progression, apoptosis, senescence, differentiation, and angiogenesis [reviewed in Indovina *et al*. (2013)]. These proteins bind and inactivate E2F transcription factors, with Rb binding E2F 1–3, and p107/p130 binding E2F4 & 5 (Figure 6) (Indovina *et al*., 2013; Kolupaeva & Janssens, 2013). E2F 1–3 are transcriptional activators and mostly express cell cycle genes such as cyclins E and A, and CDC25 [reviewed in Harbour & Dean (2000), Indovina *et al*. (2013), Nevins (2001)]. E2F4 & 5 are transcriptional repressors and are involved in maintaining genomic stability and redundant functions with Rb [reviewed in Dominguez-Brauer *et al*. (2010) and Plesca *et al*. (2007)]. The pocket proteins bind to E2F transcription factors along with their dimerization partners (DPs), preventing their translocation to the nucleus and transcriptional activation (Rubin, 2013). The pocket proteins are phosphorylated by cyclin/CDK holoenzymes on numerous residues, weakening the interaction between them and the E2Fs, causing dissociation and E2F transcriptional activation [reviewed in Kolupaeva & Janssens (2013) and Rubin (2013)] (Figure 6). Rb is phosphorylated by cyclin D/CDK4 and cyclin E/CDK2 in G1, and numerous phosphorylation events gradually lead to the release of E2F transcription factors (Brown *et al*., 1999). One possible mechanism for this gradual release is due to the association of E2F with multiple domains of Rb (Rubin *et al*., 2005). The pocket domain alone is not sufficient for E2F dimerization, as the C-terminal region of Rb adopts a stable conformation upon association with E2F1-DP and increases the binding of the complex more than 36 fold (Rubin *et al*., 2005). Loss of this interaction pre-disposes Rb-E2F to dissociate, and this region is phosphorylated by cyclin D/CDK4/6 early in G1, thus providing a model for how sequential phosphorylation events dissociate Rb-E2F (Rubin *et al*., 2005). Rb levels do not change throughout the cell cycle, indicating that phosphorylation events need to be reversed to reset Rb after cell division (Kolupaeva & Janssens, 2013).

Phosphatases in Rb regulation

The specific roles of kinases in Rb phosphorylation have been well established; however, the role of phosphatases in Rb regulation continues to be discovered. Protein phosphatase 1 and PP2A are the primary phosphatases that regulate Rb (and p107/130) function (Kolupaeva & Janssens, 2013). PP1 is responsible for complete dephosphorylation of Rb after mitosis, whereas PP2A functions throughout the cell cycle, dephosphorylating Rb and p107/130 in response to various stimuli [reviewed in Kolupaeva & Janssens (2013) and Kurimchak & Grana (2012)].

Protein phosphatase 1 (PP1) and PP2A are both known to dephosphorylate Rb, and PP1 appears to compete for the same CDK docking sites (Alberts *et al*., 1993; Hirschi *et al*., 2010). Such competitive interaction has also been suggested between CDKs and PP2A for p107 (Kolupaeva *et al*., 2013), and when CDKs are elevated they outcompete phosphatases causing an irreversible cell cycle progression signal switch. CDKs compete with phosphatases and switch the signal toward hyperphosphorylation and irreversible progression of the cell cycle (Garriga *et al*., 2004). In support of the competition hypothesis, specific overexpression of Bα induces p107 dephosphorylation (Jayadeva *et al*., 2010). Bα can directly associate with p107 but

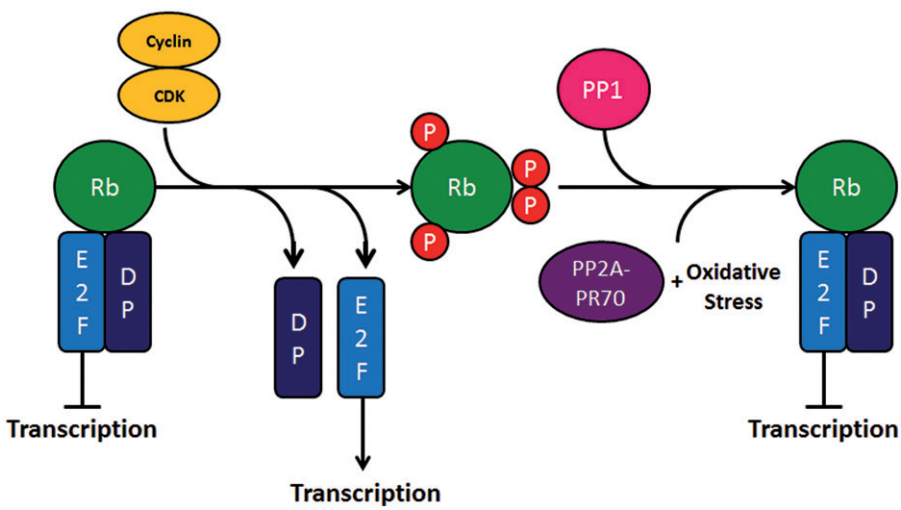

Figure 6. Rb phosphorylation promotes transcription of E2F responsive genes. Rb normally binds E2F transcription factors and their dimerization partners. When phosphorylated by cyclin/CDK heterodimers, Rb loses affinity for E2F and free E2F is allowed to promote transcription. Rb is dephosphorylated at the end of mitosis, allowing re-association with E2F. Normally, PP1 dephosphorylates Rb at the end of mitosis, but PP2A-PR70 can dephosphorylate Rb under oxidative stress conditions. (see colour version of this figure at www.informahealthcare.com/bmg).

has little affinity for pRb, therefore, additional holoenzymes may be required to mediate cell cycle arrest by pocket protein activation (Jayadeva *et al*., 2010).

In contrast to constitutive competitive interactions, extracellular signaling or stress factors can induce PP2A-modulated dephosphorylation of the pocket proteins with no significant changes in CDK activity or PP2A expression (Cicchillitti *et al*., 2003). Sustained FGF signaling can arrest cell growth in chondrocytes, which is the opposite to the effect in most other cell types (Kolupaeva *et al*., 2013). FGF signaling leads to Bα dephosphorylation, increasing Bα affinity for p107, and chondrocytes have a large constitutively expressed Bα population (Kolupaeva *et al*., 2013). Phosphorylation of Bα allows increased association of PP2A-Bα holoenzymes with p107 and subsequent dephosphorylation and cell cycle arrest (Kolupaeva *et al*., 2013). The extracellular factor all-*trans*-retinoic acid (ATRA) appears to induce PP2A-specific dephosphorylation of p130 (Purev *et al*., 2011). Upon ATRA treatment, PP2A can bind to and dephosphorylate p130, protecting it from ubiquitination and degradation (Purev *et al*., 2011). PP2A can also mediate p130's translocation to the nucleus due to dephosphorylation of S1080 and T1097, exposing the NLS and allowing binding by importins α and β (Purev *et al*., 2011; Soprano *et al*., 2006). Under oxidative stress conditions, the PP2A-PR70 holoenzyme can dephosphorylate Rb, and this activity is dependent on Ca^{2+} stimulation (Magenta *et al*., 2008) (Figure 6). One potential underlying mechanism is that oxidative stress induces an influx of Ca^{2+}, which stimulates PR70 holoenzyme formation and results in specific Rb dephosphorylation by PP2A-PR70, although further investigation is needed.

The regulation of pocket proteins by dephosphorylation is complex and results from the interplay between competition with CDKs and specific mitogenic or stress stimuli. There may also be crosstalk between various signaling pathways in this process, as pocket proteins are central effectors through which many pathways funnel. S phase induction by Rb represents a commitment by the cell to DNA synthesis and phosphatases continue to be important in regulating this process.

DNA synthesis and regulation of the origin recognition complex

Once the cell passes the G1-S checkpoint, it is committed to the process of synthesizing DNA. The genome in eukaryotes is far too large for synthesis to proceed in a linear fashion from one end to another, so synthesis proceeds from discrete origins of replication. In yeast, these origins are defined by specific DNA sequences; however, human origins are likely defined by DNA structural features [reviewed in Hyrien *et al*. (2013)]. Excluding DNA recognition, the origin recognition complex functions in a conserved manner and is highly regulated.

ORC assembly and regulation

The origin recognition complex (ORC) is a large protein complex that binds to DNA at the origins of synthesis and recruits all of the proteins required to unzip and polymerize DNA [reviewed in Bell (2002) and Duncker *et al*. (2009)]. There are and ORC proteins (ORC1–6) that bind to DNA at the origins [referred to as autonomously replicating sequences (ARS) in yeast] (Duncker *et al*., 2009). These proteins all bind and hydrolyze ATP, and ATPase activity is required for their assembly and recruitment of other complex members (Bell & Stillman, 1992). In late G1/early S, cell division control 6 protein (Cdc6) binds to the ORC proteins and is the critical component for further ORC assembly (Liang *et al*., 1995). Cdc6 facilitates the loading of Cdt1 and ORC6 to ORC1–5 which then facilitate the loading of the mini-chromosome maintenance proteins (MCM2–7) (Nishitani *et al*., 2000). Cdc6 also has ATPase activity, and hydrolysis of ATP leads to conformational changes, which increases the binding affinity of the MCM proteins for the complex (Shin *et al*., 2003). The MCM proteins are helicases, and when properly bound they begin to unwind DNA for replication. The MCM proteins are subsequently phosphorylated by Dbf4/Cdc7 which allows the recruitment of RPA and Cdc45 to the unzipped origin, facilitating the loading of DNA polymerase which then synthesizes new DNA (Sheu & Stillman, 2006; Tanaka & Nasmyth, 1998).

Regulation of Cdc6 by phosphorylation

For error free cell division, DNA must be synthesized once and only once. One of the chief ways the cell regulates this process is by allowing the origins to fire only once. This restriction is accomplished by the tight regulation of Cdc6. In the absence of phosphorylation near its N-terminal destruction motifs, the anaphase-promoting complex/cyclosome (APC/C) targets Cdc6 for ubiquitination and proteasomal degradation (Mailand & Diffley, 2005). In G1, Cdc6 is phosphorylated by cyclin E/CDK2 on S54 and S74, protecting it from degradation and allowing it to be transported into the nucleus and to bind to the ORC (Jallepalli *et al*., 1997; Mailand & Diffley, 2005) (Figure 7). After origin firing in early S phase, Cdc6 is acetylated by general control nonderepressible 5 (GCN5) and phosphorylated by cyclin A/CDK2 on S106 (Paolinelli *et al*., 2009; Petersen *et al*., 1999). These modifications tag Cdc6 for nuclear export where it is degraded in the cytoplasm. Cdc6 degradation can only happen when the protective residues are dephosphorylated, and PP2A-PR70 has been shown to dephosphorylate Cdc6 *in vivo* (Davis *et al*., 2008). Our recent study showed that Cdc6 is specifically dephosphorylated by PP2A-PR70 holoenzyme and not others (Wlodarchak *et al*., 2013). PP2A-PR70 binds Cdc6 near the phosphorylated residues, likely due to a charge recognition pattern, and a compact holoenzyme conformation is critical for optimal enzymatic activity (Wlodarchak *et al*., 2013). The *in vivo* timing and location of PP2A-PR70 dephosphorylation is not fully characterized, but it likely occurs after origin firing to prevent re-assembly and possibly before origin assembly to regulate synthesis (Figure 7).

Mitosis: PP2A as a gatekeeper from mitotic entry to mitotic exit

Inhibition of PP2A is required for mitotic entry

The transition from G2 to M phase is elicited by many factors and pathways, but one of the most critical events is the

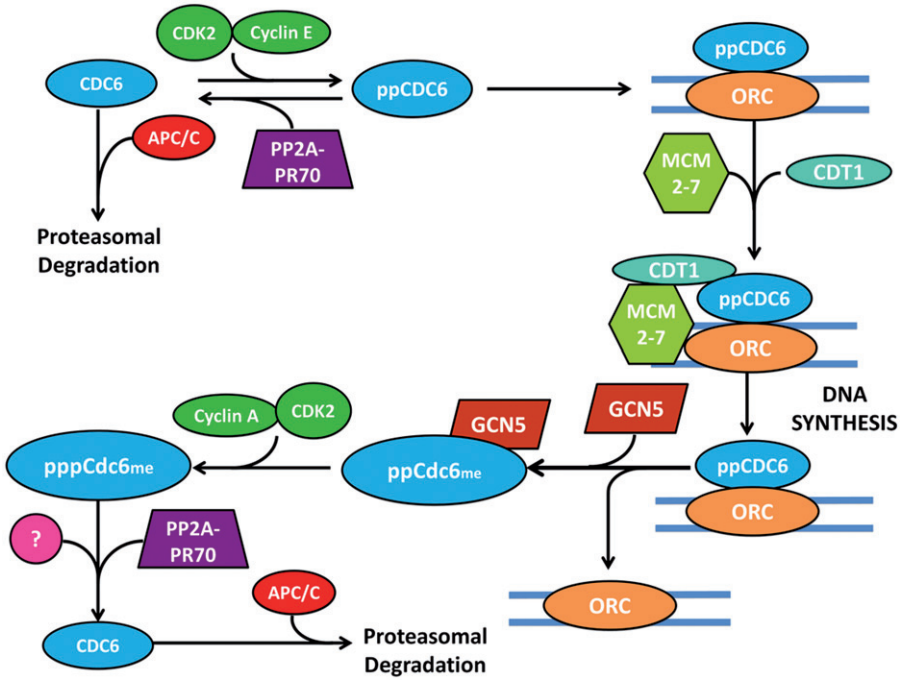

Figure 7. Cdc6 is necessary for assembly of the pre-replication complex and subsequent DNA synthesis. In G0, Cdc6 is ubiquinated by the anaphase promoting complex/cyclosome (APC/C) and degraded by the proteasome. In G1, Cyclin E/CDK2 phosphorylates Cdc6 on S54 and S74, protecting it from degradation. Cdc6 is translocated into the nucleus where it binds the origin recognition complex and is required to recruit Cdt1 and MCM2–7 and form the pre-replication complex. After firing of the origins, Cdc6 is methylated by GCN5 causing its dissociation from the ORC. Cdc6 is then phosphorylated on S106 by Cyclin A/CDK2 and translocated to the cytoplasm. PP2A-PR70 is thought to dephosphorylate Cdc6 either at this point in G2 and/or in G1, ensuring Cdc6 destruction and regulating DNA synthesis. Figure adapted from Mumby (2009). (see colour version of this figure at www.informahealthcare.com/bmg).

activation of CDK1, which is concomitant with the inactivation of PP2A-B55 holoenzyme (Mochida *et al*., 2009). The role of CDK1 was discovered over 40 years ago, but the complex regulatory pathways in which it is involved continue to be studied (Fisher *et al*., 2012). CDK1 is kept inactive by phosphorylation of S14 and Y15 by Wee1 and Myt1 (Mueller *et al*., 1995). During the G2→M transition, CDK1 is activated by a group of dual-specificity phosphatases, Cdc25a, b and c (herein collectively referred to as CDC25), which themselves are subject to a complex regulatory network involving several kinases and phosphatases (Lammer *et al*., 1998) [reviewed in Johnson & Kornbluth (2012)]. Before mitotic entry, CDC25 is phosphorylated on S216 by CaMKII and can also be phosphorylated by Chk1 to arrest the cell cycle (Hutchins *et al*., 2003). This allows 14–3-3 protein to associate with CDC25 and prevent its nuclear translocation (Margolis *et al*., 2006a). Chk1 also phosphorylates PP2A-B56δ on S37 which subsequently enhances its activity toward pT138 of CDC25, keeping CDC25 inactive (Margolis *et al*., 2006a). At the end of G2, CDK2-cyclin E phosphorylates CDC25 T138, decreasing the affinity of 14–3-3 to CDC25 (Margolis *et al*., 2006a). The decreased affinity allows gradual 14–3-3 dissociation, and the free 14–3-3 becomes bound in a phospho-keratin sink (Margolis *et al*., 2006a). The re-exposed S216 can then be dephosphorylated by PP1, preventing 14–3-3 re-association (Margolis *et al*., 2003,2006b). The now active CDC25 can dephosphorylate pT14 and pY15 of CDK2, subsequently activating it (Gautier *et al*., 1991). Once CDK1 is active, it can phosphorylate CDC25 at S214, enhancing the affinity of CDC25 for PP1 and causing activation of additional CDK1, leading to rapid mitotic progression (Margolis *et al*., 2006b) (Figure 8).

Protein phosphatase 2A (PP2A)-B55 holoenzyme provides additional mechanism for the complex CDK1 regulation. Before mitotic initiation, PP2A-B55 dephosphorylates Wee1 and Greatwall kinase, keeping both inactive (Harvey *et al*., 2011; Hegarat *et al*., 2014). It can also dephosphorylate and subsequently inactivate CDC25 at mitotic exit (Forester *et al*., 2007; Johnson & Kornbluth, 2012). In addition, cyclin A-CDK2 begins to phosphorylate Greatwall kinase at T194 and activate it at the G2→M transition (Hegarat *et al*., 2014). Greatwall phosphorylates ENSA that subsequently binds to and inhibits PP2A-B55, preventing CDC25 repression (Mochida *et al*., 2010). As more CDK1 is activated, a positive feedback loop ensures PP2A-B55 inactivation. CDK1 also phosphorylates Greatwall and FCP1, keeping a majority of ENSA phosphorylated and bound to PP2A-B55 (Hegarat *et al*., 2014). Furthermore, CDK1 inactivates Wee1 and, without the antagonistic effect of PP2A-B55, ensures its activation (Watanabe *et al*., 2005). This complex network of regulation and positive feedback loops serve to inactivate PP2A while activating CDK1, rapidly driving entry into mitosis.

PP2A in reorganization of cellular structures during mitosis

Protein phosphatase 2A (PP2A) holoenzymes play a critical role in regulating reorganization of cellular structures during mitosis, including nuclear envelope breakdown, rearrangement of intracellular organelles, such as the endo plasmic reticulum and the Golgi apparatus, assembly of mitotic chromosomes, assembly of the mitotic spindle and attachment of cytoplasmic microtubules to kinetochores, which are crucial for proper partitioning of cellular materials into emerging daughter cells during cytokinesis. A significant amount of knowledge on cellular reorganization during mitosis had been reviewed (Wurzenberger & Gerlich, 2011). Here, we primarily focus on the function of PP2A in these critical processes.

Nuclear envelop breakdown and reassembly is tightly coordinated with mitotic phosphorylation and

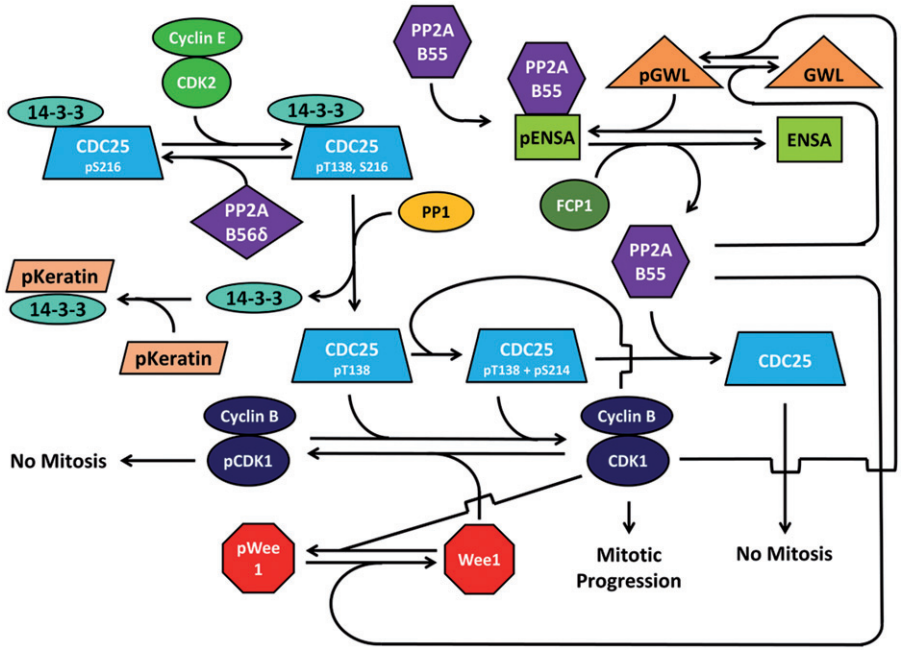

Figure 8. PP2A negatively regulates the cell cycle through CDC25 and Wee1. In G2, Greatwall, Fcp and Wee1 are dephosphorylated, keeping PP2A-B55 active and CDK1 inactive. CDC25 is phosphorylated at S216, allowing 14–3-3 association, holding it inactive. At the transition from G2 to M, CDC25 is phosphorylated at T138, weakening 14–3-3 binding and allowing dissociation with subsequent binding to a phospho-keratin pool. The now exposed S216 can be dephosphorylated by PP1 activating CDC25. Active CDC25 dephosphorylates CDK1 at T14 and Y15 thereby activating it. The active CDK1 can then phosphorylate several substrates required for mitotic progression. In addition, CDK1 participates in several positive feedback loops. It phosphorylates Wee1, preventing direct inactivation, and it phosphorylates CDC25 at S214, increasing its affinity for PP1 and allowing for more CDC25 activation. Furthermore, CDK1 can prevent CDC25 inactivation by PP2A-B55 by phosphorylating Greatwall, which in turn phosphorylates ENSA, which binds to PP2A-B55 and keeps it inactive. CDK1 also phosphorylates FCP1, preventing it from dephosphorylating ENSA and releasing PP2A-B55. Figure adapted from Johnson & Kornbluth (2012) and Hegarat *et al.* (2014). (see colour version of this figure at www.informahealthcare.com/bmg).

dephosphorylation (reviewed in Guttinger *et al.* (2009)). Nuclear envelop breakdown was facilitated by CDK1-dependent phosphorylation of lamin proteins and subsequent disassembly of the nuclear lamina (Peter *et al.*, 1990), and phosphorylation of nucleoporins-mediated disassembly of nuclear pore complexes (Laurell *et al.*, 2011). PP2A (Schmitz *et al.*, 2010) and its closely related PP1 (Thompson *et al.*, 1997) play a role in nuclear envelope reassembly during mitotic exit with unclear mechanisms. It remains to be determined whether lamin and nucleoporins are the specific substrates of PP2A. Disassembly and reassembly of the Golgi apparatus is also driven by mitotic phosphorylation and dephosphorylation. While phosphorylation of Golgi matrix protein GM130 induces disassembly (Wei & Seemann, 2009), PP2A-mediated dephosphorylation of GM130 induces Golgi reassembly during mitotic exit, which involves PP2A-B55α holoenzyme (Lowe *et al.*, 2000; Schmitz *et al.*, 2010).

Mitotic chromosomal assembly is regulated by condensin I and condensin II, which belongs to a class of conserved condensin complexes that play essential roles in mitotic chromosome condensation by collaborating with other chromosomal components (Hagstrom & Meyer, 2003; Jessberger, 2002). PP2A interacts with condensin II and plays an essential role in targeting condensin II to chromosomes (Takemoto *et al.*, 2009). Intriguingly, this process does not require the phosphatase activity of PP2A (Takemoto *et al.*, 2009). Chromatin decondensation requires PP1 and its regulatory subunits Repo-Man (recruits PP1 onto mitotic chromatin at anaphase protein) and PNUTS (phosphatase 1 nuclear targeting subunit) (Landsverk *et al.*, 2005; Vagnarelli *et al.*, 2006). The role of PP2A in this process is less characterized. Nonetheless, a recent study showed that a midzone-associated Aurora B gradient monitors chromosome position along the division axis and to prevent premature chromosome decondensation by retaining Condensin I until effective separation of sister chromatids is achieved (Afonso *et al.*, 2014). Both PP1 and PP2A phosphatases counteract this gradient and promoted chromosome decondensation (Afonso *et al.*, 2014).

Proper kinetochore–microtubule attachments are tightly controlled by Aurora B-mediated phosphorylation and PP2A/PP1-mediated dephosphorylation. Aurora B phosphorylates multiple substrates at the kinetochore to destabilize and correct erroneous kinetochore–microtubule attachments (Welburn *et al.*, 2010). While PP1 is considered the major phosphatase counteracting Aurora B (Carmena *et al.*, 2012), the PP2A-B56α holoenzyme also plays a critical role in stabilizing kinetochore–microtubule attachments by counteracting Aurora B phosphorylation (Foley *et al.*, 2011). Pseudokinase BUBR1 seems to play a critical role in integration of kinase and phosphatase activities to ensure proper formation of stable kinetochore–microtubule attachments (Suijkerbuijk *et al.*, 2012). Phosphorylation of a conserved KARD domain n BUBR1 by PLK1 (polo-like kinase 1) promotes direct interaction of BUBR1 with the PP2A-B56α phosphatase (Suijkerbuijk *et al.*, 2012), a potential mechanism for the recruitment of PP2A-B56α to the inner kinetochore prior to microtubule attachment (Foley *et al.*, 2011). Removal of BUBR1 from mitotic cells or inhibition of PLK1 reduces PP2A-B56α kinetochore binding (Suijkerbuijk *et al.*, 2012), suggesting that PLK1 and BUBR1 cooperate to stabilize kinetochore–microtubule interactions by regulating kinetochore localization of the PP2A-B56α holoenzyme.

PP2A in spindle checkpoint, regulation of APC/C-CDC20 and mitotic exit

The rise in APC/C-CDC20 activity initiates mitotic exit by targeting several mitotic determinants for degradation, resulting in the formation and separation of two interphase daughter cells. APC/C is kept inactive by the spindle assembly checkpoint until all chromosomes attach to microtubules originating from opposite spindle poles [reviewed in Musacchio & Salmon (2007)]. The early mitotic inhibitor 1 (Emi1) and 2 (Emi2) play a critical role in inhibition of APC/C, and PP2A-B56 holoenzymes was found to promote the inhibitory activity of Emi2 and maintain the spindle assembly checkpoint, which was antagonized by the activity of CDK1 (Tischer *et al*., 2012). CDK1-mediated phosphorylation of APC/C inhibitory proteins primes its own inactivation. At mitotic exit, APC/C-CDC20 induces proteasomal destruction of cyclin B, and inactivates mitotic CDK1 (Sullivan & Morgan, 2007). Inactivation of CDK1 is expected to lead to reactivation of PP2A-B55 to mediate dephosphorylation of CDK1 substrates at mitotic exit.

Adenomatous polyposis coli (APC)/C-CDC20 also mediates the degradation of securin to initiate chromosome segregation. Securin inhibits the protease separase; removal of securin allows separase to cleave the sister chromatid cohesion 1 (SCC1) subunit of the cohesin complex (Sullivan & Morgan, 2007). Cohesin function is also regulated by PLK1 and PP2A. PLK1 promotes dissociation of cohesin from chromosome arms by phosphorylating the cohesin subunit SA2 during prometaphase (Sumara *et al*., 2002). Shugoshin 1 recruits PP2A–B56 to protect SA2 against PLK1-mediated phosphorylation and thereby maintains a pool of persistent cohesion, and prevents premature separation of sister chromatids (Kitajima *et al*., 2006; Tang *et al*., 2006; Tanno *et al*., 2010; Xu *et al*., 2009).

With limited information on specific substrates targeted by diverse PP2A holoenzymes, the above knowledge likely merely represents a small fraction of PP2A function during mitosis. More questions need to be addressed regarding how PP2A holoenzyme activity is temporally and spatially controlled for tight regulation of numerous events during mitosis.

Concluding remarks

The cell cycle harbors complex and intricate processes and may be the most studied aspect in biology. This highlights its importance in understanding the origins of most of human disease and what can be done to intervene for therapeutic purposes. Great strides have been made in understanding the complex players of the cell cycle, and the importance of regulation by reversible phosphorylation cannot be underestimated.

The role of PP2A in regulating the cell cycle is only beginning to be investigated. It is involved in most major cell cycle initiation pathways as well as in regulating major checkpoints during cell cycle phase transitions. PP2A is implicated in dephosphorylating many more cell cycle pathway substrates than could be discussed here (Table 2), further highlighting its importance to properly functioning cells. The kinases involved in regulating the cell cycle typically exert their action through transcription-level changes and/or regulation of protein stability, whereas the cellular level of PP2A scaffold and catalytic subunits are stable throughout the cell cycle. Although PP2A expression differs from that leading to ''canonical'' kinase regulation, PP2A is one of the primary cell cycle regulating enzymes due to the dynamic nature of its holoenzyme assembly, activation and inhibition. As discussed, it is a major target in several key pathways, both for protein activation and inactivation, and it is frequently targeted for inhibition due to its antagonistic effects in these pathways. Although kinases may have taken center stage in the study of cell cycle regulation, the intricate connectivity between these kinases and PP2A shows its importance in the tight regulation of these processes.

In addition to its wide involvement in cellular processes, PP2A is a complex group of enzymes, and its assembly and activity are highly regulated making it challenging to study. No PP2A-substrate binding consensus sequence has been identified yet, indicating that structural and biochemical information is required to understand the mechanisms by which PP2A regulates substrate dephosphorylation. Currently, high-throughput assays are being explored to identify substrates and characterize protein–protein interactions significantly faster than traditional methods. These large scale assays combined with structural and biochemical characterization will provide an unprecedented amount of information to the PP2A field and possibly identify new targets of cell cycle regulation. These new targets may be incredibly useful in developing drugs or biomarkers for preventing, diagnosing or treating human disease, and more refined knowledge on existing PP2A-substrate interactions may help improve current treatments.

Declaration of interest

This project is supported by NIH RO1 GM096060–01 (Y. Xing). N. Wlodarchak is supported by NIH T32 (CA009135) and the Hartwell Foundation (133-PRJ24TF).

References

Abdelmohsen K, Srikantan S, Yang X, *et al*. (2009). Ubiquitin-mediated proteolysis of HuR by heat shock. EMBO J 28:1271–82.

Adams DG, Coffee Jr RL, Zhang H, *et al*. (2005). Positive regulation of Raf1-MEK1/2-ERK1/2 signaling by protein serine/threonine phosphatase 2A holoenzymes. J Biol Chem 280:42644–54.

Adler HT, Nallaseth FS, Walter G, Tkachuk DC. (1997). HRX leukemic fusion proteins form a heterocomplex with the leukemia-associated protein SET and protein phosphatase 2A. J Biol Chem 272:28407–14.

Afonso O, Matos I, Pereira AJ, *et al*. (2014). Feedback control of chromosome separation by a midzone Aurora B gradient. Science 345: 332–6.

Ahn JH, Mcavoy T, Rakhilin SV, *et al*. (2007a). Protein kinase A activates protein phosphatase 2A by phosphorylation of the B56delta subunit. Proc Natl Acad Sci USA 104:2979–84.

Ahn JH, Sung JY, Mcavoy T, *et al*. (2007b). The B″/PR72 subunit mediates Ca2+-dependent dephosphorylation of DARPP-32 by protein phosphatase 2A. Proc Natl Acad Sci USA 104:9876–81.

Aichem A, Kalveram B, Spinnenhirn V, *et al*. (2012). The proteomic analysis of endogenous FAT10 substrates identifies p62/SQSTM1 as a substrate of FAT10ylation. J Cell Sci 125:4576–85.

Alberts AS, Thorburn AM, Shenolikar S, *et al*. (1993). Regulation of cell cycle progression and nuclear affinity of the retinoblastoma protein by protein phosphatases. Proc Natl Acad Sci USA 90:388–92.

Alvarado-Kristensson M, Andersson T. (2005). Protein phosphatase 2A regulates apoptosis in neutrophils by dephosphorylating both p38 MAPK and its substrate caspase 3. J Biol Chem 280:6238–44.

Amit S, Hatzubai A, Birman Y, *et al*. (2002). Axin-mediated CKI phosphorylation of beta-catenin at Ser 45: a molecular switch for the Wnt pathway. Genes Dev 16:1066–76.

Ammosova T, Washington K, Debebe Z, *et al*. (2005). Dephosphorylation of CDK9 by protein phosphatase 2A and protein phosphatase-1 in Tat-activated HIV-1 transcription. Retrovirology 2:47.

Arbuckle MI, Komiyama NH, Delaney A, *et al*. (2010). The SH3 domain of postsynaptic density 95 mediates inflammatory pain through phosphatidylinositol-3-kinase recruitment. EMBO Rep 11:473–8.

Arnold HK, Sears RC. (2006). Protein phosphatase 2A regulatory subunit B56alpha associates with c-myc and negatively regulates c-myc accumulation. Mol Cell Biol 26:2832–44.

Arnold HK, Zhang X, Daniel CJ, *et al*. (2009). The Axin1 scaffold protein promotes formation of a degradation complex for c-Myc. EMBO J 28:500–12.

Asencio C, Davidson IF, Santarella-Mellwig R, *et al*. (2012). Coordination of kinase and phosphatase activities by Lem4 enables nuclear envelope reassembly during mitosis. Cell 150:122–35.

Avdi NJ, Malcolm KC, Nick JA, Worthen GS. (2002). A role for protein phosphatase-2A in p38 mitogen-activated protein kinase-mediated regulation of the c-Jun NH(2)-terminal kinase pathway in human neutrophils. J Biol Chem 277:40687–96.

Baroja ML, Vijayakrishnan L, Bettelli E, *et al*. (2002). Inhibition of CTLA-4 function by the regulatory subunit of serine/threonine phosphatase 2A. J Immunol 168:5070–8.

Bauman AL, Apparsundaram S, Ramamoorthy S, *et al*. (2000). Cocaine and antidepressant-sensitive biogenic amine transporters exist in regulated complexes with protein phosphatase 2A. J Neurosci 20: 7571–8.

Beaulieu JM, Sotnikova TD, Marion S, *et al*. (2005). An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. Cell 122:261–73.

Behrens J, Von Kries JP, Kuhl M, *et al*. (1996). Functional interaction of beta-catenin with the transcription factor LEF-1. Nature 382:638–42.

Bell SP. (2002). The origin recognition complex: from simple origins to complex functions. Genes Dev 16:659–72.

Bell SP, Stillman B. (1992). ATP-dependent recognition of eukaryotic origins of DNA replication by a multiprotein complex. Nature 357: 128–34.

Belle R, Cormier P, Poulhe R, *et al*. (1990). Protein phosphorylation during meiotic maturation of Xenopus oocytes: cdc2 protein kinase targets. Int J Dev Biol 34:111–15.

Bennett EJ, Rush J, Gygi SP, Harper JW. (2010). Dynamics of cullin-RING ubiquitin ligase network revealed by systematic quantitative proteomics. Cell 143:951–65.

Bennin DA, Don AS, Brake T, *et al*. (2002). Cyclin G2 associates with protein phosphatase 2A catalytic and regulatory B' subunits in active complexes and induces nuclear aberrations and a G1/S phase cell cycle arrest. J Biol Chem 277:27449–67.

Bishop JD, Nien WL, Dauphinee SM, Too CK. (2006). Prolactin activates mammalian target-of-rapamycin through phosphatidylinositol 3-kinase and stimulates phosphorylation of p70S6K and 4E-binding protein-1 in lymphoma cells. J Endocrinol 190:307–12.

Bisson N, James DA, Ivosev G, *et al*. (2011). Selected reaction monitoring mass spectrometry reveals the dynamics of signaling through the GRB2 adaptor. Nat Biotechnol 29:653–8.

Bobulescu IA, Quinones H, Gisler SM, *et al*. (2010). Acute regulation of renal Na+/H+exchanger NHE3 by dopamine: role of protein phosphatase 2A. Am J Physiol Renal Physiol 298:F1205–13.

Bononi A, Agnoletto C, De Marchi E, *et al*. (2011). Protein kinases and phosphatases in the control of cell fate. Enzyme Res 2011:329098.

Borsotto M, Cavarec L, Bouillot M, *et al*. (2007). PP2A-Bgamma subunit and KCNQ2 K+channels in bipolar disorder. Pharmacogenomics J 7:123–32.

Breitman M, Zilberberg A, Caspi M, Rosin-Arbesfeld R. (2008). The armadillo repeat domain of the APC tumor suppressor protein interacts with Striatin family members. Biochim Biophys Acta 1783:1792–802.

Brown EJ, Albers MW, Shin TB, *et al*. (1994). A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Nature 369: 756–8.

Brown VD, Phillips RA, Gallie BL. (1999). Cumulative effect of phosphorylation of pRB on regulation of E2F activity. Mol Cell Biol 19:3246–56.

Burnett PE, Barrow RK, Cohen NA, *et al*. (1998). RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. Proc Natl Acad Sci USA 95:1432–7.

Cafferkey R, Young PR, Mclaughlin MM, *et al*. (1993). Dominant missense mutations in a novel yeast protein related to mammalian phosphatidylinositol 3-kinase and VPS34 abrogate rapamycin cytotoxicity. Mol Cell Biol 13:6012–23.

Cannavo E, Gerrits B, Marra G, *et al*. (2007). Characterization of the interactome of the human MutL homologues MLH1, PMS1, and PMS2. J Biol Chem 282:2976–86.

Carlson CJ, White MF, Rondinone CM. (2004). Mammalian target of rapamycin regulates IRS-1 serine 307 phosphorylation. Biochem Biophys Res Commun 316:533–9.

Carmena M, Wheelock M, Funabiki H, Earnshaw WC. (2012). The chromosomal passenger complex (CPC): from easy rider to the godfather of mitosis. Nat Rev Mol Cell Biol 13:789–803.

Chan SF, Sucher NJ. (2001). An NMDA receptor signaling complex with protein phosphatase 2A. J Neurosci 21:7985–92.

Chatr-Aryamontri A, Breitkreutz BJ, Oughtred R, *et al*. (2015). The BioGRID interaction database: 2015 update. Nucleic Acids Res 43: D470–8.

Chen GI, Tisayakorn S, Jorgensen C, *et al*. (2008). PP4R4/KIAA1622 forms a novel stable cytosolic complex with phosphoprotein phosphatase 4. J Biol Chem 283:29273–84.

Chen HW, Yang CC, Hsieh CL, *et al*. (2013). A functional genomic approach reveals the transcriptional role of EDD in the expression and function of angiogenesis regulator ACVRL1. Biochim Biophys Acta 1829:1309–19.

Chen J, Alberts I, Li X. (2014). Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. Int J Dev Neurosci 35:35–41.

Cho US, Xu W. (2007). Crystal structure of a protein phosphatase 2A heterotrimeric holoenzyme. Nature 445:53–7.

Chowdhury D, Keogh MC, Ishii H, *et al*. (2005). gamma-H2AX dephosphorylation by protein phosphatase 2A facilitates DNA double-strand break repair. Mol Cell 20:801–9.

Chuang JY, Wang SA, Yang WB, *et al*. (2012). Sp1 phosphorylation by cyclin-dependent kinase 1/cyclin B1 represses its DNA-binding activity during mitosis in cancer cells. Oncogene 31:4946–59.

Cicchillitti L, Fasanaro P, Biglioli P, *et al*. (2003). Oxidative stress induces protein phosphatase 2A-dependent dephosphorylation of the pocket proteins pRb, p107, and p130. J Biol Chem 278:19509–17.

Clevers H, Nusse R. (2012). Wnt/β-catenin signaling and disease. Cell 149:1192–205.

Colland F, Jacq X, Trouplin V, *et al*. (2004). Functional proteomics mapping of a human signaling pathway. Genome Res 14:1324–32.

Cox JL, Wilder PJ, Gilmore JM, *et al*. (2013). The SOX2-interactome in brain cancer cells identifies the requirement of MSI2 and USP9X for the growth of brain tumor cells. PLoS One 8:e62857.

Crews CM, Alessandrini A, Erikson RL. (1992). The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product. Science 258:478–80.

Creyghton MP, Roel G, Eichhorn PJ, *et al*. (2005). PR72, a novel regulator of Wnt signaling required for Naked cuticle function. Genes Dev 19:376–86.

Creyghton MP, Roel G, Eichhorn PJ, *et al*. (2006). PR130 is a modulator of the Wnt-signaling cascade that counters repression of the antagonist Naked cuticle. Proc Natl Acad Sci USA 103:5397–402.

Crossthwaite AJ, Ciruela A, Rayner TF, Cooper DM. (2006). A direct interaction between the N terminus of adenylyl cyclase AC8 and the catalytic subunit of protein phosphatase 2A. Mol Pharmacol 69: 608–17.

Dagda RK, Barwacz CA, Cribbs JT, Strack S. (2005). Unfolding-resistant translocase targeting: a novel mechanism for outer mitochondrial membrane localization exemplified by the Bbeta2 regulatory subunit of protein phosphatase 2A. J Biol Chem 280:27375–82.

Dajani R, Fraser E, Roe SM, *et al*. (2003). Structural basis for recruitment of glycogen synthase kinase 3beta to the axin-APC scaffold complex. EMBO J 22:494–501.

Davis AJ, Yan Z, Martinez B, Mumby MC. (2008). Protein phosphatase 2A is targeted to cell division control protein 6 by a calcium-binding regulatory subunit. J Biol Chem 283:16104–14.

Dehde S, Rohaly G, Schub O, *et al*. (2001). Two immunologically distinct human DNA polymerase alpha-primase subpopulations are involved in cellular DNA replication. Mol Cell Biol 21:2581–93.

Dobierzewska A, Giltiay NV, Sabapathi S, *et al*. (2011). Protein phosphatase 2A and neutral sphingomyelinase 2 regulate IRAK-1 protein ubiquitination and degradation in response to interleukin-1beta. J Biol Chem 286:32064–73.

Dodge-Kafka KL, Bauman A, Mayer N, *et al*. (2010). cAMP-stimulated protein phosphatase 2A activity associated with muscle A kinase-anchoring protein (mAKAP) signaling complexes inhibits the phosphorylation and activity of the cAMP-specific phosphodiesterase PDE4D3. J Biol Chem 285:11078–86.

Dohoney KM, Guillerm C, Whiteford C, *et al*. (2004). Phosphorylation of p53 at serine 37 is important for transcriptional activity and regulation in response to DNA damage. Oncogene 23:49–57.

Dominguez-Brauer C, Brauer PM, Chen YJ, *et al*. (2010). Tumor suppression by ARF: gatekeeper and caretaker. Cell Cycle 9:86–9.

Dovega R, Tsutakawa S, Quistgaard EM, *et al*. (2014). Structural and biochemical characterization of human PR70 in isolation and in complex with the scaffolding subunit of protein phosphatase 2A. PLoS One 9:e101846.

Duncker BP, Chesnokov IN, Mcconkey BJ. (2009). The origin recognition complex protein family. Genome Biol 10:214.

Egan SE, Giddings BW, Brooks MW, *et al*. (1993). Association of Sos Ras exchange protein with Grb2 is implicated in tyrosine kinase signal transduction and transformation. Nature 363:45–51.

Eichhorn PJ, Creyghton MP, Bernards R. (2009). Protein phosphatase 2A regulatory subunits and cancer. Biochim Biophys Acta 1795:1–15.

Eichhorn PJ, Creyghton MP, Wilhelmsen K, *et al*. (2007). A RNA interference screen identifies the protein phosphatase 2A subunit PR55gamma as a stress-sensitive inhibitor of c-SRC. PLoS Genet 3: e218.

Ewing RM, Chu P, Elisma F, *et al*. (2007). Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol Syst Biol 3:89.

Fan GH, Yang W, Sai J, Richmond A. (2001). Phosphorylation-independent association of CXCR2 with the protein phosphatase 2A core enzyme. J Biol Chem 276:16960–8.

Ferrarese A, Marin O, Bustos VH, *et al*. (2007). Chemical dissection of the APC Repeat 3 multistep phosphorylation by the concerted action of protein kinases CK1 and GSK3. Biochemistry 46: 11902–10.

Firulli BA, Howard MJ, Mcdaid JR, *et al*. (2003). PKA, PKC, and the protein phosphatase 2A influence HAND factor function: a mechanism for tissue-specific transcriptional regulation. Mol Cell 12: 1225–37.

Fisher D, Krasinska L, Coudreuse D, Novak B. (2012). Phosphorylation network dynamics in the control of cell cycle transitions. J Cell Sci 125:4703–11.

Foerster S, Kacprowski T, Dhople VM, *et al*. (2013). Characterization of the EGFR interactome reveals associated protein complex networks and intracellular receptor dynamics. Proteomics 13:3131–44.

Foley EA, Maldonado M, Kapoor TM. (2011). Formation of stable attachments between kinetochores and microtubules depends on the B56-PP2A phosphatase. Nat Cell Biol 13:1265–71.

Forester CM, Maddox J, Louis JV, *et al*. (2007). Control of mitotic exit by PP2A regulation of Cdc25C and Cdk1. Proc Natl Acad Sci USA 104:19867–72.

Franklin CC, Kraft AS. (1997). Conditional expression of the mitogen-activated protein kinase (MAPK) phosphatase MKP-1 preferentially inhibits p38 MAPK and stress-activated protein kinase in U937 cells. J Biol Chem 272:16917–23.

Franklin CC, Srikanth S, Kraft AS. (1998). Conditional expression of mitogen-activated protein kinase phosphatase-1, MKP-1, is cytoprotective against UV-induced apoptosis. Proc Natl Acad Sci USA 95: 3014–19.

Freedman TS, Sondermann H, Friedland GD, *et al*. (2006). A Ras-induced conformational switch in the Ras activator Son of sevenless. Proc Natl Acad Sci USA 103:16692–7.

Fritz A, Brayer KJ, Mccormick N, *et al*. (2006). Phosphorylation of serine 526 is required for MEKK3 activity, and association with 14-3-3 blocks dephosphorylation. J Biol Chem 281:6236–45.

Fruman DA, Rommel C. (2014). PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov 13:140–56.

Fu DX, Kuo YL, Liu BY, *et al*. (2003). Human T-lymphotropic virus type I tax activates I-kappa B kinase by inhibiting I-kappa B kinase-associated serine/threonine protein phosphatase 2A. J Biol Chem 278:1487–93.

Fuhrer DK, Yang YC. (1996). Complex formation of JAK2 with PP2A, P13K, and Yes in response to the hematopoietic cytokine interleukin-11. Biochem Biophys Res Commun 224:289–96.

Galea MA, Eleftheriou A, Henderson BR. (2001). ARM domain-dependent nuclear import of adenomatous polyposis coli protein is stimulated by the B56 alpha subunit of protein phosphatase 2A. J Biol Chem 276:45833–9.

Garriga J, Jayaraman AL, Limon A, *et al*. (2004). A dynamic equilibrium between CDKs and PP2A modulates phosphorylation of pRB, p107 and p130. Cell Cycle (Georgetown, Tx) 3:1320–30.

Gautier J, Solomon MJ, Booher RN, *et al*. (1991). cdc25 is a specific tyrosine phosphatase that directly activates p34cdc2. Cell 67:197–211.

Gil-Bernabe AM, Romero F, Limon-Mortes MC, Tortolero M. (2006). Protein phosphatase 2A stabilizes human securin, whose phosphorylated forms are degraded via the SCF ubiquitin ligase. Mol Cell Biol 26:4017–27.

Glatter T, Wepf A, Aebersold R, Gstaiger M. (2009). An integrated workflow for charting the human interaction proteome: insights into the PP2A system. Mol Syst Biol 5:237.

Goodarzi AA, Jonnalagadda JC, Douglas P, *et al*. (2004). Autophosphorylation of ataxia-telangiectasia mutated is regulated by protein phosphatase 2A. EMBO J 23:4451–61.

Gordon J, Hwang J, Carrier KJ, *et al*. (2011). Protein phosphatase 2a (PP2A) binds within the oligomerization domain of striatin and regulates the phosphorylation and activation of the mammalian Ste20-Like kinase Mst3. BMC Biochem 12:54.

Gotz J, Probst A, Mistl C, *et al*. (2000). Distinct role of protein phosphatase 2A subunit Calpha in the regulation of E-cadherin and beta-catenin during development. Mech Dev 93:83–93.

Grant MM. (2010). Identification of SUMOylated proteins in neuroblastoma cells after treatment with hydrogen peroxide or ascorbate. BMB Rep 43:720–5.

Greco TM, Yu F, Guise AJ, Cristea IM. (2011). Nuclear import of histone deacetylase 5 by requisite nuclear localization signal phosphorylation. Mol Cell Proteomics 10:M110.004317.

Griswold-Prenner I, Kamibayashi C, Maruoka EM, *et al*. (1998). Physical and functional interactions between type I transforming growth factor beta receptors and Balpha, a WD-40 repeat subunit of phosphatase 2A. Mol Cell Biol 18:6595–604.

Guo F, Stanevich V, Wlodarchak N, *et al*. (2014). Structural basis of PP2A activation by PTPA, an ATP-dependent activation chaperone. Cell Res 24:190–203.

Guo Z, Song E, Ma S, *et al*. (2012). Proteomics strategy to identify substrates of LNX, a PDZ domain-containing E3 ubiquitin ligase. J Proteome Res 11:4847–62.

Guttinger S, Laurell E, Kutay U. (2009). Orchestrating nuclear envelope disassembly and reassembly during mitosis. Nat Rev Mol Cell Biol 10:178–91.

Ha NC, Tonozuka T, Stamos JL, *et al*. (2004). Mechanism of phosphorylation-dependent binding of APC to beta-catenin and its role in beta-catenin degradation. Mol Cell 15:511–21.

Hagstrom KA, Meyer BJ. (2003). Condensin and cohesin: more than chromosome compactor and glue. Nat Rev Genet 4:520–34.

Hall DD, Feekes JA, Arachchige Don AS, *et al*. (2006). Binding of protein phosphatase 2A to the L-type calcium channel Cav1.2 next to Ser1928, its main PKA site, is critical for Ser1928 dephosphorylation. Biochemistry 45:3448–59.

Harbour JW, Dean DC. (2000). Rb function in cell-cycle regulation and apoptosis. Nat Cell Biol 2:E65–7.

Hartley D, Cooper GM. (2002). Role of mTOR in the degradation of IRS-1: regulation of PP2A activity. J Cell Biochem 85:304–14.

Harvey SL, Enciso G, Dephoure N, *et al*. (2011). A phosphatase threshold sets the level of Cdk1 activity in early mitosis in budding yeast. Mol Biol Cell 22:3595–608.

Hashigasako A, Machide M, Nakamura T, Matsumoto K. (2004). Bi-directional regulation of Ser-985 phosphorylation of c-met via protein kinase C and protein phosphatase 2A involves c-Met activation and cellular responsiveness to hepatocyte growth factor. J Biol Chem 279: 26445–52.

He TC, Sparks AB, Rago C, *et al*. (1998). Identification of c-MYC as a target of the APC pathway. Science 281:1509–12.

Hegarat N, Vesely C, Vinod PK, *et al*. (2014). PP2A/B55 and Fcp1 Regulate Greatwall and Ensa Dephosphorylation during Mitotic Exit. PLoS Genet 10:e1004004.

Heijman J, Dewenter M, El-Armouche A, Dobrev D. (2013). Function and regulation of serine/threonine phosphatases in the healthy and diseased heart. J Mol Cell Cardiol 64:90–8.

Heikkinen PT, Nummela M, Leivonen SK, *et al*. (2010). Hypoxia-activated Smad3-specific dephosphorylation by PP2A. J Biol Chem 285:3740–9.

Hirschi A, Cecchini M, Steinhardt RC, *et al*. (2010). An overlapping kinase and phosphatase docking site regulates activity of the retinoblastoma protein. Nat Struct Mol Biol 17:1051–7.

Hoffmann C, Gaietta G, Bunemann M, *et al*. (2005). A FlAsH-based FRET approach to determine G protein-coupled receptor activation in living cells. Nat Methods 2:171–6.

Holland AJ, Bottger F, Stemmann O, Taylor SS. (2007). Protein phosphatase 2A and separase form a complex regulated by separase autocleavage. J Biol Chem 282:24623–32.

Holt LJ. (2012). Regulatory modules: coupling protein stability to phopshoregulation during cell division. FEBS Lett 586:2773–7.

Hommes DW, Peppelenbosch MP, Deventer SJHV. (2003). Mitogen activated protein (MAP) kinase signal transduction pathways and novel anti-inflammatory targets. Gut 52:144–51

Horn V, Thelu J, Garcia A, *et al*. (2007). Functional interaction of Aurora-A and PP2A during mitosis. Mol Biol Cell 18:1233–41.

Hsu PP, Kang SA, Rameseder J, *et al*. (2011). The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science 332:1317–22.

Huang HK, Forsburg SL, John UP, *et al*. (2001). Isolation and characterization of the Pin1/Ess1p homologue in *Schizosaccharomyces pombe*. J Cell Sci 114:3779–88.

Hunter T. (1995). Protein kinases and phosphatases: the yin and yang of protein phosphorylation and signaling. Cell 80:225–36.

Hutchins JR, Dikovskaya D, Clarke PR. (2003). Regulation of Cdc2/cyclin B activation in Xenopus egg extracts via inhibitory phosphorylation of Cdc25C phosphatase by Ca(2+)/calmodulin-dependent protein [corrected] kinase II. Mol Biol Cell 14:4003–14.

Hyrien O, Rappailles A, Guilbaud G, *et al*. (2013). From simple bacterial and archaeal replicons to replication N/U-domains. J Mol Biol 425: 4673–89.

Imajo M, Tsuchiya Y, Nishida E. (2006). Regulatory mechanisms and functions of MAP kinase signaling pathways. IUBMB Life 58: 312–17.

Indovina P, Marcelli E, Casini N, *et al*. (2013). Emerging roles of RB family: new defense mechanisms against tumor progression. J Cell Physiol 228:525–35.

Inoki K, Ouyang H, Zhu T, *et al*. (2006). TSC2 integrates Wnt and energy signals via a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth. Cell 126:955–68.

Ishiguro T, Tanaka K, Sakuno T, Watanabe Y. (2010). Shugoshin-PP2A counteracts casein-kinase-1-dependent cleavage of Rec8 by separase. Nat Cell Biol 12:500–6.

Ito A, Kataoka TR, Watanabe M, *et al*. (2000). A truncated isoform of the PP2A B56 subunit promotes cell motility through paxillin phosphorylation. EMBO J 19:562–71.

Jackson JB, Pallas DC. (2012). Circumventing cellular control of PP2A by methylation promotes transformation in an Akt-dependent manner. Neoplasia 14:585–99.

Jager S, Cimermancic P, Gulbahce N, *et al*. (2012). Global landscape of HIV-human protein complexes. Nature 481:365–70.

Jallepalli PV, Brown GW, Muzi-Falconi M, *et al*. (1997). Regulation of the replication initiator protein p65cdc18 by CDK phosphorylation. Genes Dev 11:2767–79.

Janssens V, Goris J. (2001). Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. Biochem J 353:417–39.

Janssens V, Longin S, Goris J. (2008). PP2A holoenzyme assembly: in cauda venenum (the sting is in the tail). Trends Biochem Sci 33: 113–21.

Jaumot M, Hancock JF. (2001). Protein phosphatases 1 and 2A promote Raf-1 activation by regulating 14-3-3 interactions. Oncogene 20: 3949–58.

Jayadeva G, Kurimchak A, Garriga J, *et al*. (2010). B55alpha PP2A holoenzymes modulate the phosphorylation status of the retinoblastoma-related protein p107 and its activation. J Biol Chem 285: 29863–73.

Jessberger R. (2002). The many functions of SMC proteins in chromosome dynamics. Nat Rev Mol Cell Biol 3:767–78.

Jho E, Lomvardas S, Costantini F. (1999). A GSK3beta phosphorylation site in axin modulates interaction with beta-catenin and Tcf-mediated gene expression. Biochem Biophys Res Commun 266:28–35.

Jiang L, Stanevich V, Satyshur KA, *et al*. (2013). Structural basis of protein phosphatase 2A stable latency. Nat Commun 4:1699.

Johnson ES, Kornbluth S. (2012). Phosphatases driving mitosis: pushing the gas and lifting the brakes. Prog Mol Biol Transl Sci 106:327–41.

Joshi P, Greco TM, Guise AJ, *et al*. (2013). The functional interactome landscape of the human histone deacetylase family. Mol Syst Biol 9: 672.

Julius MA, Schelbert B, Hsu W, *et al*. (2000). Domains of axin and disheveled required for interaction and function in wnt signaling. Biochem Biophys Res Commun 276:1162–9.

Junttila MR, Puustinen P, Niemela M, *et al*. (2007). CIP2A inhibits PP2A in human malignancies. Cell 130:51–62.

Kanemitsu MY, Jiang W, Eckhart W. (1998). Cdc2-mediated phosphorylation of the gap junction protein, connexin43, during mitosis. Cell Growth Differ 9:13–21.

Kawabe T, Muslin AJ, Korsmeyer SJ. (1997). HOX11 interacts with protein phosphatases PP2A and PP1 and disrupts a G2/M cell-cycle checkpoint. Nature 385:454–8.

Keen JC, Zhou Q, Park BH, *et al*. (2005). Protein phosphatase 2A regulates estrogen receptor alpha (ER) expression through modulation of ER mRNA stability. J Biol Chem 280:29519–24.

Kiely PA, O'Gorman D, Luong K, *et al*. (2006). Insulin-like growth factor I controls a mutually exclusive association of RACK1 with protein phosphatase 2A and beta1 integrin to promote cell migration. Mol Cell Biol 26:4041–51.

Kim DH, Sarbassov DD, Ali SM, *et al*. (2002). mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110:163–75.

Kim DH, Sarbassov DD, Ali SM, *et al*. (2003). GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol Cell 11: 895–904.

Kim J, Kundu M, Viollet B, Guan KL. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 13:132–41.

Kim ST, Lim DS, Canman CE, Kastan MB. (1999). Substrate specificities and identification of putative substrates of ATM kinase family members. J Biol Chem 274:37538–43.

Kinzler KW, Nilbert MC, Su LK, *et al*. (1991). Identification of FAP locus genes from chromosome 5q21. Science 253:661–5.

Kitajima TS, Sakuno T, Ishiguro K, *et al*. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. Nature 441:46–52.

Klippel A, Kavanaugh WM, Pot D, Williams LT. (1997). A specific product of phosphatidylinositol 3-kinase directly activates the protein kinase Akt through its pleckstrin homology domain. Mol Cell Biol 17: 338–44.

Kolupaeva V, Daempfling L, Basilico C. (2013). The B55alpha regulatory subunit of protein phosphatase 2A mediates fibroblast growth factor-induced p107 dephosphorylation and growth arrest in chondrocytes. Mol Cell Biol 33:2865–78.

Kolupaeva V, Janssens V. (2013). PP1 and PP2A phosphatases–cooperating partners in modulating retinoblastoma protein activation. FEBS J 280:627–43.

Kotlo K, Johnson KR, Grillon JM, *et al*. (2012). Phosphoprotein abundance changes in hypertensive cardiac remodeling. J Proteomics 77:1–13.

Krahn MP, Egger-Adam D, Wodarz A. (2009). PP2A antagonizes phosphorylation of Bazooka by PAR-1 to control apical-basal polarity in dividing embryonic neuroblasts. Dev Cell 16:901–8.

Kray AE, Carter RS, Pennington KN, *et al*. (2005). Positive regulation of IkappaB kinase signaling by protein serine/threonine phosphatase 2A. J Biol Chem 280:35974–82.

Kristensen AR, Gsponer J, Foster LJ. (2012). A high-throughput approach for measuring temporal changes in the interactome. Nat Methods 9:907–9.

Krueger KM, Daaka Y, Pitcher JA, Lefkowitz RJ. (1997). The role of sequestration in G protein-coupled receptor resensitization. Regulation of beta2-adrenergic receptor dephosphorylation by vesicular acidification. J Biol Chem 272:5–8.

Kumar A, Pandurangan AK, Lu F, *et al*. (2012). Chemopreventive sphingadienes downregulate Wnt signaling via a PP2A/Akt/GSK3beta pathway in colon cancer. Carcinogenesis 33:1726–35.

Kunz J, Henriquez R, Schneider U, *et al*. (1993). Target of rapamycin in yeast, TOR2, is an essential phosphatidylinositol kinase homolog required for G1 progression. Cell 73:585–96.

Kuo YC, Huang KY, Yang CH, *et al*. (2008). Regulation of phosphorylation of Thr-308 of Akt, cell proliferation, and survival by the B55alpha regulatory subunit targeting of the protein phosphatase 2A holoenzyme to Akt. J Biol Chem 283:1882–92.

Kurimchak A, Grana X. (2012). PP2A holoenzymes negatively and positively regulate cell cycle progression by dephosphorylating pocket proteins and multiple CDK substrates. Gene 499:1–7.

Lammer C, Wagerer S, Saffrich R, *et al*. (1998). The cdc25B phosphatase is essential for the G2/M phase transition in human cells. J Cell Sci 111:2445–53.

Landsverk HB, Kirkhus M, Bollen M, *et al*. (2005). PNUTS enhances in vitro chromosome decondensation in a PP1-dependent manner. Biochem J 390:709–17.

Lao DH, Yusoff P, Chandramouli S, *et al*. (2007). Direct binding of PP2A to Sprouty2 and phosphorylation changes are a prerequisite for ERK inhibition downstream of fibroblast growth factor receptor stimulation. J Biol Chem 282:9117–26.

Laplante M, Sabatini DM. (2012). mTOR signaling in growth control and disease. Cell 149:274–93.

Latres E, Chiaur DS, Pagano M. (1999). The human F box protein beta-Trcp associates with the Cul1/Skp1 complex and regulates the stability of beta-catenin. Oncogene 18:849–54.

Laurell E, Beck K, Krupina K, *et al*. (2011). Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry. Cell 144:539–50.

Lechward K, Zolnierowicz S, Hemmings BA. (1999). Eukaryotic translation termination factor 1 associates with protein phosphatase 2A and targets it to ribosomes. Biochemistry (Mosc) 64:1373–81.

Lee JA, Pallas DC. (2007). Leucine carboxyl methyltransferase-1 is necessary for normal progression through mitosis in mammalian cells. J Biol Chem 282:30974–84.

Lee WJ, Kim DU, Lee MY, Choi KY. (2007). Identification of proteins interacting with the catalytic subunit of PP2A by proteomics. Proteomics 7:206–14.

Lees JA, Buchkovich KJ, Marshak DR, *et al*. (1991). The retinoblastoma protein is phosphorylated on multiple sites by human cdc2. EMBO J 10:4279–90.

Letourneux C, Rocher G, Porteu F. (2006). B56-containing PP2A dephosphorylate ERK and their activity is controlled by the early gene IEX-1 and ERK. EMBO J 25:727–38.

Leung-Hagesteijn C, Mahendra A, Naruszewicz I, Hannigan GE. (2001). Modulation of integrin signal transduction by ILKAP, a protein phosphatase 2C associating with the integrin-linked kinase, ILK1. EMBO J 20:2160–70.

Leung-Pineda V, Ryan CE, Piwnica-Worms H. (2006). Phosphorylation of Chk1 by ATR is antagonized by a Chk1-regulated protein phosphatase 2A circuit. Mol Cell Biol 26:7529–38.

Li HH, Cai X, Shouse GP, *et al*. (2007). A specific PP2A regulatory subunit, B56gamma, mediates DNA damage-induced dephosphorylation of p53 at Thr55. EMBO J 26:402–11.

Li M, Makkinje A, Damuni Z. (1996). The myeloid leukemia-associated protein SET is a potent inhibitor of protein phosphatase 2A. J Biol Chem 271:11059–62.

Li S, Wang L, Berman MA, *et al*. (2006). RNAi screen in mouse astrocytes identifies phosphatases that regulate NF-kappaB signaling. Mol Cell 24:497–509.

Liang C, Weinreich M, Stillman B. (1995). ORC and Cdc6p interact and determine the frequency of initiation of DNA replication in the genome. Cell 81:667–76.

Liedtke CM, Wang X, Smallwood ND. (2005). Role for protein phosphatase 2A in the regulation of Calu-3 epithelial Na+-K+-2Cl-, type 1 co-transport function. J Biol Chem 280:25491–8.

Lim J, Hao T, Shaw C, *et al*. (2006). A protein–protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell 125:801–14.

Lin SS, Bassik MC, Suh H, *et al*. (2006). PP2A regulates BCL-2 phosphorylation and proteasome-mediated degradation at the endoplasmic reticulum. J Biol Chem 281:23003–12.

Liu J, Prickett TD, Elliott E, *et al*. (2001). Phosphorylation and microtubule association of the Opitz syndrome protein mid-1 is regulated by protein phosphatase 2A via binding to the regulatory subunit alpha 4. Proc Natl Acad Sci USA 98:6650–5.

Liu L, Eisenman RN. (2012). Regulation of c-Myc protein abundance by a protein phosphatase 2A-glycogen synthase kinase 3β-negative feedback pathway. Genes Cancer 3:23–36.

Longin S, Zwaenepoel K, Louis JV, *et al*. (2007). Selection of protein phosphatase 2A regulatory subunits is mediated by the C terminus of the catalytic Subunit. J Biol Chem 282:26971–80.

Louis JV, Martens E, Borghgraef P, *et al*. (2011). Mice lacking phosphatase PP2A subunit PR61/B'delta (Ppp2r5d) develop spatially restricted tauopathy by deregulation of CDK5 and GSK3beta. Proc Natl Acad Sci USA 108:6957–62.

Low C, Quistgaard EM, Kovermann M, *et al*. (2014). Structural basis for PTPA interaction with the invariant C-terminal tail of PP2A. Biol Chem 395:881–9.

Lowe M, Gonatas NK, Warren G. (2000). The mitotic phosphorylation cycle of the cis-Golgi matrix protein GM130. J Cell Biol 149:341–56.

Luo W, Peterson A, Garcia BA, *et al*. (2007). Protein phosphatase 1 regulates assembly and function of the beta-catenin degradation complex. EMBO J 26:1511–21.

Ma J, Arnold HK, Lilly MB, *et al*. (2007). Negative regulation of Pim-1 protein kinase levels by the B56beta subunit of PP2A. Oncogene 26: 5145–53.

Ma OK, Sucher NJ. (2004). Molecular interaction of NMDA receptor subunit NR3A with protein phosphatase 2A. Neuroreport 15:1447–50.

Ma XM, Blenis J. (2009). Molecular mechanisms of mTOR-mediated translational control. Nat Rev Mol Cell Biol 10:307–18.

Macdonald BT, Tamai K, He X. (2009). Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell 17:9–26.

Magenta A, Fasanaro P, Romani S, *et al*. (2008). Protein phosphatase 2A subunit PR70 interacts with pRb and mediates its dephosphorylation. Mol Cell Biol 28:873–82.

Mailand N, Diffley JF. (2005). CDKs promote DNA replication origin licensing in human cells by protecting Cdc6 from APC/C-dependent proteolysis. Cell 122:915–26.

Manning G, Whyte DB, Martinez R, *et al*. (2002). The protein kinase complement of the human genome. Science 298:1912–34.

Mao L, Yang L, Arora A, *et al*. (2005). Role of protein phosphatase 2A in mGluR5-regulated MEK/ERK phosphorylation in neurons. J Biol Chem 280:12602–10.

Margolis SS, Perry JA, Forester CM, *et al*. (2006a). Role for the PP2A/B56delta phosphatase in regulating 14-3-3 release from Cdc25 to control mitosis. Cell 127:759–73.

Margolis SS, Perry JA, Weitzel DH, *et al*. (2006b). A role for PP1 in the Cdc2/Cyclin B-mediated positive feedback activation of Cdc25. Mol Biol Cell 17:1779–89.

Margolis SS, Walsh S, Weiser DC, *et al*. (2003). PP1 control of M phase entry exerted through 14-3-3-regulated Cdc25 dephosphorylation. EMBO J 22:5734–45.

Marmorstein LY, Mclaughlin PJ, Stanton JB, *et al*. (2002). Bestrophin interacts physically and functionally with protein phosphatase 2A. J Biol Chem 277:30591–7.

Martin L, Latypova X, Wilson CM, *et al*. (2013). Tau protein phosphatases in Alzheimer's disease: the leading role of PP2A. Ageing Res Rev 12:39–49.

Mathiasen DP, Egebjerg C, Andersen SH, *et al*. (2012). Identification of a c-Jun N-terminal kinase-2-dependent signal amplification cascade that regulates c-Myc levels in ras transformation. Oncogene 31:390–401.

Mayer C, Zhao J, Yuan X, Grummt I. (2004). mTOR-dependent activation of the transcription factor TIF-IA links rRNA synthesis to nutrient availability. Genes Dev 18:423–34.

Mcconnell JL, Gomez RJ, Mccorvey LR, *et al*. (2007). Identification of a PP2A-interacting protein that functions as a negative regulator of phosphatase activity in the ATM/ATR signaling pathway. Oncogene 26:6021–30.

Mccubrey JA, Steelman LS, Chappell WH, *et al*. (2007). Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta 1773:1263–84.

Meilleur MA, Akpovi CD, Pelletier RM, Vitale ML. (2007). Tumor necrosis factor-alpha-induced anterior pituitary folliculostellate TtT/GF cell uncoupling is mediated by connexin 43 dephosphorylation. Endocrinology 148:5913–24.

Meloche S, Pouyssegur J. (2007). The ERK1/2 mitogen-activated protein kinase pathway as a master regulator of the G1- to S-phase transition. Oncogene 26:3227–39.

Merrill RA, Slupe AM, Strack S. (2013). N-terminal phosphorylation of protein phosphatase 2A/Bbeta2 regulates translocation to

mitochondria, dynamin-related protein 1 dephosphorylation, and neuronal survival. FEBS J 280:662–73.
Michniewicz M, Zago MK, Abas L, *et al*. (2007). Antagonistic regulation of PIN phosphorylation by PP2A and PINOID directs auxin flux. Cell 130:1044–56.
Milburn MV, Tong L, Devos AM, *et al*. (1990). Molecular switch for signal transduction: structural differences between active and inactive forms of protooncogenic ras proteins. Science 247:939–45.
Mitra A, Menezes ME, Pannell LK, *et al*. (2012). DNAJB6 chaperones PP2A mediated dephosphorylation of GSK3beta to downregulate beta-catenin transcription target, osteopontin. Oncogene 31:4472–83.
Mitsuhashi S, Shima H, Tanuma N, *et al*. (2005). Protein phosphatase type 2A, PP2A, is involved in degradation of gp130. Mol Cell Biochem 269:183–7.
Mochida S, Hunt T. (2012). Protein phosphatases and their regulation in the control of mitosis. EMBO Rep 13:197–203.
Mochida S, Ikeo S, Gannon J, Hunt T. (2009). Regulated activity of PP2A-B55 delta is crucial for controlling entry into and exit from mitosis in Xenopus egg extracts. EMBO J 28:2777–85.
Mochida S, Maslen SL, Skehel M, Hunt T. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. Science 330:1670–3.
Monje P, Hernandez-Losa J, Lyons RJ, *et al*. (2005). Regulation of the transcriptional activity of c-Fos by ERK. A novel role for the prolyl isomerase PIN1. J Biol Chem 280:35081–4.
Moreno CS, Park S, Nelson K, *et al*. (2000). WD40 repeat proteins striatin and S/G2 nuclear autoantigen are members of a novel family of calmodulin-binding proteins that associate with protein phosphatase 2A. J Biol Chem 275:5257–63.
Mueller PR, Coleman TR, Kumagai A, Dunphy WG. (1995). Myt1: a membrane-associated inhibitory kinase that phosphorylates Cdc2 on both threonine-14 and tyrosine-15. Science 270:86–90.
Mumby M. (2001). A new role for protein methylation: switching partners at the phosphatase ball. Sci STKE 2001:pe1
Mumby M. (2009). Lab Webpage [Online]. Dallas (TX): UT Southwestern
Musacchio A, Salmon ED. (2007). The spindle-assembly checkpoint in space and time. Nat Rev Mol Cell Biol 8:379–93.
Naji S, Ambrus G, Cimermancic P, *et al*. (2012). Host cell interactome of HIV-1 Rev includes RNA helicases involved in multiple facets of virus production. Mol Cell Proteomics 11:M111.015313.
Nakashima A, Tanimura-Ito K, Oshiro N, *et al*. (2013). A positive role of mammalian Tip41-like protein, TIPRL, in the amino-acid dependent mTORC1-signaling pathway through interaction with PP2A. FEBS Lett 587:2924–9.
Narayanan U, Nalavadi V, Nakamoto M, *et al*. (2007). FMRP phosphorylation reveals an immediate-early signaling pathway triggered by group I mGluR and mediated by PP2A. J Neurosci 27: 14349–57.
Nevins JR. (2001). The Rb/E2F pathway and cancer. Hum Mol Genet 10: 699–703.
Nimmo ER, Stevens C, Phillips AM, *et al*. (2011). TLE1 modifies the effects of NOD2 in the pathogenesis of Crohn's disease. Gastroenterology 141:972–81.e1–2.
Nishisho I, Nakamura Y, Miyoshi Y, *et al*. (1991). Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 253:665–9.
Nishitani H, Lygerou Z, Nishimoto T, Nurse P. (2000). The Cdt1 protein is required to license DNA for replication in fission yeast. Nature 404: 625–8.
Nojima H, Tokunaga C, Eguchi S, *et al*. (2003). The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. J Biol Chem 278:15461–4.
Nozawa RS, Nagao K, Masuda HT, *et al*. (2010). Human POGZ modulates dissociation of HP1alpha from mitotic chromosome arms through Aurora B activation. Nat Cell Biol 12:719–27.
Oberg EA, Nifoussi SK, Gingras AC, Strack S. (2012). Selective proteasomal degradation of the B'β subunit of protein phosphatase 2A by the E3 ubiquitin ligase adaptor Kelch-like 15. J Biol Chem 287: 43378–89.
Oellerich T, Bremes V, Neumann K, *et al*. (2011). The B-cell antigen receptor signals through a preformed transducer module of SLP65 and CIN85. EMBO J 30:3620–34.
Ohnishi T, Yamashita A, Kashima I, *et al*. (2003). Phosphorylation of hUPF1 induces formation of mRNA surveillance complexes containing hSMG-5 and hSMG-7. Mol Cell 12:1187–200.
Okamoto K, Kamibayashi C, Serrano M, *et al*. (1996). p53-dependent association between cyclin G and the B′ subunit of protein phosphatase 2A. Mol Cell Biol 16:6593–602.
Okamoto K, Li H, Jensen MR, *et al*. (2002). Cyclin G recruits PP2A to dephosphorylate Mdm2. Mol Cell 9:761–71.
Olah J, Vincze O, Virok D, *et al*. (2011). Interactions of pathological hallmark proteins: tubulin polymerization promoting protein/p25, beta-amyloid, and alpha-synuclein. J Biol Chem 286:34088–100.
Ory S, Zhou M, Conrads TP, *et al*. (2003). Protein phosphatase 2A positively regulates Ras signaling by dephosphorylating KSR1 and Raf-1 on critical 14-3-3 binding sites. Curr Biol 13:1356–64.
Palkowitsch L, Leidner J, Ghosh S, Marienfeld RB. (2008). Phosphorylation of serine 68 in the IkappaB kinase (IKK)-binding domain of NEMO interferes with the structure of the IKK complex and tumor necrosis factor-alpha-induced NF-kappaB activity. J Biol Chem 283:76–86.
Paolinelli R, Mendoza-Maldonado R, Cereseto A, Giacca M. (2009). Acetylation by GCN5 regulates CDC6 phosphorylation in the S phase of the cell cycle. Nat Struct Mol Biol 16:412–20.
Paroni G, Cernotta N, Dello Russo C, *et al*. (2008). PP2A regulates HDAC4 nuclear import. Mol Biol Cell 19:655–67.
Peter M, Nakagawa J, Doree M, *et al*. (1990). Identification of major nucleolar proteins as candidate mitotic substrates of cdc2 kinase. Cell 60:791–801.
Petersen BO, Lukas J, Sorensen CS, *et al*. (1999). Phosphorylation of mammalian CDC6 by cyclin A/CDK2 regulates its subcellular localization. EMBO J 18:396–410.
Peterson RT, Desai BN, Hardwick JS, Schreiber SL. (1999). Protein phosphatase 2A interacts with the 70-kDa S6 kinase and is activated by inhibition of FKBP12-rapamycinassociated protein. Proc Natl Acad Sci USA 96:4438–42.
Peterson TR, Laplante M, Thoreen CC, *et al*. (2009). DEPTOR is an mTOR inhibitor frequently overexpressed in multiple myeloma cells and required for their survival. Cell 137:873–86.
Pitman MR, Barr RK, Gliddon BL, *et al*. (2011). A critical role for the protein phosphatase 2A B'α regulatory subunit in dephosphorylation of sphingosine kinase 1. Int J Biochem Cell Biol 43:342–7.
Plesca D, Crosby ME, Gupta D, Almasan A. (2007). E2F4 function in G2: maintaining G2-arrest to prevent mitotic entry with damaged DNA. Cell Cycle 6:1147–52.
Prickett TD, Brautigan DL. (2007). Cytokine activation of p38 mitogen-activated protein kinase and apoptosis is opposed by alpha-4 targeting of protein phosphatase 2A for site-specific dephosphorylation of MEK3. Mol Cell Biol 27:4217–27.
Purev E, Soprano DR, Soprano KJ. (2011). PP2A interaction with Rb2/p130 mediates translocation of Rb2/p130 into the nucleus in all-trans retinoic acid-treated ovarian carcinoma cells. J Cell Physiol 226: 1027–34.
Qian J, Beullens M, Lesage B, Bollen M. (2013). Aurora B defines its own chromosomal targeting by opposing the recruitment of the phosphatase scaffold Repo-Man. Curr Biol 23:1136–43.
Rajakulendran T, Sahmi M, Lefrancois M, *et al*. (2009). A dimerization-dependent mechanism drives RAF catalytic activation. Nature 461: 542–5.
Rajgopal A, Young DW, Mujeeb KA, *et al*. (2007). Mitotic control of RUNX2 phosphorylation by both CDK1/cyclin B kinase and PP1/PP2A phosphatase in osteoblastic cells. J Cell Biochem 100: 1509–17.
Ricotta D, Hansen J, Preiss C, *et al*. (2008). Characterization of a protein phosphatase 2A holoenzyme that dephosphorylates the clathrin adaptors AP-1 and AP-2. J Biol Chem 283:5510–17.
Rimerman RA, Gellert-Randleman A, Diehl JA. (2000). Wnt1 and MEK1 cooperate to promote cyclin D1 accumulation and cellular transformation. J Biol Chem 275:14736–42.
Rual JF, Venkatesan K, Hao T, *et al*., (2005). Towards a proteome-scale map of the human protein-protein interaction network. Nature 437: 1173–8.
Rubin SM. (2013). Deciphering the retinoblastoma protein phosphorylation code. Trends Biochem Sci 38:12–9.
Rubin SM, Gall AL, Zheng N, Pavletich NP. (2005). Structure of the Rb C-terminal domain bound to E2F1-DP1: a mechanism for phosphorylation-induced E2F release. Cell 123:1093–106.

Ruvolo VR, Kurinna SM, Karanjeet KB, *et al*. (2008). PKR regulates B56(alpha)-mediated BCL2 phosphatase activity in acute lymphoblastic leukemia-derived REH cells. J Biol Chem 283:35474–85.

Sablina AA, Chen W, Arroyo JD, *et al*. (2007). The tumor suppressor PP2A Abeta regulates the RalA GTPase. Cell 129:969–82.

Samstag Y, Nebl G. (2003). Interaction of cofilin with the serine phosphatases PP1 and PP2A in normal and neoplastic human T lymphocytes. Adv Enzyme Regul 43:197–211.

Sancak Y, Peterson TR, Shaul YD, *et al*. (2008). The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science 320: 1496–501.

Sangodkar J, Farrington C, Mcclinch K, *et al*. (2015). All roads lead to PP2A: exploiting the therapeutic potential of this phosphatase. FEBS J. [Epub ahead of print]. doi:10.1111/febs.13573.

Saraf A, Oberg EA, Strack S. (2010). Molecular determinants for PP2A substrate specificity: charged residues mediate dephosphorylation of tyrosine hydroxylase by the PP2A/B' regulatory subunit. Biochemistry 49:986–95.

Sathyanarayanan S, Zheng X, Xiao R, Sehgal A. (2004). Posttranslational regulation of Drosophila PERIOD protein by protein phosphatase 2A. Cell 116:603–15.

Satoh J, Kawana N, Yamamoto Y. (2013). Pathway analysis of ChIP-Seq-based NRF1 target genes suggests a logical hypothesis of their involvement in the pathogenesis of neurodegenerative diseases. Gene Regul Syst Bio 7:139–52.

Schlaitz AL, Srayko M, Dammermann A, *et al*. (2007). The C. elegans RSA complex localizes protein phosphatase 2A to centrosomes and regulates mitotic spindle assembly. Cell 128:115–27.

Schmitz MH, Held M, Janssens V, *et al*. (2010). Live-cell imaging RNAi screen identifies PP2A-B55alpha and importin-beta1 as key mitotic exit regulators in human cells. Nat Cell Biol 12:886–93.

Sciarretta S, Volpe M, Sadoshima J. (2014). Mammalian target of rapamycin signaling in cardiac physiology and disease. Circ Res 114: 549–64.

Scott GK, Gu F, Crump CM, *et al*. (2003). The phosphorylation state of an autoregulatory domain controls PACS-1-directed protein traffic. EMBO J 22:6234–44.

Seeling JM, Miller JR, Gil R, *et al*. (1999). Regulation of beta-catenin signaling by the B56 subunit of protein phosphatase 2A. Science 283: 2089–91.

Seth A, Sheth P, Elias BC, Rao R. (2007). Protein phosphatases 2A and 1 interact with occludin and negatively regulate the assembly of tight junctions in the CACO-2 cell monolayer. J Biol Chem 282:11487–98.

Shanley TP, Vasi N, Denenberg A, Wong HR. (2001). The serine/threonine phosphatase, PP2A: endogenous regulator of inflammatory cell signaling. J Immunol 166:966–72.

Shern JF, Sharer JD, Pallas DC, *et al*. (2003). Cytosolic Arl2 is complexed with cofactor D and protein phosphatase 2A. J Biol Chem 278:40829–36.

Sheu YJ, Stillman B. (2006). Cdc7-Dbf4 phosphorylates MCM proteins via a docking site-mediated mechanism to promote S phase progression. Mol Cell 24:101–13.

Shi Y. (2009). Serine/threonine phosphatases: mechanism through structure. Cell 139:468–84.

Shimobayashi M, Hall MN. (2014). Making new contacts: the mTOR network in metabolism and signalling crosstalk. Nat Rev Mol Cell Biol 15:155–62.

Shin JH, Grabowski B, Kasiviswanathan R, *et al*. (2003). Regulation of minichromosome maintenance helicase activity by Cdc6. J Biol Chem 278:38059–67.

Short KM, Hopwood B, Yi Z, Cox TC. (2002). MID1 and MID2 homo- and heterodimerise to tether the rapamycin-sensitive PP2A regulatory subunit, alpha 4, to microtubules: implications for the clinical variability of X-linked Opitz GBBB syndrome and other developmental disorders. BMC Cell Biol 3:1.

Shtrichman R, Sharf R, Barr H, *et al*. (1999). Induction of apoptosis by adenovirus E4orf4 protein is specific to transformed cells and requires an interaction with protein phosphatase 2A. Proc Natl Acad Sci USA 96:10080–5.

Soprano KJ, Purev E, Vuocolo S, Soprano DR. (2006). Rb2/p130 and protein phosphatase 2A: key mediators of ovarian carcinoma cell growth suppression by all-trans retinoic acid. Oncogene 25: 5315–25.

Sowa ME, Bennett EJ, Gygi SP, Harper JW. (2009). Defining the human deubiquitinating enzyme interaction landscape. Cell 138:389–403.

Stanevich V. (2013). Protein phosphatase 2A methylation and stable latency. PhD Thesis, University of Wisconsin-Madison, Madison, WI

Stanevich V, Jiang L, Satyshur KA, *et al*. (2011). The structural basis for tight control of PP2A methylation and function by LCMT-1. Mol Cell 41:331–42.

Suijkerbuijk SJ, Vleugel M, Teixeira A, Kops GJ. (2012). Integration of kinase and phosphatase activities by BUBR1 ensures formation of stable kinetochore-microtubule attachments. Dev Cell 23:745–55.

Sullivan M, Morgan DO. (2007). Finishing mitosis, one step at a time. Nat Rev Mol Cell Biol 8:894–903.

Sumara I, Vorlaufer E, Stukenberg PT, *et al*. (2002). The dissociation of cohesin from chromosomes in prophase is regulated by Polo-like kinase. Mol Cell 9:515–25.

Sun L, Stoecklin G, Van Way S, *et al*. (2007). Tristetraprolin (TTP)-14-3-3 complex formation protects TTP from dephosphorylation by protein phosphatase 2a and stabilizes tumor necrosis factor-alpha mRNA. J Biol Chem 282:3766–77.

Sung U, Jennings JL, Link AJ, Blakely RD. (2005). Proteomic analysis of human norepinephrine transporter complexes reveals associations with protein phosphatase 2A anchoring subunit and 14-3-3 proteins. Biochem Biophys Res Commun 333:671–8.

Surpili MJ, Delben TM, Kobarg J. (2003). Identification of proteins that interact with the central coiled-coil region of the human protein kinase NEK1. Biochemistry 42:15369–76.

Takahashi K, Suzuki K. (2006). Regulation of protein phosphatase 2A-mediated recruitment of IQGAP1 to beta1 integrin by EGF through activation of Ca2+/calmodulin-dependent protein kinase II. J Cell Physiol 208:213–19.

Takahashi M, Shibata H, Shimakawa M, *et al*. (1999). Characterization of a novel giant scaffolding protein, CG-NAP, that anchors multiple signaling enzymes to centrosome and the golgi apparatus. J Biol Chem 274:17267–74.

Takemoto A, Maeshima K, Ikehara T, *et al*. (2009). The chromosomal association of condensin II is regulated by a noncatalytic function of PP2A. Nat Struct Mol Biol 16:1302–8.

Tanaka T, Nasmyth K. (1998). Association of RPA with chromosomal replication origins requires an Mcm protein, and is regulated by Rad53, and cyclin- and Dbf4-dependent kinases. EMBO J 17: 5182–91.

Tang Z, Shu H, Qi W, *et al*. (2006). PP2A is required for centromeric localization of Sgo1 and proper chromosome segregation. Dev Cell 10:575–85.

Tanno Y, Kitajima TS, Honda T, *et al*. (2010). Phosphorylation of mammalian Sgo2 by Aurora B recruits PP2A and MCAK to centromeres. Genes Dev 24:2169–79.

Tao GZ, Toivola DM, Zhou Q, *et al*. (2006). Protein phosphatase-2A associates with and dephosphorylates keratin 8 after hyposmotic stress in a site- and cell-specific manner. J Cell Sci 119:1425–32.

Thompson LJ, Bollen M, Fields AP. (1997). Identification of protein phosphatase 1 as a mitotic lamin phosphatase. J Biol Chem 272: 29693–7.

Tischer T, Hormanseder E, Mayer TU. (2012). The APC/C inhibitor XErp1/Emi2 is essential for Xenopus early embryonic divisions. Science 338:520–4.

Tran H, Bustos D, Yeh R, *et al*. (2013). HectD1 E3 ligase modifies adenomatous polyposis coli (APC) with polyubiquitin to promote the APC-axin interaction. J Biol Chem 288:3753–67.

Trzcinska AM, Girstun A, Piekielko A, *et al*. (2002). Potential protein partners for the N-terminal domain of human topoisomerase I revealed by phage display. Mol Biol Rep 29:347–52.

Tu LC, Yan X, Hood L, Lin B. (2007). Proteomics analysis of the interactome of N-myc downstream regulated gene 1 and its interactions with the androgen response program in prostate cancer cells. Mol Cell Proteomics 6:575–88.

Turowski P, Myles T, Hemmings BA, *et al*. (1999). Vimentin dephosphorylation by protein phosphatase 2A is modulated by the targeting subunit B55. Mol Biol Cell 10:1997–2015.

Ugi S, Imamura T, Ricketts W, Olefsky JM. (2002). Protein phosphatase 2A forms a molecular complex with Shc and regulates Shc tyrosine phosphorylation and downstream mitogenic signaling. Mol Cell Biol 22:2375–87.

Vagnarelli P, Hudson DF, Ribeiro SA, *et al*. (2006). Condensin and Repo-Man-PP1 co-operate in the regulation of chromosome architecture during mitosis. Nat Cell Biol 8:1133–42.

van Kanegan MJ, Strack S. (2009). The protein phosphatase 2A regulatory subunits B′beta and B'delta mediate sustained TrkA neurotrophin receptor autophosphorylation and neuronal differentiation. Mol Cell Biol 29:662–74.

van Noort M, Meeldijk J, van der Zee R, *et al*. (2002). Wnt signaling controls the phosphorylation status of beta-catenin. J Biol Chem 277: 17901–5.

Varjosalo M, Keskitalo S, van Drogen A, *et al*. (2013a). The protein interaction landscape of the human CMGC kinase group. Cell Rep 3: 1306–20.

Varjosalo M, Sacco R, Stukalov A, *et al*. (2013b). Interlaboratory reproducibility of large-scale human protein-complex analysis by standardized AP-MS. Nat Methods 10:307–14.

Varlamov O, Kalinina E, Che FY, Fricker LD. (2001). Protein phosphatase 2A binds to the cytoplasmic tail of carboxypeptidase D and regulates post-trans-Golgi network trafficking. J Cell Sci 114: 311–22.

Vastiau A, Cao L, Jaspers M, *et al*. (2005). Interaction of the protein phosphatase 2A with the regulatory domain of the cystic fibrosis transmembrane conductance regulator channel. FEBS Lett 579: 3392–6.

Virshup DM, Shenolikar S. (2009). From promiscuity to precision: protein phosphatases get a makeover. Mol Cell 33:537–45.

Voorhoeve PM, Hijmans EM, Bernards R. (1999). Functional interaction between a novel protein phosphatase 2A regulatory subunit, PR59, and the retinoblastoma-related p107 protein. Oncogene 18: 515–24.

Wainszelbaum MJ, Liu J, Kong C, *et al*. (2012). TBC1D3, a hominoid-specific gene, delays IRS-1 degradation and promotes insulin signaling by modulating p70 S6 kinase activity. PLoS One 7:e31225.

Wang PY, Weng J, Anderson RG. (2005). OSBP is a cholesterol-regulated scaffolding protein in control of ERK 1/2 activation. Science 307:1472–6.

Wang W, Huang J, Wang X, *et al*. (2012). PTPN14 is required for the density-dependent control of YAP1. Genes Dev 26:1959–71.

Watanabe N, Arai H, Iwasaki J, *et al*. (2005). Cyclin-dependent kinase (CDK) phosphorylation destabilizes somatic Wee1 via multiple pathways. Proc Natl Acad Sci USA 102:11663–8.

Weber JD, Raben DM, Phillips PJ, Baldassare JJ. (1997). Sustained activation of extracellular-signal-regulated kinase 1 (ERK1) is required for the continued expression of cyclin D1 in G1 phase. Biochem J 326:61–8.

Wei JH, Seemann J. (2009). Mitotic division of the mammalian Golgi apparatus. Semin Cell Dev Biol 20:810–16.

Welburn JP, Vleugel M, Liu D, *et al*. (2010). Aurora B phosphorylates spatially distinct targets to differentially regulate the kinetochore-microtubule interface. Mol Cell 38:383–92.

Westphal RS, Anderson KA, Means AR, Wadzinski BE. (1998). A signaling complex of Ca2+-calmodulin-dependent protein kinase IV and protein phosphatase 2A. Science 280:1258–61.

Westphal RS, Coffee Jr RL,, Marotta A, *et al*. (1999). Identification of kinase-phosphatase signaling modules composed of p70 S6 kinase-protein phosphatase 2A (PP2A) and p21-activated kinase-PP2A. J Biol Chem 274:687–92.

Wlodarchak N, Guo F, Satyshur KA, *et al*. (2013). Structure of the Ca2+-dependent PP2A heterotrimer and insights into Cdc6 dephosphorylation. Cell Res 23:931–46.

Woods NT, Mesquita RD, Sweet M, *et al*. (2012). Charting the landscape of tandem BRCT domain-mediated protein interactions. Sci Signal 5:rs6.

Wu GS. (2007). Role of mitogen-activated protein kinase phosphatases (MKPs) in cancer. Cancer Metastasis Rev 26:579–85.

Wu JQ, Hansen DV, Guo Y, *et al*. (2007). Control of Emi2 activity and stability through Mos-mediated recruitment of PP2A. Proc Natl Acad Sci USA 104:16564–9.

Wu X, Noh SJ, Zhou G, *et al*. (1996). Selective activation of MEK1 but not MEK2 by A-Raf from epidermal growth factor-stimulated Hela cells. J Biol Chem 271:3265–71.

Wu Z, Chen Y, Yang T, *et al*. (2012). Targeted ubiquitination and degradation of G-protein-coupled receptor kinase 5 by the DDB1-CUL4 ubiquitin ligase complex. PLoS One 7:e43997.

Wurzenberger C, Gerlich DW. (2011). Phosphatases: providing safe passage through mitotic exit. Nat Rev Mol Cell Biol 12:469–82.

Xie Y, Avello M, Schirle M, *et al*. (2013). Deubiquitinase FAM/USP9X interacts with the E3 ubiquitin ligase SMURF1 protein and protects it from ligase activity-dependent self-degradation. J Biol Chem 288: 2976–85.

Xin M, Deng X. (2006). Protein phosphatase 2A enhances the proapoptotic function of Bax through dephosphorylation. J Biol Chem 281:18859–67.

Xing H, Hong Y, Sarge KD. (2007). Identification of the PP2A-interacting region of heat shock transcription factor 2. Cell Stress Chaperones 12:192–7.

Xing Y, Li Z, Chen Y, *et al*. (2008). Structural mechanism of demethylation and inactivation of protein phosphatase 2A. Cell 133: 154–63.

Xing Y, Xu Y, Chen Y, *et al*. (2006). Structure of protein phosphatase 2A core enzyme bound to tumor-inducing toxins. Cell 127:341–53.

Xu P, Raetz EA, Kitagawa M, *et al*. (2013). BUBR1 recruits PP2A via the B56 family of targeting subunits to promote chromosome congression. Biol Open 2:479–86.

Xu Y, Chen Y, Zhang P, *et al*. (2008). Structure of a protein phosphatase 2A holoenzyme: insights into B55-mediated Tau dephosphorylation. Mol Cell 31:873–85.

Xu Y, Xing Y, Chen Y, *et al*. (2006). Structure of the protein phosphatase 2A holoenzyme. Cell 127:1239–51.

Xu Z, Cetin B, Anger M, *et al*. (2009). Structure and function of the PP2A-shugoshin interaction. Mol Cell 35:426–41.

Xu Z, Williams BR. (2000). The B56alpha regulatory subunit of protein phosphatase 2A is a target for regulation by double-stranded RNA-dependent protein kinase PKR. Mol Cell Biol 20:5285–99.

Yamamoto H, Hinoi T, Michiue T, *et al*. (2001). Inhibition of the Wnt signaling pathway by the PR61 subunit of protein phosphatase 2A. J Biol Chem 276:26875–82.

Yan L, Mieulet V, Burgess D, *et al*. (2010). PP2A T61 epsilon is an inhibitor of MAP4K3 in nutrient signaling to mTOR. Mol Cell 37: 633–42.

Yang CS, Xin HW, Kelley JB, *et al*. (2007). Ligand binding to the androgen receptor induces conformational changes that regulate phosphatase interactions. Mol Cell Biol 27:3390–404.

Yang J, Fan GH, Wadzinski BE, *et al*. (2001). Protein phosphatase 2A interacts with and directly dephosphorylates RelA. J Biol Chem 276: 47828–33.

Yatim A, Benne C, Sobhian B, *et al*. (2012). NOTCH1 nuclear interactome reveals key regulators of its transcriptional activity and oncogenic function. Mol Cell 48:445–58.

Yeong FM, Hombauer H, Wendt KS, *et al*. (2003). Identification of a subunit of a novel Kleisin-beta/SMC complex as a potential substrate of protein phosphatase 2A. Curr Biol 13:2058–64.

Yokoyama N, Miller WT. (2001). Protein phosphatase 2A interacts with the Src kinase substrate p130(CAS). Oncogene 20:6057–65.

Yokoyama N, Reich NC, Miller WT. (2001). Involvement of protein phosphatase 2A in the interleukin-3-stimulated Jak2-Stat5 signaling pathway. J Interferon Cytokine Res 21:369–78.

Yoo SJ, Jimenez RH, Sanders JA, *et al*. (2008). The alpha4-containing form of protein phosphatase 2A in liver and hepatic cells. J Cell Biochem 105:290–300.

Yu XX, Du X, Moreno CS, *et al*. (2001). Methylation of the protein phosphatase 2A catalytic subunit is essential for association of Balpha regulatory subunit but not SG2NA, striatin, or polyomavirus middle tumor antigen. Mol Biol Cell 12:185–99.

Yuan M, Pino E, Wu L, *et al*. (2012). Identification of Akt-independent regulation of hepatic lipogenesis by mammalian target of rapamycin (mTOR) complex 2. J Biol Chem 287:29579–88.

Zhang W, Yang J, Liu Y, *et al*. (2009). PR55 alpha, a regulatory subunit of PP2A, specifically regulates PP2A-mediated beta-catenin dephosphorylation. J Biol Chem 284: 22649–56.

Zhu D, Kosik KS, Meigs TE, *et al*. (2004). Galpha12 directly interacts with PP2A: evidence FOR Galpha12-stimulated PP2A phosphatase activity and dephosphorylation of microtubule-associated protein, tau. J Biol Chem 279:54983–6.

Zwaenepoel K, Goris J, Erneux C, *et al*. (2010). Protein phosphatase 2A PR130/B″alpha1 subunit binds to the SH2 domain-containing inositol polyphosphate 5-phosphatase 2 and prevents epidermal growth factor (EGF)-induced EGF receptor degradation sustaining EGF-mediated signaling. FASEB J 24:538–47.