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## **Connections between the cell cycle, cell adhesion and the cytoskeleton**

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### **ABSTRACT**

Cell division, the purpose of which is to enable cell replication, and in particular to distribute complete, accurate copies of genetic material to daughter cells, is essential for the propagation of life. At a morphological level, division not only necessitates duplication of cellular structures, but it also relies on polar segregation of this material followed by physical scission of the parent cell. For these fundamental changes in cell shape and positioning to be achieved, mechanisms are required to link the cell cycle to the modulation of cytoarchitecture. Outside of mitosis, the three main cytoskeletal networks not only endow cells with a physical cytoplasmic skeleton, but they also provide a mechanism for spatiotemporal sensing via integrin-associated adhesion complexes and site-directed delivery of cargoes. During mitosis, some interphase functions are retained, but the architecture of the cytoskeleton changes dramatically, and there is a need to generate a mitotic spindle for chromosome segregation. An economical solution is to re-use existing cytoskeletal molecules: transcellular actin stress fibres remodel to create a rigid cortex and a cytokinetic furrow, while unipolar radial microtubules become the primary components of the bipolar spindle. This remodelling implies the existence of specific mechanisms that link the cell cycle machinery to the control of adhesion and the cytoskeleton. In this article, we review the intimate three-way connection between microenvironmental sensing, adhesion signalling and cell proliferation, particularly in the contexts of normal growth control and aberrant tumour progression. As the morphological changes that occur during mitosis are ancient, the mechanisms linking the cell cycle to the cytoskeleton/adhesion signalling network are likely to be primordial in nature and we discuss recent advances that have elucidated elements of this link. A particular focus is the connection between CDK1 and cell adhesion.

### **INTRODUCTION**

#### **Stromal rigidity and tumour progression**

A defining characteristic of malignancy is the loss of adhesion dependence of proliferation, which implies that the mechanisms normally controlling the coordination between adhesion and cell division are subverted. In this context, many tumours develop in a highly rigid tissue context, which has the potential to interfere with the normally carefully controlled morphological changes that take place during mitosis. In particular, the stromal microenvironment of many carcinomas is characterised by a dense desmoplastic response and evidence is accumulating for a correlation between stromal density and poor clinical outcome [1-3]. This connection is best established in the breast, where intermediate and high mammographic density have been linked to a significantly elevated risk of local recurrence [4]. A high stromal index in pancreatic and colorectal adenocarcinoma also inversely correlates with survival [5-8]. Stratification of human breast, pancreatic and colorectal carcinomas according to the gene expression and protein profile of their

constituent stromal cells is predictive of treatment outcome [9-14]. Mammographic density correlates with extracellular matrix (ECM) rigidity [15], and changes in breast tumour- and stroma-derived ECM components contribute causally to metastatic spread [16].

Stromal rigidity is controlled by a combination of paracrine stimulation of ECM deposition and covalent cross-linking [17-21]. A number of the most abundant ECM molecules and ECM cross-linking enzymes are elevated in tumour stroma and correlate with poor patient prognosis [22-24]. Conversely, inhibition or reversal of these changes reduces tumour growth and increases survival in animal models, e.g. enzymatic destruction of hyaluronan [25], genetic deletion of the collagen-binding integrin  $\alpha 11\beta 1$  [26], pharmacological inhibition of lysyl oxidase (LOX) [26-31], knockdown of tissue transglutaminase [22, 32] and induction of stromal quiescence using the vitamin D receptor ligand calcipotriol [33]. Treatment with gemcitabine in combination with hyaluronidase treatment, vitamin D receptor agonism or LOX inhibition results in increased overall survival in mouse models [30, 34]. Recent studies imply a direct role for the ECM in resistance to small molecule therapeutics through effects on stromal fibroblasts [35]. Thus, while it is established that anti-adhesive agents are efficacious in conjunction with other treatment regimens [36-42], stromal normalisation offers an additional route to therapy.

### **Transduction of tissue rigidity into intracellular signals by adhesion receptors**

At a cellular level, early studies demonstrated that cell shape is directly coupled to cell division and fate for fibroblasts, epithelial and endothelial cells [43-49], and gene expression patterns and cell phenotype can be altered by choice of adhesive substrate [29, 50, 51]. The mechanical properties of the ECM also alter differentiation and morphogenesis in mammary and endothelial cell models [52-54]. Mesenchymal stem cells are tuned to differentiate in response to the mechanical properties of their environment, with flattened cells undergoing osteogenesis and round cells favouring adipogenesis [55], and direct presentation of synthetic matrices of increasing rigidity stimulates first neuronal, then myogenic and finally osteogenic differentiation [56-60]. Application of external force or shear stress also modulates both mesenchymal stem cell [55, 61] and human embryonic stem cell fate [62].

Stromal rigidity is primarily sensed by integrin-associated cell-ECM adhesion complexes *in vitro* and *in vivo* that are distributed focally rather than diffusely [63, 64]. These adhesion nexi transmit short-range tensile and elastic force across the plasma membrane, and interpret long-range alterations in tissue flow [65]. The adhesion nexus functions as a mechanosensitive molecular clutch in 2D and 3D ECMs [66, 67]. Data from both literature curation [68-70] and mass spectrometric analysis of the adhesion nexus [71-76] demonstrate that a small number of proteins (tens) establish its framework and a larger cohort of more transient proteins (hundreds) tune its function to intra- and extracellular stimuli [77]. Analysis of the protein-protein interaction network of the adhesion nexus identifies four interconnected axes that relay force to the cytoskeleton [73, 75-79]. Candidate sensors of mechanical force include LIM domain-containing proteins that bind strain sites in actin [80-83], integrins themselves as they form force-stabilised catch bonds that undergo cyclic mechanical reinforcement [84, 85], and cytoskeletal adaptors, such as vinculin, talin and p130Cas, which undergo force-dependent activation [86-93]. Therefore the composition and physical characteristics of the ECM can have profound effects on cellular signalling and behaviour via changes in adhesion complex signalling.

### **Regulation of cell cycle progression by adhesion signalling**

For most cells in multicellular organisms, the ECM anchorage dependence of normal cell growth and the propensity of tumour cells to evade this requirement have been established for many decades

(Fig. 1) [94, 95]. During the commitment phase of the cell cycle, sustained adhesion signalling is required to initiate DNA synthesis [96, 97] and suppress apoptosis [95, 98]. Integrin-dependent signalling is required for cell cycle progression during the G1 phase, in particular the induction of cyclin D1 and the down-regulation of cyclin-dependent kinase (CDK) inhibitors [46, 99-101]. There is accumulating evidence that extracellular force can feed into cell cycle checkpoints, e.g. a focal adhesion kinase (FAK)/Rac signalling module relays force-dependent signals to the G1/S checkpoint [100], increased ECM rigidity affects cell cycle progression by activating the Hippo pathway [102, 103], FAK is required to reorientate the mitotic spindle in response to mechanical compression [104], and mechanical stretching drives the ATR kinase to the nuclear envelope where it prevents replication errors [105].

During the replication and division phases of the cell cycle, major changes in cell shape, adhesiveness and cytoskeletal architecture are obligatory for chromosome segregation and cytokinesis [106-109]. These changes are highly conserved, implying the existence of a primordial regulatory mechanism. Across all metazoa, the remodelling events can be so extensive that cells become round and virtually lose their adhesion. Despite the risks to tissue integrity, the optimally symmetrical geometry of a sphere appears to enable the high degree of precision required for chromosome capture and division plane orientation [110-112]. Persistent adhesion and frustrated rounding prolong division and increase aneuploidy [113-116]. Aneuploidy is a common feature of human cancer [117, 118], suggesting that its origin may be not only genetic, but also due to an aberrant physical microenvironment and the ability of cells to interpret this environment via integrin-dependent adhesion signalling.

## **LINKS BETWEEN THE CELL CYCLE MACHINERY AND ADHESION**

### **Cell adhesion changes in a cell cycle-dependent manner**

Aside from the identification of anchorage-dependent growth in normal cells and the influence of adhesion on mitosis, very little is known about how adhesion complexes are regulated during cell cycle progression or how adhesion signalling influences the transition between cell cycle phases (Fig. 1). We have recently demonstrated that, as cells progress through S phase, adhesion complex area increases alongside the formation of robust actin stress fibres. Subsequently adhesion complex area decreases and stress fibres disassemble when cells enter G2 [119]. These changes in adhesion complexes and the cytoskeleton correlate with changes in traction forces observed in cells progressing through the cell cycle [120] and with the observation that in epithelial monolayers cellular tension is decreased in G2 several hours prior to mitosis [121].

A number of proteins that regulate adhesion complexes and the actin cytoskeleton make key contributions to cell division (Fig. 2); for example, the activation of RhoA and the promotion of myosin-dependent contractility are required for both mitotic cell rounding and cytokinesis to occur [122-125]. Furthermore, formin activity is required to maintain cortical actin in mitotic cells [126]. Therefore it is logical for the actomyosin machinery that regulates adhesion complexes to be redistributed and recycled for use during mitosis, where generation of a round morphology is critical for spindle positioning and chromosome capture [110, 127, 128]. Preventing the reduction in adhesion complexes observed in G2 leads to fewer cells entering mitosis and aberrant cell division [113, 119, 129], highlighting that these changes in adhesion and the cytoskeleton are key events that occur in G2 in preparation for entry into mitosis.

### **CDK1 regulates cell adhesion**

These observations demonstrate a reciprocal link between the cell cycle machinery and adhesion complexes/cytoskeleton. This link from the cell cycle machinery to adhesion complexes is primarily mediated by cyclin-dependent kinase 1 (CDK1) [74, 119]. CDK1 is a promiscuous serine/threonine kinase that has been shown to phosphorylate a wide range of substrates during mitosis [130, 131] and ultimately drive the major changes in cell morphology associated with mitosis. A number of known adhesion complex proteins and regulators of the cytoskeleton are phosphorylated by CDK1 [132-136] and a recent phosphoproteomic study suggested that a high proportion of protein phosphorylation sites identified within adhesion complexes may be attributed to CDK1 (185 sites out of 1109 detected phosphorylation sites; 16.7%) [74]. These observations are consistent with an additional non-mitotic role for CDK1 in regulating adhesion and the cytoskeleton. Consistent with this dual function of CDK1 is the identification of the formin FMNL2 as a novel CDK1 substrate that is phosphorylated during both interphase and mitosis [119]. Regulation of CDK1 activity and association with other proteins such as cyclins therefore represents an elegant solution to the question of how changes in adhesion complexes are coordinated with cell cycle progression. The ability of CDK1 to maintain adhesion complexes requires cyclin A2 [119, 137], whereas the induction of cyclin B1 in G2 led to increased levels of Wee1-dependent inactive cyclin-CDK1 complexes [119, 138, 139]. CDK1 activity is therefore reduced in G2 and coordinated with induction of cyclin B1 expression. Upon activation of cyclin B1-CDK1, the first event that occurs in mitotic entry is mitotic cell rounding [140], therefore it is tempting to suggest CDK1 has cyclin-dependent effects on adhesion complexes. When associated with cyclin B1, CDK1 drives adhesion complex disassembly during mitotic entry, but during interphase when associated with cyclin A2-CDK1 promotes adhesion complex formation. This hypothesis goes hand in hand with the idea that it is the cyclin that CDKs associate with that confers substrate specificity [141-144] and also suggests that the role for CDK1 in regulating all stages of cell cycle progression in yeast [145-147] has in part been conserved in mammalian cells; in particular, the role for CDK1 in regulating the yeast cytoskeleton [148-153] along with entry into mitosis.

### **Cell adhesion during mitosis**

Upon activation of cyclin B1-CDK1 and translocation of this active complex into the nucleus, cells disassemble adhesion complexes, round up and enter mitosis. It is established that adhesion geometry prior to mitosis can inform the positioning of the mitotic spindle [111] and spatial memory between cell generations [154]. Furthermore, integrin-mediated adhesion is important in cytokinesis and the respreading and repulsive migration of daughter cells [155-159]. These observations are consistent with the presence of a mitotic anchor that stabilises mitotic cells and also provides a footprint upon which dividing cells can form new adhesion complexes that facilitate cytokinesis and daughter cell respreading.

Much of the previous work on mitotic adhesion has focused on cells dividing on fibronectin and the role of  $\beta 1$  integrins that localise to the detached cell cortex [160] and to the cleavage furrow during cytokinesis [155, 157-159, 161]. Whilst  $\beta 1$  integrin influences cytokinesis, it is not observed interacting with the ECM during earlier stages of mitosis other than in cell 'tails' that have not fully retracted into the cell body [162]. However, in cells attached to vitronectin or in cell culture dishes the integrin  $\alpha V\beta 5$  is preferentially used by cells to mediate cell-ECM attachment [163].  $\alpha V\beta 5$  is found in two distinct structures: classical focal adhesions that are positive for consensus adhesion components [77] and associated with actin fibres and novel structures termed reticular adhesions [163]. These reticular adhesions form and mediate cell adhesion in the absence of actin fibres and talin, and therefore represent a unique mechanism by which adhesion may be maintained during mitosis. Indeed,  $\alpha V\beta 5$ -positive structures remain associated with ECM during mitotic cell rounding where they localise at the tips of retraction fibres and beneath the cell body. These complexes subsequently provide a footprint over which daughter cells respread following cytokinesis and

perturbation of reticular adhesions leads to aberrant cell division due to defects in mitotic axis orientation, cytokinesis and respreading [163]. Therefore,  $\alpha$ V $\beta$ 5-positive reticular adhesion complexes are essential for the normal progression of mitosis in cultured cells.

## **FUTURE DIRECTIONS**

### **Regulation of cell cycle-dependent adhesion transitions**

Having established a novel fundamental link between cell cycle progression and cell-ECM adhesion, a number of questions are outstanding. For example, how is adhesion complex growth in S phase promoted and what is its functional significance? This adhesion complex growth requires cyclin A2, so it is logical that it is coordinated with the induction of cyclin A2 expression during S phase [164-167]. Association of cyclin A2 with CDK1 requires phosphorylation of CDK1 by the CDK-activating kinase (CAK) [168], a complex of CDK7 with cyclin H [169], so it is possible that CAK plays a role in regulating adhesion complexes. Furthermore, identification of S phase-specific CDK1 phosphorylation substrates would provide potential mechanisms by which the growth of adhesion complexes and induction of actin stress fibres is achieved. One potential candidate for this is the Rho GEF GEF-H1, which plays a role in facilitating force transduction through adhesion complexes [170] and is also phosphorylated by CDK1 during cytokinesis [171], although given the promiscuity of CDK1 there are likely to be a host of target proteins that are able to influence this process.

The induction of adhesion complexes and actin stress fibres may subsequently influence progression through S phase and into G2 by promoting downstream signalling events that regulate this process. For example, the transcription factors YAP/TAZ and SRF/MAL are activated by cellular tension and an increase in the F/G actin ratio, respectively [103, 172]. These pathways may therefore be activated in S phase to facilitate expression of downstream target genes involved in cell cycle progression. Alternatively, these changes in adhesion complexes and actin may influence gene transcription by exerting force on the nucleus and altering nuclear mechanics. Inhibition of FAK kinase activity leads to a reduction in cell proliferation [173] and FAK phosphorylation and activation increase as cells enter S phase (Jones, M.C., unpublished data); however, how FAK subsequently influences cell cycle progression has yet to be determined. It is possible therefore that signalling events activated downstream of adhesion complex formation are able to directly influence factors that mediate the transition from S into G2.

How cyclin B1-CDK1 drives the disassembly of residual adhesion complexes upon mitotic entry remains poorly understood, although a number of adhesion components have been shown to be phosphorylated during mitosis [133-136] and, in the case of  $\alpha$ -parvin, FAK, paxillin and p130Cas, this phosphorylation is reversed following cytokinesis to allow daughter cell spreading [133, 134, 136]. This suggests that active cyclin B1-CDK1 undertakes a program of adhesion complex protein phosphorylation that drives rapid disassembly. Alternatively, the high activation of cortical RhoA downstream of CDK1-dependent Ect2 phosphorylation [125] that drives mitotic cell rounding may result in the rapid loss of adhesion complexes. In this regard, it would be interesting to determine whether adhesion complex disassembly is still observed in compressed mitotic cells that are unable to round up. Entry into mitosis does not lead to the disassembly of reticular adhesions, so these adhesion complexes would appear to be regulated in a different way to focal adhesions; however, whether they are altered in a cell cycle-dependent manner has yet to be determined. The balance of focal to reticular adhesions may therefore be an important consideration when determining the influence of individual adhesion proteins and signalling events to cell cycle progression and the accuracy of cell division.

## The 'adhesion checkpoint'

Ultimately, we hypothesise that cell cycle-dependent changes in adhesion complexes and the cytoskeleton are essential for cell cycle progression and division. Disruption of the actin cytoskeleton leads to arrest of cells in S phase [174, 175] and increased cell adhesion in G2 leads to fewer cells entering mitosis and perturbed cell division [119, 129]. This demonstrates that adhesion signalling is able to feed into cell cycle checkpoints and in instances of aberrant adhesion signalling cells are able to alter cell cycle dynamics. This is consistent with a recent study identifying cellular tension in epithelial layers as being the key determinant of cell cycle phase length [121]. The primary G1/S phase checkpoint is characterised by hyperphosphorylation of Rb by cyclin D-CDK4/6 and cyclin E-CDK2 and activation of E2F-dependent transcription, with members of the INK4 and CIP/KIP CDK inhibitor families being able to exert checkpoint control. Non-adherent cells are unable to activate cyclin D and cyclin E complexes due to increased levels of p21 Cip1 and p27 Kip1 [176] and decreased levels of C-Myc [177] and consequently are unable to progress through S phase. Similarly, knockdown of talin-1 leads to reduced proliferation as a consequence of increased p21 expression [178] and disruption of the actin cytoskeleton results in retinoblastoma protein (Rb) hypophosphorylation. Furthermore, S-phase progression can also be enhanced by increasing actin stress fibres as a consequence of disrupting microtubules with nocodazole [179]. Specifically perturbing the growth of adhesion complexes seen in S phase may therefore lead to G1/S phase checkpoint activation and alter cell cycle progression into G2.

The maintenance of adhesion complexes in G2 perturbs activation of cyclin B1-CDK1 [129] and results in fewer cells entering mitosis, suggesting that adhesion signalling is also able to impact upon the G2/M checkpoint. Given that increased cell adhesion and perturbation of  $\alpha$ V $\beta$ 5-positive mitotic adhesion complexes also leads to defects in division orientation and cytokinesis [119, 163], this suggests that changes in adhesion signalling may also impact upon the spindle assembly checkpoint (SAC) during mitosis. Understanding the cell cycle checkpoint signalling events that are influenced by adhesion complex signalling during G2 and mitosis is therefore a key avenue of future investigation. Likewise, how other cell cycle regulators are able to influence adhesion complexes and the cytoskeleton remains to be determined. Greatwall kinase/MASTL has been identified as a negative regulator of  $\beta$ 1-integrin function [180] and p27 Kip1 influences adhesion complexes and cell migration via modulation of RhoA activity [181]. Therefore it is likely that the coordination of cell cycle control with that of adhesion complexes and the cytoskeleton is complex and multi-layered, with a number of proteins being able to influence these processes.

Taken together, these observations suggest that normal cells are able to sense their surrounding ECM environment through integrin-associated adhesion complexes and determine whether to proceed through S phase or enter mitosis. In this regard, two distinct 'adhesion checkpoints' that contribute to cell cycle progression are present. In proliferative disorders such as cancer these checkpoints are likely to be dysregulated. Changes in ECM composition and stiffness that alter adhesion signalling could impact upon the ability of cells to progress through S phase and accurately divide, leading to increased aneuploidy and contributing to tumour progression. Reciprocally, changes in cell cycle signalling will also alter how cells perceive their ECM environment and could therefore impact upon a number of processes linked to tumour progression such as survival, invasion and colonisation of metastatic niches. Developing a deeper understanding of this reciprocal relationship between cell cycle and adhesion signalling will therefore contribute to our understanding of how tumour progression occurs and could also lead to novel therapeutic strategies targeting tumour matrix signalling alongside the use of anti-proliferative drugs.

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## AUTHOR CONTRIBUTIONS

MJH developed the concept behind the review and all authors contributed equally to its writing.

## KEYWORDS

Adhesion, cytoskeleton, integrin, cell cycle, CDK1, checkpoint.

## FIGURE LEGENDS

### Figure 1. Cross-talk between adhesion complexes and the cell cycle machinery

Progress through S phase is associated with a CDK1-cyclin A2-dependent increase in adhesion complex area. Increased expression of cyclin B1 and inhibition of CDK1-cyclin B1 by Wee1/Myt1 results in a reduction in adhesion complexes in G2 prior to complete loss following mitotic cell rounding. Integrin-mediated attachment is required for the G1-S transition via the induction of cyclin D1 and cyclin E expression through the signals shown, but it remains unclear how adhesion signalling influences the S-G2 and G2-M transitions, and how adhesion complex turnover feeds into the cell cycle regulation machinery.

### Figure 2. Examples of adhesion-associated proteins that are reused during mitotic cell rounding and cytokinesis

A number of proteins that regulate the actin cytoskeleton and adhesion complexes also play key roles in regulating mitotic cell rounding and cytokinesis. Four groups of proteins are highlighted and representative examples are presented in the table above together with key publications [124, 126, 134, 156, 170, 171, 182-205]. The background colour of the references matches the role of the protein in adhesion complex formation, mitotic cell rounding or cytokinesis regulation. The re-use of these regulators highlights the fundamental role of crosstalk between the cell cycle machinery and adhesion complex signalling.

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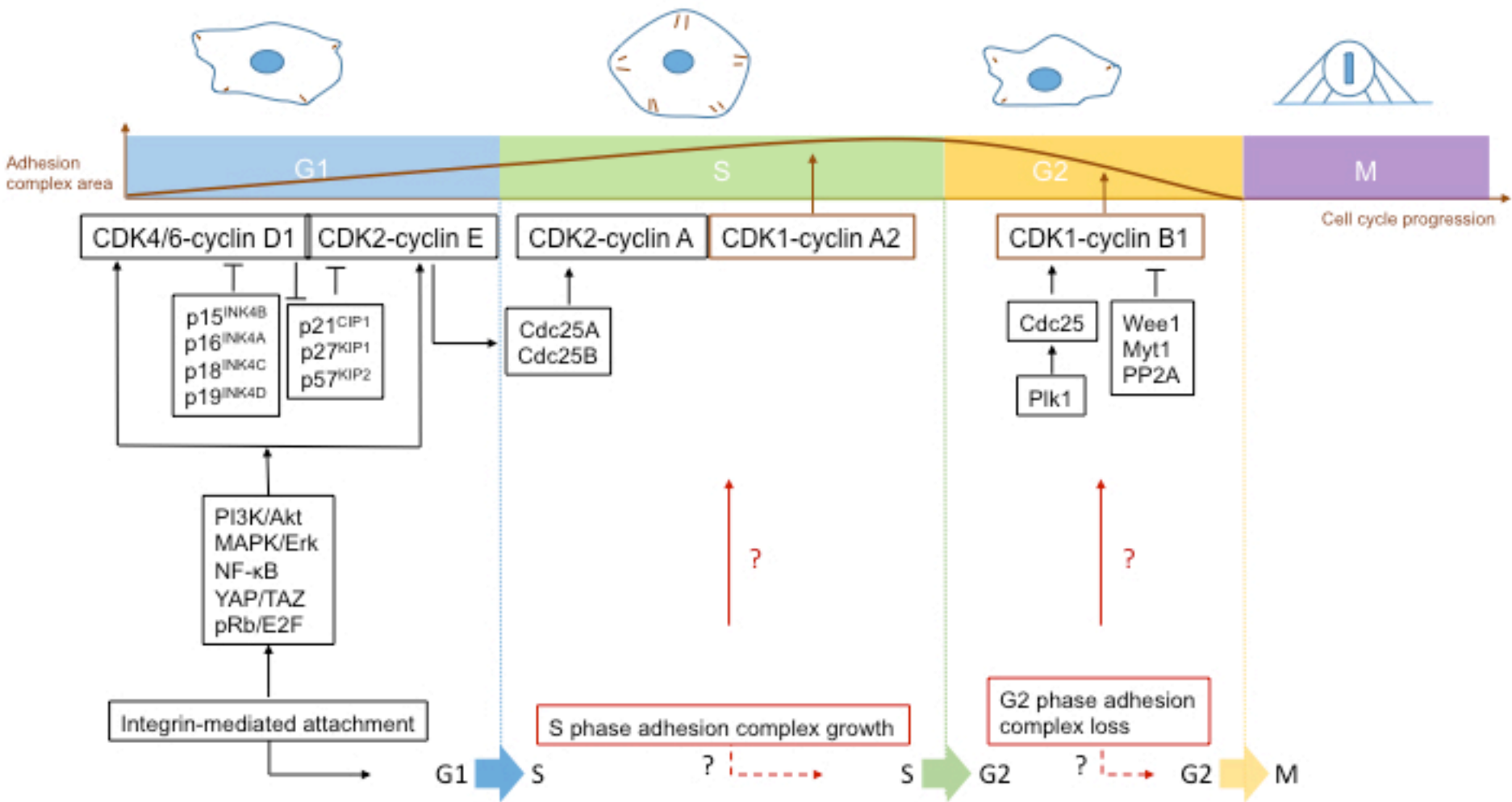
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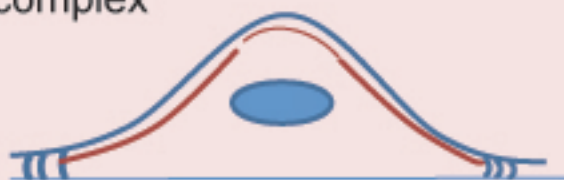
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### Adhesion complex formation



### Mitotic rounding



### Cytokinesis



Rho GTPases		GTPase regulators		Actin regulators		Adhesion complex proteins	
RhoA	Ridley & Hall (1992) [194]	p190-RhoGAP	Wildenberg et al. (2006) [204]	Formins	Riveline et al. (2001) [196]	Talin	Burrige & Connell (1983) [184]
	Maddox & Burridge (2003) [124]		Su et al. (2003) [200]		Ramanathan et al. (2015) [126]		Hock et al. (1989) [188]
	Drechsel et al. (1997) [185]		Su et al. (2009) [201]		Watanabe et al. (2008) [203]		Bellissent-Waydelich et al. (1999) [182]
Cdc42	Nobes & Hall (1995) [192]	RacGAP	Morishita et al. (2015) [190]	Myosin II	Wakatsuki et al. (2003) [202]	FAK	Schaller et al. (1992) [197]
	Oceguera-Yanez et al. (2005) [193]		Matthews et al. (2012)		Ramanathan et al. (2015) [126]		Yamakita et al. (1999) [134]
	Drechsel et al. (1997) [185]		Somers & Saint (2003) [199]		Zang et al. (1997) [205]		Kamranvar et al. (2016) [189]
Rac1	Ridley et al. (1992) [195]	GEF-H1	Guilluy et al. (2011) [170]	IQGAP1	Schiefermeier et al. (2014) [198]	Vinculin	Geiger et al. (1980) [186]
	-		Birkenfeld et al. (2007) [171]		Nakajima et al. (2005) [191]		Taneja et al. (2016) [156]
	-		Birkenfeld et al. (2007) [171]		Bielak-Zmijewska et al. (2008) [183]		Higashi et al. (2016) [187]