Review

Minor Kinases with Major Roles in Cytokinesis Regulation

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Abstract: Cytokinesis, the conclusive act of cell division, allows cytoplasmic organelles and chromosomes to be faithfully partitioned between two daughter cells. In animal organisms, its accurate regulation is a fundamental task for normal development and for preventing aneuploidy. Cytokinesis failures produce genetically unstable tetraploid cells and ultimately result in chromosome instability, a hallmark of cancer cells. In animal cells, the assembly and constriction of an actomyosin ring drive cleavage furrow ingression, resulting in the formation of a cytoplasmic intercellular bridge, which is severed during abscission, the final event of cytokinesis. Kinase-mediated phosphorylation is a crucial process to orchestrate the spatio-temporal regulation of the different stages of cytokinesis. Several kinases have been described in the literature, such as cyclin-dependent kinase, polo-like kinase 1, and Aurora B, regulating both furrow ingression and/or abscission. However, others exist, with well-established roles in cell-cycle progression but whose specific role in cytokinesis has been poorly investigated, leading to considering these kinases as “minor” actors in this process. Yet, they deserve additional attention, as they might disclose unexpected routes of cell division regulation. Here, we summarize the role of multifunctional kinases in cytokinesis with a special focus on those with a still scarcely defined function during cell cleavage. Moreover, we discuss their implication in cancer.

Keywords: cytokinesis; cancer; casein kinase 2 (CK2); P21-activated kinases (PAK); checkpoint kinase 2 (Chk2)

1. Introduction

1.1. Importance of Cytokinesis in Living Cells

Cytokinesis, the conclusive process of cell division, ensures the correct distribution of cytoplasmic organelles and the nuclear content of the mother cell between two daughter cells [1]. Because of the universal requirement for cytokinesis in all dividing cells, it is not surprising that the fundamental machinery, as well as the key regulatory pathways, are conserved in animal and fungal cells [2,3]. Besides being essential for normal growth and the survival of all eukaryotic organisms, cytokinesis is also a fundamental process during animal development and for avoiding aneuploidy in adult tissues. Indeed, defects in cytokinesis have been associated with various human pathological conditions, including cancer [4–6]. In the context of tumorigenesis, cytokinesis failures generate genetically unstable tetraploid cells and consequently lead to chromosome instability (CIN), a hallmark of cancer cells [4–7]. Importantly, tetraploidy represents a driver event of tumorigenesis, and CIN has also been associated with cancer evolution and heterogeneity and with poor survival in cancer patients [4–7].

1.2. Overview of Cytokinesis in Animal Cells

A schematic representation of the main event occurring in animal cytokinesis is depicted in Figure 1. In animal cells, cytokinesis starts after anaphase onset and drives a pro-
found reorganization of the spindle microtubules, which are subdivided into two distinct subpopulations, i.e., polar astral microtubules and central spindle microtubules [8]. Polar astral microtubules are dynamic structures emanating from the spindle poles and have been mainly associated with the relaxation of the non-equatorial cortex [9]. Central spindle microtubules interdigitate and overlap into antiparallel arrays at the cell equator of dividing cells [8]. Central spindle assembly and stability require the activities of many microtubule-associated proteins, kinesin-like proteins, and signaling proteins [1,8]. Signals from central spindle microtubules play an important role in specifying the Rho GTPase-dependent assembly of a contractile ring (CR), an annular structure composed of F-actin filaments and non-muscle myosin II (NM II) that is required for animal cell cytokinesis [1,2]. The evolutionarily conserved complex centralspindlin, composed of two molecules of the kinesin-6 isoform KIF23 (mitotic kinesin-like protein 1, MKLP1 in humans) and two molecules of the Rho family GTPase-activating protein (GAP) Cyk-4/MgcRacGAP, has a primary role in positioning the CR [10,11]. KIF23 enables the centralspindlin to move towards the plus ends of antiparallel microtubules, whereas Cyk-4/MgcRacGAP interacts with and recruits the Rho guanine nucleotide exchange factor ECT2 to the equatorial cortex, which activates RhoA at the cleavage site [12–16]. The targeting of active RhoA to the equatorial cortex activates two parallel downstream pathways, resulting in formin-dependent F-actin polymerization and NM II cortical contractility [17]. In animal cells undergoing symmetric division, the CR is assembled around the cell equator on the inner face of the plasma membrane, anchored to the plasma membrane, and connected to the central spindle by the scaffolding proteins anillin and septins [18–21]. Anillin binds to plasma membrane phosphoinositides and interacts with several proteins required for cytokinesis, such as Rho-GTP, formins, septins, F-actin, NM II, and Citron kinase/Sticky [18–23]. Septins are a family of highly conserved GTP-binding proteins that associate with each other to form filaments and higher-order oligomers at the plasma membrane [24–27]. Besides associating with anillin, septins directly bind with NM II, allowing for its full activation in dividing cells [24–27]. During the early stages of animal cell cytokinesis, actomyosin ring constriction drives cleavage furrow ingression, resulting in the formation of a cytoplasmic intercellular bridge that contains an electron-dense structure known as the midbody (MB). The MB consists of components required to regulate the final step of cytokinesis, in which the intercellular bridge is eventually severed in a process known as abscission [1,28–30]. At the center of the bridge, the MB forms a platform for the recruitment of proteins essential for abscission, including the endosomal sorting complex required for transport (ESCRT)-III components [28–30]. Abscission takes place at one side of the MB and is mediated by ESCRT-III filament helices, which are required for the final bridge constriction [31–33]. In human cells, abscission depends on the activity of the centrosomal-associated protein Cep55, which interacts with the centralspindlin and recruits ALIX and TSG101 proteins, which control the assembly of ESCRT-III filament helices on one side of the MB arms [33,34]. Both cleavage furrow ingression and abscission require tight crosstalk between the elements of the actin/microtubule/septin cytoskeleton and membrane lipids as well as new membrane transport from the internal secretory and endocytic/recycling trafficking compartments [1,28].

1.3. Spatio-Temporal Control of Cytokinesis through Phosphorylation

Reversible kinase-mediated phosphorylation contributes to a fine spatial and temporal regulation of the multiple proteins and different stages of cytokinesis [34]. Protein phosphorylation requires two main actors: protein kinases (which transfer a γ-phosphate group from ATP to serine, threonine, or tyrosine residues) and protein phosphatases (which remove it) [35,36]. Kinases and phosphatases are involved in virtually every cellular process and affect a wide range of protein behaviors and characteristics, including their activity, interactions, and localization [37–39]. Furthermore, the enzymatic activity of both may specifically act on only one or a few target proteins, while others are multifunctional and have a very large number of substrates [40]. The role of some multifunctional kinases in controlling crucial cytokinesis events has been extensively discussed in the literature [41–47].
For some of them, a clear role has been ascribed to early events of cytokinesis. For example, central spindle formation and Rho activation require the close coordination of the serine–threonine kinases polo-like mitotic kinase (Plk) 1 and Aurora B, both of which control earlier aspects of mitosis [41–47]. The Aurora B-mediated phosphorylation of MKLP1 controls centralspindlin formation, whereas Plk1-mediated phosphorylation of MgcRacGAP enables the centralspindlin association with ECT2 [41–47]. Plk1 and Aurora B also regulate the timing of abscission. The Plk1-mediated phosphorylation of Cep55 prevents its interaction with KIF23 and its accumulation at the midzone during cleavage furrow ingression [48]. In turn, by controlling the timing of Cep55 localization, Plk1 regulates the timing of ESCRT-III accumulation at the MB ring until late cytokinesis. Aurora B localizes to the MB together with the centralspindlin and phosphorylates the human ESCRT-III subunit charged multivesicular body protein 4C (CHMP4C) [49] and the abscission/NoCut checkpoint regulator (ANCHR) [50].

Figure 1. Schematic illustrating the different stages of cytokinesis in dividing animal cells and the proteins that take part in this process. Microtubules are depicted in black, centrioles in green, the contractile ring and the midbody ring in red, anaphase chromosomes and telophase nuclei in grey, Golgi organelles and Golgi-derived vesicles in blue, cortex in yellow. ECT2, epithelial cell-transforming sequence 2 oncogene; CPC, chromosomal passenger complex; RhoA, ras homolog family member A; Plk1, polo-like kinase 1; NM II, non-muscle myosin II; Cit-K, citron kinase; ESCRT-III, endosomal sorting complexes required for transport-III; Cep55, centrosomal protein 55; Alix, ALG-2-interacting protein X; TSG101, tumor susceptibility gene 101 protein.
In this review, we will deal with those multifunctional kinases, with a well-described function in other cellular processes but whose specific role in cytokinesis is still poorly defined, making them currently “minor” actors during these stages of cell division. Indeed, recent data suggest that the number of kinases involved in cytokinesis is underestimated and that additional kinases play an important role in cell division. In particular, we report data linking three multifunctional kinases (namely, CK2, PAK, and Chk2) and different steps of cytokinesis, and how these proteins affect the central steps of this cell phase. In addition, we also report on a few papers that have shown the reciprocal crosstalk of these kinases in some aspects of cell-cycle progression, suggesting that they might act similarly during cytokinesis by interacting with each other.

2. Casein Kinase 2 (CK2)

2.1. Structure and Function of CK2

The multifunction ser/thr casein kinase 2 (CK2) is a constitutively active protein kinase that forms a hetero-tetrameric complex made of two alpha subunits with kinase activity and two regulatory beta subunits [51] (Figure 2A).

![Diagram of CK2 complex](A)

- Catalytic subunit
- Regulatory subunit

Most organisms harbor two distinct alpha subunits (alpha and alpha-prime) [52,53] and a single beta unit encoded by different genes. In contrast, the genomes of *Drosophila melanogaster* and *Schizosaccharomyces pombe* encode a single CK2 alpha and multiple beta subunit isoforms [54,55]. Mammalian CK2 complexes may contain identical (i.e., two CK2 alpha or two CK2 alpha-prime) or non-identical (i.e., one CK2 alpha and one CK2 alpha-prime) catalytic subunits [56]. CK2 kinases display messenger-independent activity, which
preferentially phosphorylates ser/thr residues in the consensus sequence S/T-E/D-x-E/D [57,58] (Table 1).

Table 1. Table illustrating the roles of the CK2, Pak, and Chk2 kinases in cytokinesis, identified in model organisms and/or human cultured cells, and the relative phosphorylation target proteins. GBF1, Golgi brefeldin A-resistant guanine nucleotide exchange factor 1; NM II, non-muscle myosin II; NMHC II, non-muscle myosin II heavy chain; Bni1, diaphanous-related formin; Mid1, anillin-related medial ring protein; Rlc1, non-muscle myosin II regulatory light chain; Cdc15, cell division control protein 15; MLCK, non-muscle myosin II light chain kinase; MRLC, non-muscle myosin II regulatory light chain; MKLP1, mitotic kinesin-like protein1; CPC, chromosomal passenger complex.

| CK2 Kinase | Organism | Cytokinesis Functions | Phosphorylation Target | Phosphorylated Residues | Ref. |
|------------|----------|-----------------------|------------------------|-------------------------|-----|
| CK2        | Homo sapiens | Intercellular bridge stabilization | GBF1 | Ser292, Ser297 | [59] |
| CK2        | Homo sapiens | NM II filament disassembly | NMHC II | Ser1944 | [60] |

| PAK Kinase | Organism | Cytokinesis Functions | Phosphorylation Target | Phosphorylated Residues | Ref. |
|------------|----------|-----------------------|------------------------|-------------------------|-----|
| Ste20      | Saccharomyces cerevisiae | Formin activation, F-actin ring assembly and dynamics | Bni1 | ND | [61] |
| Cla4       | Saccharomyces cerevisiae | Formin activation, F-actin ring assembly and dynamics | Bni1 | ND | [61] |
| Cla4       | Saccharomyces cerevisiae | Septin ring assembly | Septins | ND | [62–66] |
| Pak1       | Schizosaccharomyces pombe | CR positioning | Mid1 | N-terminus phosphorylation | [67] |
| Pak1       | Schizosaccharomyces pombe | CR assembly | Cdc15 | ND | [67] |
| Pak2       | Homo sapiens | CR constriction | Rlc1 | Ser35 and Ser36 | [68] |
| Pak2       | Homo sapiens | MLCK inhibition | MLCK | Ser439 and Ser991 | [69] |
| Pak2       | Homo sapiens | MRLC activation | MRLC | Ser19 | [70] |
| Pak2       | Homo sapiens | Midbody dynamics | MKLP1 | tail domain * | [71] |

| Chk2 Kinase | Organism | Cytokinesis Functions | Phosphorylation Target | Phosphorylated Residues | Ref. |
|------------|----------|-----------------------|------------------------|-------------------------|-----|
| Chk2       | Homo sapiens | CPC localization | INCENP | Ser91 | [72] |

* PAK2 consensus sequence (K/RRXS) in the tail domain, amino acids 804–808.

CK2 localizes in both the nucleus and the cytoplasm and is also associated with specific cellular structures or organelles, including the Golgi complex, the endoplasmic reticulum (ER), and the ribosomes [73]. In addition, it has been also detected as an ecto-protein kinase at the outer surface of the plasma membrane [74–77]. This ubiquitous distribution reflects both its pleiotropic role and its involvement in many protein phosphorylation events. Indeed, ample biochemical and genetic evidence indicates the requirement for CK2 for the phosphorylation of more than 300 substrates [78]. In agreement with this, CK2 has been involved in the regulation of many cellular processes, mostly related to signaling pathways and cell-cycle control [79–92]. Although cyclin-dependent kinase 1 (CDK1), Plk1, and Aurora A/Aurora B are the most active mitotic kinases [93], multiple lines of evidence link CK2 and several aspects of the regulation of cell-cycle progression and cell division, particularly during mitotic exit [94–100]. For example, condensin I,
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a protein complex required for chromosome condensation, is inactivated by CK2 kinase-mediated phosphorylation [94]. However, during the G2/M transition, the phosphoprotein phosphatase Protein Phosphatase 6 (PP6) activates condensin I by removing this inhibitory phosphorylation [101]. Several studies on *Saccharomyces cerevisiae* have also shown that CK2 function is essential for G1/S and G2/M transitions and, indeed, CK2 depletion blocks cell-cycle progression [102–106]. Moreover, CK2 interacts with many proteins whose roles are required for normal progression through mitosis, such as Cdc25B, phosphoprotein phosphatase 2A (PP2A), HDAC1/2, and Topoisomerase IIα/β [107–111].

2.2. Role of CK2 in Tumorigenesis

Because CK2 is constitutively active in eukaryotic cells [112], its function in cancer development is strictly linked to its overexpression [113], which reaches particularly high levels in several types of cancer such as breast cancer, lung cancer, prostate cancer, colorectal cancer, renal cancer, various types of leukemia, and glioblastoma [114,115]. The study of CK2 action in cancerogenesis is very complex; indeed, using the PubMed search string “ck2 and cancer”, it is possible to retrieve more than 1000 results, allowing for the identification of hundreds of targets, as previously said [116,117]. This also reflects the highly dynamic behavior of CK2, which has been localized—as a response to numerous growth stimuli (such as epidermal growth factor—EGF)—to several different cellular compartments, including the Golgi apparatus, endoplasmic reticulum, mitochondria, cytoskeleton, centrosomes, and plasma membrane [118]. In addition, it has been shown that CK2 intracellular concentration increases in dividing cells and that its subcellular distribution changes from uniform in normal cells to strongly enriched in the nucleus of malignant cells [119]. The ability to interact with all DNA-dependent RNA polymerases has suggested a role for CK2 in gene regulation [120]. Among CK2 targets, we recall here the RPB1 subunit of RNA polymerase II [121], several transcription factors [122–127], various components of the spliceosome [128–130] and its regulators [121,131], as well as some components of the chromatin, thus influencing its remodeling (reviewed in [118]). As such, CK2 is one of the most studied kinases as a promising target for anti-cancer drug development [132]. The data in our review involve CK2 in cytokinesis, further expanding its roles in cell proliferation and possibly providing new routes of targeted therapy for cancer patients, although this role has been recently questioned [133].

2.3. Role of CK2 in Cytokinesis

CK2 has been implicated in the regulation of cytokinesis in several model systems. One of the first studies involving CK2 in cytokinesis dates back to the 1990s. Roussou and Draetta showed that the overexpression of Ckb1, which is the ortholog of the CK2β subunit in *S. pombe*, induces multiple septation events and impairs cell growth and cytokinesis [111]. The CK2 catalytic subunit KIN-3/CK2α of *C. elegans* was located within the nucleus, at the centrosomes, and in the MBs [112]. In nematode early embryos, the depletion of KIN-3 impairs chromosome segregation, centrosome duplication, and cytokinesis. Time-lapse imaging of worm embryos depleted of KIN-3 revealed incomplete cytokinetic furrow formation, indicating a defect in the early steps of cytokinesis [134].

Several lines of evidence have involved mammalian CK2 in late cytokinesis. The regulatory subunit CK2β and the catalytic subunit CK2α have been found localized to the MB of mammalian cells in two different studies [135,136]. A recent study on HeLa cells described a CK2-dependent regulatory mechanism linking postmitotic Golgi reassembly with the completion of cytokinesis [59]. The Golgi-specific brefeldin A-resistance guanine nucleotide exchange factor 1 (GBF1) acts as a guanine nucleotide exchange factor for the small ADP-ribosylation factor-1 (ARF1) [137,138]. In turn, the GBF1-mediated activation of ARF1 is required for maintaining Golgi architecture and intra-Golgi trafficking [138]. During mitosis, the CK2-mediated phosphorylation of GBF1 on Ser292 and Ser297 allows for its recognition by the F-box protein beta-transducin repeat containing E3 ubiquitin protein ligase (ßTrCP), which recruits GBF1 into the ubiquitin ligase complex SCFßTrCP,
targeting it for degradation [59]. In turn, the phosphorylation and proteolysis of GBF1 along the microtubules of telophase cells controls Golgi inheritance and postmitotic reassembly, while the expression of a non-degradable GBF1 (S292A/S297A) mutant destabilizes the intercellular bridge and delays abscission, leading to cytokinesis failures [59]. Additionally, possible links among CK2, cytokinesis, and Golgi dynamics are suggested by the association of CK2 with NM II [60,139,140]. NM II is a collective term defining three distinct isoforms in vertebrates: non-muscle myosin IIA (NM IIA), IIB (NM IIB), and IIC (NM IIC). Our current knowledge of the function of NM II is partly derived from Dictyostelium discoideum and Drosophila melanogaster. Both model organisms harbor a single NM II encoding gene, (mhcA and Zip, respectively), facilitating genetic and biochemical analyses [141,142]. NM II mainly participates in cytokinesis [142,143] and in cell motility in conjunction with filamentous actin [144]. By using papain cleavage fragments of NM II, the 120-kDa rod domain of NM IIA heavy chain was shown to directly bind to Golgi stacks. However, this interaction was abolished when the rod domain was phosphorylated in vitro by CK2, indicating a role for CK2-mediated phosphorylation in regulating the binding and/or release of myosin-II from the Golgi [139]. Although Drosophila CK2 has not yet been found to be involved in cytokinesis, it has been recently found that the CK2 alpha subunit can be isolated from Drosophila testis extracts together with Golgi phosphoprotein 3 (GOLPH3) protein, a peripheral Golgi protein that interacts with NM II and regulates Golgi structure and actomyosin ring dynamics during cytokinesis [145]. Thus, it will be interesting to assess whether CK2 binds to and phosphorylates GOLPH3 during cytokinesis. Four phosphorylation sites on the unique C-terminus of the CK2 catalytic subunit CK2α have been involved in a regulatory mechanism controlling CK2 localization during mitosis [146]. CK2α phosphorylation controls its binding to the peptidyl-prolyl isomerase Pin1, which is required for CK2α mitotic spindle localization [146]. These data indicate the existence of a general mechanism that can direct the constitutively active CK2 kinase towards its mitotic substrates [146]. Importantly, Pin1 plays a central role during cytokinesis in regulating abscission, as shown by the analysis of Pin1 knockout in mouse embryonic fibroblasts and HeLa cells [147]. However, it remains to be investigated whether Pin1 regulates CK2 localization and activity during abscission.

In summary, research data in model organisms and human cultured cells indicate that CK2 might be involved in cytokinesis both directly, i.e., by regulating furrow ingression (in C. elegans), and indirectly, for example, in controlling Golgi reassembly, which is necessary for the successful completion of cytokinesis (in HeLa cells).

3. P21-Activated Kinase (PAK)

3.1. Structure and Function of PAKs

PAK serine-threonine kinases, which are conserved among eukaryotes (Figure S1), were originally identified as downstream effectors of the Rac1 and Cdc42-related GTPases [148,149]. The number of members belonging to the Pak kinase family varies among different species. Homo sapiens harbors six PAK members divided into two main groups: group I (PAK1 to PAK3) and group II (PAK4 to PAK6) [150,151]. Drosophila melanogaster has three PAK members, which are classified into group I (dPAK1, dPAK3) and group II (Mbt/dPAK2) [152]. Two PAK members have been identified in Schizosaccharomyces pombe (PAK1p/Orb2p/Shk1p and PAK2p/Shk2p) and three in Saccharomyces cerevisiae: Sterile 20 (Ste20), Cla4, and Skm1 [153,154].

PAK proteins bind to activated (GTP-bound) forms of GTPases related to Cdc42 and Rac1, but not to other small GTPases such as Ras or Rho; the result of this binding is the activation of PAKs [155–157]. Rac1 and Cdc42 GTPases are known to regulate F-actin, microtubules, focal adhesion assembly in cellular morphodynamics, and migration [158]. PAK family proteins usually contain an auto-inhibitory domain, a kinase domain, a p21- binding domain, and N-terminal proline-rich motifs that have the characteristic PXXP (where X indicates a variable amino acid) structure of SH3 binding domains (Figure 2B). The kinase activity of group I PAK proteins is activated after their binding to small GTPases
or other proteins, whereas group II PAK members are constitutively activated [159–162]. The activity of group I PAK members is inhibited through a homodimerization mechanism. The homodimers assume a closed conformation, and the kinase activity is very low because the p21-binding domain, which overlaps with the auto-inhibitory domain, binds to the kinase domain of another PAK molecule [163,164]. The binding of Rac1 or Cdc42 proteins to the p21-binding domain of PAK1 induces a conformational change in PAK1, which leads to homodimer dissociation and an increase in its kinase activity [165]. Full kinase activity is reached after phosphorylation at Ser223 and through auto-phosphorylation at Ser144, (or at the equivalent sites for the other PAKs) [165]. The phosphorylation of PAK1 at Ser144 stabilizes the open conformation and sustains high kinase activity [166]. The regulatory mechanisms that depend on small GTPases are not the only ones that affect the activity of PAK kinases. For example, group I PAKs are stimulated by (i) the interaction of its PXXP motif with the SH3 domain of substrate molecules, e.g., Growth factor receptor-bound protein 2 (Grb2), PAK-interacting exchange (PIX), adaptor protein Nck [167,168], (ii) phosphorylation by 3-phospho-inositide dependent kinase-1, AKT and JAK [169,170], and (iii) the binding of phospholipids, exchange factor β-PIX, or SH3 proteins such as NCK1 [170] and GRB2 [167]. Instead, members of group II are constitutively active and lack the auto-inhibitory domain.

3.2. Role of PAKs in Tumorigenesis

The literature available in databases regarding “PAK kinase and cancer” is even more abundant than that for CK2, counting more than 1500 hits. PAK serine/threonine kinases are downstream effectors of Ras-related Rho GTPase Cdc42 and Rac [149,155,156,171], and, as such, they are involved in several oncogenic pathways, such as cell growth and proliferation, apoptosis, immune response and inflammation, motility, epithelial-to-mesenchymal transition (EMT), therapeutic resistance, angiogenesis, DNA repair, cytoskeleton remodeling, and gene expression [172]. Indeed, alterations of PAK either by mutation, upregulation, or amplification, have been linked to several cancer types with the involvement of multiple interactions with dozens of proteins, as expected from a multifunctional kinase [172]. Although some functions are shared by all six PAKs, several others are not, thus explaining the distinct types of roles in various tumors and the associated high frequency of mutation in most of them. Among PAKs, PAK1, PAK2, and PAK4 exhibit a higher expression level in most cancer types; PAK1 and PAK4 are the most studied and better characterized, yet PAK2 has the highest alteration frequency among all PAKs, especially in lung cancer [173]. In contrast, PAK6 shows both oncogenic and oncosuppressive features, depending on the cancer type. In colon and gastric cancer, the upregulation of PAK6 promotes cancer progression and chemotherapy resistance, while in clear cell renal cell carcinoma and hepatocellular carcinoma, its downregulation is linked to cancer progression and patients’ survival [174–177].

As a general rule, PAKs influence cell-cycle progression via their interaction with cyclin-dependent kinases and cyclins. Additional substrates for PAK1 include Aurora A [178], tubulin cofactor B [179], mitotic centromere-associated kinesin [180], Plk1 [181], histone H3 [182], and the epigenetic-related ATPase MORC2, a member of the Microphthalmia family of proteins [183]. Several cancer-related pathways are affected by PAK malfunction; among the others, we recall here the WNT/β-catenin, EGFR/HER2/MAPK, the PI3K/AKT signaling pathways, NF-κB cascades, the EMT signaling pathway, and the DNA damage response signaling pathway [173] (and references therein). In consideration of their multiple roles, several lines of investigations have been developed over time, aimed at identifying chemical compounds impairing PAK function [184].

3.3. Role of PAKs in Cytokinesis

Research studies on several model organisms have revealed the role of PAK family proteins in multiple aspects related to cytokinesis (Table 1). The genome of S. cerevisiae encodes three members of the PAK family, of which Ste20 and Cla4 play essential yet partially redundant functions, while Skm1 is not an essential protein [185]. The inactivation
of these proteins during mitosis prevents actin polarization at the bud neck, the site of constriction between the mother and the daughter cell [61]. These data indicate a role for Ste20 and Cla4 in regulating a group of polarity-determining proteins known as the polarisome, required for actin cable organization during budding yeast cytokinesis. This action could be carried out through the phosphorylation of the diaphanous-related formin Bni1p (bud neck-involved) and Bud6p [61,186,187]. It has been shown that Ste20 acts in concert with Cdc42 to control the localization of cytokinesis factors to the bud neck and allow for proper cell division [154,188]. The Cla4 kinase regulates the function of some septins during bud morphology and cytokinesis [62,63,66,189,190]. In S. cerevisiae, the septin ring formation requires the copolymerization of the septins Cdc3p, Cdc10p, Cdc11p, Cdc12p, and Shs1/Sep7p into filaments [64,65]. Studies in vitro and in vivo have shown that Cla4 interacts directly with and phosphorylates Cdc3, Cdc10, Cdc11, and Cdc12 [62], leading to initial septin ring assembly and collar formation during bud emergence and cytokinesis [62–66]. Furthermore, combining Cla4 mutations with mutations affecting the septin GTP-binding domain enhances the cytokinesis defects associated with the septin collar assembly [62]. These results suggest that Cla4 organizes septins into higher-order structures necessary for cell division in a GTP-dependent manner.

In the fission yeast S. pombe, PAK1 is involved in cytokinesis through two mechanisms. It regulates the activation of the myosin regulatory light chain (Rlc1). Additionally, it controls the localization of several proteins necessary for the assembly of the CR, such as the anillin-related protein Mid1 and cell division control protein 15 (Cdc15) [67]. PAK1 colocalizes with the essential myosin II (Myo II) in the CR, where it phosphorylates Rlc1 at Ser35 and Ser36 [68]. In turn, the phosphorylation of Rlc1 on these residues inhibits actomyosin ring constriction and ensures the arrest of cytokinesis until complete segregation of the genetic material. The loss of PAK1 or phosphomutant forms of Rlc1 lead to premature actomyosin ring constriction [68]. PAK1 also phosphorylates the anillin-like protein Mid1 within its N-terminus and regulates its association with the plasma membrane through phosphorylation. Because contractile ring assembly and cytokinesis depend on Mid1, defects in the PAK1-Mid1 signaling pathway lead to misplaced and defective division planes [67].

Human PAK1 and PAK2 (HuPAK1 and HuPAK2) are involved in the regulation of NM II. It has been shown that the enzymatic activity of both kinases inhibits myosin light chain kinase (MLCK), which cannot activate its substrate, the myosin II regulatory light chain (MRLC) [69,191]. However, another study demonstrated that PAK directly phosphorylates MRLC and activates myosin-II [70]. These apparently conflicting observations suggest a complex regulation of myosin by PAK during cytokinesis. The HuPAK2 protein is also involved in cytokinesis. Interestingly, the tail domain of MKLP1 (amino acids 804-808,) contains a consensus sequence (K/RRXS) recognized by HuPAK2 [71,192]. Furthermore, HuPAK2 has been identified as a direct molecular interactor of MKLP1, the kinesin required for the assembly of the central spindle midzone during cytokinesis. More importantly, the MKLP1-HuPAK2 interaction is crucial for the localization of the kinesin and for the correct execution of cytokinesis [71]. Indeed, in Hek293 cells depleted of HuPAK2, MKLP1 fails to localize to the midbody, resulting in binucleated cells [71]. Taken together, these data demonstrate that protein kinases, traditionally working as mediators of actin and focal adhesion reorganization, may also carry out an important role during cytokinesis [193,194]. Interestingly, this action is also evolutionarily conserved from yeast to humans, indicating that the role of PAKs in cytokinesis is likely underestimated and needs further investigation.

4. Checkpoint Kinase 2 (Chk2)

4.1. Structure and Function of Chk2

The highly conserved protein Chk2 is a serine–threonine kinase, originally discovered in S. cerevisiae as a Rad53-related kinase [195].

Human Chk2 protein is a single polypeptide of 543 residues containing three distinct functional domains, namely the SQ/TQ cluster domain (SCD), the forhead associated
domain (FHA), and the serine/threonine kinase domain (KD) \[196\] (Figure 2C). The SQ/TQ cluster domain, located at the N-terminus, is enriched in serine–glutamine and threonine–glutamine pairs \[197\] and contains ataxia telangiectasia-mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) phosphorylation sites \[197\]. The SCD domain mediates protein interactions with phosphorylated proteins, which include the phosphorylated SCD domain of a second Chk2 molecule, thus allowing for its dimerization \[198\]. The C-terminal half contains the kinase domain.

The activation of kinase enzymatic activity requires the phosphorylation of the Chk2 kinase domain within a region named the activation ring or T-loop, located marginally to the active site \[199,200\]. The T-loop contains autophosphorylated residues required for kinase activity \[199,200\]. The autophosphorylation of the Chk2 dimer triggers a conformational change, causing the dissociation of the dimers into fully active monomers. In addition, the C-terminal region has a nuclear localization signal \[201\]. An analysis of the mutations of Thr68 or changes inside the FHA domain of residues involved in phosphothreonine binding demonstrated that dimerization requires the interaction between the phosphorylated Thr68-containing SCD segment of one Chk2 molecule with the FHA domain of a second molecule \[198,202\]. Although Thr68 is found within an amino acid sequence recognized preferentially by kinases related to the PI3-kinase family, such as ATM, ATR, and DNA-dependent protein kinase (DNA-PK), they can also be targeted by other kinases, such as Mps1, MRK, and Plk1 \[199,203–205\]. DNA damage causes ATM kinase activation \[206\], which phosphorylates the Chk2 Thr68 residue, leading to Chk2 dimerization. Chk2 dimerization promotes kinase activation through autophosphorylation of the T-loop \[207\] (Table 1).

DNA double-strand breaks (DSBs) and related lesions arrest the cell cycle at cell-cycle checkpoints, and DNA repair is activated \[208\]. DNA damage response (DDR) is initiated by the activation of ATM and ATR kinases, which leads to phosphorylation and activation of Chk2. Once activated, Chk2 dissociates from the damaged sites, then amplifies and transduces the signal initiated by ATM and ATR \[209–211\].

The substrates of Chk2 include not only proteins involved in DDR, such as breast cancer type 1 susceptibility protein (BRCA1), BRCA2, and p53 \[211–214\], but also proteins required for cell-cycle arrest at checkpoints, such as Cdc25, whose phosphorylation by Chk2 promotes its degradation by the proteasome, thus preventing the activation of cyclin-dependent kinase 2 (Cdk2), which is necessary for the G1/S transition and progression to the S phases \[210\]. Moreover, in cells with irreparable damage, Chk2 also intervenes in the activation of the apoptotic pathway. In this context, a substrate of Chk2 is represented by the transcription factor E2F-1 which, once phosphorylated by the kinase, promotes the transcription of proapoptotic genes \[215\].

4.2. Role of Chk2 in Tumorigenesis

A PubMed search of “Chk2 and cancer” had plenty of results, with the total number of retrieved articles exceeding 1500. As said, this serine–threonine kinase is a cell-cycle checkpoint regulator mainly involved in cell-cycle arrest during G1 and S in response to DNA damage \[210,216\]. Chk2 was first identified in 1998 \[195\], and it was shown that its conserved, single FHA domain is essential for its ATM-dependent activation in response to stimuli \[216\]. Chk2 is activated through phosphorylation in response to ionizing radiation and hydroxyurea treatment, although a functional ATM is required only for the first type of DNA insult \[217\]. In turn, Chk2 regulates multiple targets through phosphorylation; beyond the above-mentioned BRCA1 \[218\], E2F-1 \[215\], and Cdc25 \[210\], its interactors also include the NBS1/MRE11 axis \[219\], the inducer of acute promyelocytic leukemia, PML, \[220\], and the ATR/ATM/p53 pathway, both of which induce apoptosis \[221\]. The role of CK2 as an oncosuppressor was first hypothesized in 1999, when Bell and coworkers found frequent heterozygous mutations in Li–Fraumeni syndrome patients, who are ca. 25x more cancer-prone than average \[222\]. These data were subsequently confirmed by other groups \[223,224\], yet the final role of Chk2 in this syndrome is still a debated topic \[225\].
Nonetheless, evidence has accumulated over the years for the involvement of CHK2 in cancer, with reports of CHK2 mutations also found in sarcoma, breast cancer, colon cancer, ovarian cancer, osteosarcoma, lung cancer, prostate cancer, kidney cancer, thyroid cancer, and brain tumors [222,224,226–230]. Some reports also associated CHK2 with mitotic spindle damage, through its action on BRCA1 [231]; these data, coupled with those linking this kinase to cytokinesis, indicate CHK2 as a possible target for treating cancer cells using drugs aimed at impairing the last phases of cell division [232].

4.3. Role of Chk2 in Cytokinesis

The G1/S transition is not the only checkpoint activated by Chk2. Indeed, a recent study on cultured human cells involved human Chk2 in the activation of the abscission checkpoint [72]. The abscission checkpoint, which delays cytokinesis in response to chromosome segregation defects [233–235] to prevent chromatin breakage and tetraploidization by regression of the cleavage furrow, is maintained by Aurora B kinase localized to the MB [236,237]. The activity and recruitment of Aurora B are strictly dependent on its partners in the chromosomal passenger complex (CPC), which includes the scaffolding protein INCENP and the subunits Survivin and Borealin [47,238]. In turn, the localization of the CPC requires the binding of INCENP to Mklp2 kinesin [239,240]. It was demonstrated that ATM phosphorylates and activates Chk2 at the MB center in late cytokinesis in normal cells and that active Chk2 phosphorylates human INCENP on Ser91 to promote INCENP binding to Mklp2 [72]. In turn, INCENP allows Aurora B localization to the MB, which delays abscission in normally segregating cells [72]. If these data were confirmed, then the localization and activation of Aurora B at abscission would be significantly dependent on Chk2 function, thus opening new routes for understanding the events leading to the final separation of daughter cells in eukaryotes. This would add a new, important player in the field of cytokinesis completion.

5. On the Crosstalk between Minor Kinases—Novel Insight into Cell-Cycle Control?

It is noteworthy to underline that a few reports have highlighted functional links among the three kinases described here, suggesting that, at least in some instances, they cooperate in regulating the cell cycle. It has been shown that CK2α colocalizes with PAK1 through the association with CKIP-1 at the plasma membrane as a response to EGF, and CK2α phosphorylates PAK1, promoting its cancer-related functions [165,241]. It has been demonstrated by Zhang and collaborators that the overexpression of PAK5 can downregulate p-CHK2 in hepatocellular carcinoma cells [242]. Kim showed that CK2 interacts with Chk2 and phosphorylates MRE11, thus indicating CK2 as a potential upstream regulator of MRE11 function [243]. Bjørling-Poulsen and coworkers showed that the beta-subunit of CK2 specifically interacts with Chk2 in vitro and in cultured cells, and that the activation of Chk2 leads to a reduction of this interaction. Moreover, the presence of the CK2 beta-subunit significantly reduced the Chk2-catalyzed phosphorylation of p53 in vitro [244]. Finally, Kroonen and collaborators showed that CK2 protein depletion inhibited NF-κB activation and altered the Tyr68 phosphorylation of Chk2 in malignant glioma cells [245]. Although these data need further validation, the crosslinks among these three kinases unveil a novel network of cell-cycle controllers that surely needs additional investigation. The advances in linking these three kinases to cytokinesis either directly or indirectly further confirm their role in tumorigenesis, increasing the complexity of their interactome but also expanding the possible routes of investigation regarding possible therapeutic approaches in cancer treatment. In this context, recent work has shown that inducing cytokinesis failures could provide an effective strategy to block cell division and promote cell death in cancer cells [246–248].

6. Conclusions

The events occurring during cytokinesis are under strict genetic control. The complexity of these events is reflected by the number of proteins involved in the completion
of cell division. Some of these proteins have a structural role, being an integral part of molecular architectures that build up structures such as MB or CR (myosin, kinesin, etc.). Others have a gene regulation function and are responsible for determining which proteins should be present in a given cell phase (e.g., E2F-1). Finally, a third group of proteins controls the function of other target proteins by post-translational modifications, mainly phosphorylation, such as kinases. Their action is exerted in several different ways; they can activate or deactivate the substrate protein or promote its degradation via the proteasome pathway. Many kinases have been strongly linked to cytokinesis, their role is well known, and most of their targets, as well as the effects of their mutation, are described in the literature; examples include cyclin-dependent kinase, polo-like, and Aurora B. However, the number of kinases involved in cytokinesis is likely underestimated. Increasing evidence is accumulating, describing the role of multifunctional kinases in this process. To date, the data available about these enzymes are still fragmented and need both further validation and additional investigation. Yet, their role in cell division is far from unnecessary or merely redundant. Rather, their role can be central in this process, as their targets in some cases include the well-known above-mentioned kinases; for example, the action of Chk2 on Aurora B. Understanding the role of these multifunctional kinases may allow for identifying novel ways of controlling the final phases of cell division, a phenomenon that is at the basis of neoplastic transformation. Indeed, the connection between cytokinesis failure and tumorigenesis is a well-established fact [249]. Moreover, cancer treatment can be accomplished not only by trying to patch cytokinesis impairment but also by inducing it [247]. Thus, identifying the main actors involved in cytokinesis and learning how they interact and how to alter their function (either inhibiting or activating them) is crucial to discover new, useful approaches for the development of new diagnostic and/or therapeutic strategies in cancer treatment. Indeed, protein kinases are one of the most successful drug targets for oncology due to their critical role in different mechanisms that drive malignant transformation [21–23], and discovering additional functions in the cytokinesis of undervalued kinases will be pivotal for improving the research in this field.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cells11223639/s1, Figure S1: Percent identity of the kinase domain of the PAKs mentioned in the text. The reference sequences used were identified with the Prosite software and the alignment was done with Clustal Omega.

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Abbreviations

Acronyms | Full name
---|---
ALIX | ALG-2-interacting protein X
AKT | Protein kinase B
ANCHR | Abscission/NoCut checkpoint regulator
ARF1 | ADP-ribosylation factor-1
ATM | Ataxia telangiectasia-mutated
ATR | Ataxia telangiectasia and Rad3-related
Bni1 | Diaphanous-related formin
ßPIX | PAK-interacting exchange factor beta
BRCA1 | Breast cancer type 1 susceptibility protein
BRCA2 | Breast cancer type 2 susceptibility protein
ßTrCP | Beta-transducin repeat containing E3 ubiquitin protein ligase
| Acronyms  | Full name                                                      |
|----------|---------------------------------------------------------------|
| Bud6     | Bud site selection protein 6                                   |
| Cdc3     | Cell division control protein 3                               |
| Cdc10    | Cell division control protein 10                              |
| Cdc11    | Cell division control protein 11                              |
| Cdc12    | Cell division control protein 12                              |
| Cdc15    | Cell division control protein 15                              |
| Cdc25    | Cell division cycle 25                                        |
| Cdc25B   | Cell division cycle 25B                                       |
| Cdc42    | Cell division control protein 42 homolog                     |
| CDK1     | Cyclin-dependent kinase 1                                     |
| Cep55    | Centrosomal protein 55                                        |
| Chk2     | Checkpoint kinase 2                                           |
| CHMP4C   | Charged multivesicular body protein 4C                        |
| CIN      | Chromosome instability                                        |
| Cit-K    | Citron kinase                                                 |
| CK2      | Casein kinase 2                                               |
| CK2α     | Casein kinase 2 subunit alpha                                  |
| CK2β     | Casein kinase 2 subunit beta                                   |
| Ckb1     | Casein kinase 2 subunit beta                                   |
| CKIP-1   | Casein kinase 2 interacting protein 1                          |
| Cla4     | Serine/threonine protein kinase CLA4                          |
| CPC      | Chromosomal passenger complex                                  |
| CR       | Contractile ring                                              |
| Cyk-4    | Cytokinesis defect-4                                          |
| DNA-PK   | DNA-dependent protein kinase                                   |
| DDR      | DNA damage response                                           |
| E2F1     | Transcription factor                                          |
| ECT2     | Epithelial cell-transforming sequence 2 oncogene              |
| EGF      | Epidermal growth factor                                       |
| EGFR     | Epidermal growth factor receptor                               |
| ER       | Endoplasmic reticulum                                         |
| ESCRT-III| Endosomal sorting complexes required for transport-III        |
| FHA      | Forkhead-associated domain                                    |
| GBF1     | Golgi brefeldin A-resistant guanine nucleotide exchange factor 1|
| GOLPH3   | Golgi phosphoprotein 3                                        |
| GRB2     | Growth factor receptor-bound protein 2                        |
| HDAC1    | Histone deacetylase 1                                         |
| HDAC2    | Histone deacetylase 2                                         |
| INCENP   | Inner centromere protein                                      |
| JAK      | Janus tyrosine kinase                                         |
| KD       | Serine/threonine kinase domain                                 |
| KIF23    | Kinesin-like protein                                          |
| MAPK     | Mitogen-activated protein Kinases                             |
| MB       | Midbody                                                       |
| mbt      | Mushroom bodies tiny                                         |
| MgcRacGAP| Rac GTPase-activating protein 1                                |
| Mid1     | Anillin-related medial ring protein mid1                      |
| mhcA     | Myosin heavy chain A                                          |
| MKLP1    | Mitotic kinesin-like protein1                                  |
| MLCK     | Myosin light chain kinase                                     |
| MORC2    | Microrchidia family CW-type zinc finger protein 2              |
| MPS1     | Monopolar spindle 1                                           |
| MRE11    | Double-strand break repair protein MRE11                       |
| MRK      | MLK-related kinase                                            |
| MRLC     | Myosin II regulatory light chain                               |
Acronyms | Full name
--- | ---
Myo II | Myosin II
NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells
NBS1 | Nijmegen breakage syndrome 1
Nck | Non-catalytic region of tyrosine kinase
NM IIA | Non-muscle myosin II isoform A
Orb2p | Translational regulator orb2
PAK | P21-activated kinases
PI3K | Phosphatidylinositol 3-kinase
PIN1 | Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1
PIX | PAK-interacting exchange
Plk1 | Polo-like kinase 1
PML | Promyelocytic leukemia
PP2A | Phosphoprotein phosphatase 2A
PP6 | Protein phosphatase 6
PXXP | Proline-Xaa-Xaa-Proline
Rac1 | Ras-related C3 botulinum toxin substrate 1
Rlcl | Myosin regulatory light chain
RhoA | Ras homolog family member A
SCD | SQ/TQ cluster domain
SCF | Skp1/Cul-1/F-box protein complex
Sep7 | Septation protein 7
SH3 | SRC homology 3 domain
Shs1 | Seventh homolog of septin 1
Shk1 | Serine/threonine protein kinase shk1/pak1
Shk2 | Serine/threonine protein kinase shk2
Skm1 | Serine/threonine protein kinase shk1/pak1
Ste20 | Serine/threonine protein kinase STE20
TSG101 | Tumor susceptibility gene 101 protein
zip | Zipper

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