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Spatiotemporal regulation of the Dma1-mediated mitotic checkpoint coordinates mitosis with cytokinesis

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Abstract

During cell division, the timing of mitosis and cytokinesis must be ordered to ensure that each daughter cell receives a complete, undamaged copy of the genome. In fission yeast, the septation initiation network (SIN) is responsible for this coordination, and a mitotic checkpoint dependent on the E3 ubiquitin ligase Dma1 and the protein kinase CK1 controls SIN signaling to delay cytokinesis when there are errors in mitosis. The participation of kinases and ubiquitin ligases in cell cycle checkpoints that maintain genome integrity is conserved from yeast to human, making fission yeast an excellent model system in which to study checkpoint mechanisms. In this review, we highlight recent advances and remaining questions related to checkpoint regulation, which requires the synchronized modulation of protein ubiquitination, phosphorylation, and subcellular localization.

Keywords

cell division; mitosis; cytokinesis; cell cycle checkpoint; SIN; Dma1; CHFR; CK1

Cell cycle checkpoints ensure genome integrity

In order to successfully divide, all cells must faithfully segregate both their genetic material and cellular contents. This requires spatial and temporal coordination of mitosis with cytokinesis to ensure that each daughter cell inherits a complete copy of the genome. The core cell cycle machinery has been conserved throughout evolution, allowing us to study the signaling mechanisms that regulate cell cycle checkpoints in genetically and biochemically tractable model organisms such as *Schizosaccharomyces pombe* (Botchkarev and Haber, 2018; Palou et al., 2017; Sánchez-Mir et al., 2018; Sveiczer and Horváth, 2017). In *S. pombe*, cytokinesis is controlled by the septation initiation network (SIN), a kinase cascade activated by polo-like kinase Plo1 that promotes constriction of the contractile ring once cyclin dependent kinase activity drops in anaphase (reviewed in Botchkarev and Haber, 2018; Simanis, 2015).

Over the past 15 years, our lab and others have elucidated a checkpoint pathway that inhibits the SIN to prevent cytokinesis in the event of mitotic spindle stress (Guertin et al., 2002;

Murone and Simanis, 1996). In this way, delays in mitosis are coupled to delays in cytokinesis. Occurring at the spindle pole body (SPB) and mediated by the E3 ubiquitin ligase Dma1, this checkpoint operates in parallel to the spindle assembly checkpoint at the kinetochore (Johnson et al., 2013; Murone and Simanis, 1996). While the spindle assembly checkpoint monitors microtubule attachments to kinetochores to ensure that chromosomes are equally segregated between daughter cells (reviewed in Musacchio, 2015), the Dma1-mediated checkpoint temporally restricts cytokinetic ring ingression until segregation is complete so that chromosomes are not caught in the division plane or in the incorrect daughter cell; both of these mechanisms prevent abnormal chromosome gain, loss, or damage. When the Dma1-mediated checkpoint is activated, the CK1 family members Hhp1 and Hhp2 concentrate at the SPB via an interaction between their kinase domains and the SPB scaffold Ppc89 (Elmore et al., 2018). CK1 phosphorylates Thr275 and Ser278 of Sid4, creating a docking site for the forkhead-associated (FHA) domain of Dma1 (Johnson et al., 2013). Dma1 subsequently ubiquitinates Sid4, sterically blocking recruitment of Plo1 to the SPB and preventing activation of the SIN (Johnson and Gould, 2011).

Dma1 and other FHA-RING ligases are dynamic signaling proteins

While Dma1 is not essential, *dma1* deletion increases the rate of chromosome loss (Murone and Simanis, 1996), and disruption of the Dma1-mediated mitotic checkpoint results in premature septation and unequal division of the genetic material (Johnson and Gould, 2011). Conversely, Dma1 overexpression is lethal, and overstimulation of the checkpoint results in elongated, multinucleate cells (Guertin et al., 2002; Jones et al., 2018; Murone and Simanis, 1996). Mice lacking the Dma1 homolog CHFR have similar defects in chromosome segregation and cytokinesis, which lead to chromosome instability (Yu et al., 2005).

Dma1 homologs are a family of E3 ubiquitin ligases that share a distinctive architecture with an N-terminal FHA domain and a C-terminal RING domain (Brooks et al., 2008). Maintaining genome integrity through participation in cell cycle checkpoints is a conserved function of FHA-RING ligases. The *Saccharomyces cerevisiae* proteins Dma1 and Dma2 mediate the spindle positioning checkpoint and regulate septin disassembly at the end of mitosis (Chahwan et al., 2013; Fraschini et al., 2004; Merlini et al., 2012). A key component of the antephasis checkpoint, CHFR delays metaphase entry upon mitotic spindle stress (Burgess et al., 2008; Chin and Yeong, 2010; Matsusaka and Pines, 2004; Scolnick and Halazonetis, 2000), and similarly to Dma1, it could potentially exert this effect via Plk1 (Kang et al., 2002; Kim et al., 2011; Shtivelman, 2003; Yu et al., 2005). RNF8, another human FHA-RING ligase, antagonizes mitotic exit (Chahwan et al., 2013; Plans et al., 2008; Tuttle et al., 2007) and has additional functions in protecting against DNA double strand breaks, replication stress, and genomic instability (Halaby et al., 2013; Sy et al., 2011). CHFR and RNF8 knockout mice have an increased susceptibility to cancer (Li et al., 2010; Yu et al., 2005), and CHFR is epigenetically silenced in a large variety of human tumors and cell lines (reviewed in Sanbhnani and Yeong, 2012). Low expression of CHFR correlates with poor patient prognosis and increased metastasis, but also with increased susceptibility to taxanes (reviewed in Sanbhnani and Yeong, 2012). So while the checkpoint function of Dma1 and its homologues is essential to ensure faithful cell division that maintains genome

integrity, and loss of this function has implications for cancer progression and treatment, the mechanisms by which FHA-RING ligases are regulated remain largely unknown.

Dma1 is regulated via subcellular localization and other mechanisms

For example, Dma1's ubiquitination of Sid4 was known to be a vital step in checkpoint signaling in *S. pombe*, but a lingering question was how this process was reversed to deactivate the checkpoint upon resolution of spindle stress. Recently, we discovered that an apparent switch in preference from Sid4 ubiquitination to Dma1 autoubiquitination causes Dma1 to transiently leave the SPB during anaphase B (Jones et al., 2018). Later in anaphase, SIN activity drives the return of Dma1 to SPBs. Permanently tethering Dma1 to Sid4 prevents SIN activation and cytokinesis, frequently resulting in cell death. Dynamic localization to PML bodies (Daniels et al., 2004) and the nucleus (Kwon et al., 2009) have also been found to regulate CHFR checkpoint function, so the rapid movement of FHA-RING ligases between cellular compartments could be a conserved regulatory mechanism. The dynamic localization of Dma1 was dependent on its catalytic activity, and we showed that autoubiquitination disrupts its interaction with Sid4 *in vitro* (Jones et al., 2018). These findings are consistent with previous work showing that other FHA-RING ligases autoubiquitinate (Bothos et al., 2003; Chaturvedi et al., 2002; Loring et al., 2008) and that this activity is important for overcoming the checkpoint (Castiel et al., 2011; Kim et al., 2011).

But what signals Dma1 to stop ubiquitinating Sid4 and begin autoubiquitinating itself? *S. cerevisiae* Dma1 and Dma2 utilize Ubc4 as an E2 for autoubiquitination and a G1 cell cycle delay, while Ubc13 is required for a G2 delay (Loring et al., 2008). We know that *S. pombe* Dma1 can use both UBE2D1 and Ubc13/Uev1a, the human homologs of Ubc4 and Ubc13, *in vitro* (Johnson and Gould, 2011; Jones et al., 2018), but it remains to be discovered which E2 protein(s) are important for Dma1 checkpoint function *in vivo* and if E2 specificity can confer substrate specificity.

The transient and reversible nature of Dma1's localization is consistent with a hypothesis that post-translational modifications may control the underlying substrate switching. Modification of CHFR by poly(ADP-ribosyl)ation (Ahel et al., 2008; Kashima et al., 2012) and phosphorylation (Bothos et al., 2003; Shtivelman, 2003) is important for its antephase checkpoint function. Dma1 is also known to be phosphorylated (Koch et al., 2011), making the phosphorylation-dependent regulation of Dma1 particularly interesting for future study. Since the SIN is required for the late-anaphase relocalization of Dma1 to SPBs (Jones et al., 2018), an intriguing possibility is that SIN kinases may regulate Dma1 itself, counteracting deubiquitinating enzymes, or other targets that may modulate Dma1. Mitotic kinases such as Cdc2 or Plt1 could act similarly to control Dma1 localization in a cell cycle dependent manner. The FHA domain is essential for the checkpoint function of FHA-RING ligases (Bieganowski et al., 2004; Guertin et al., 2002; Huen et al., 2007; Kolas et al., 2007; Mailand et al., 2007; Scolnick and Halazonetis, 2000; Wang and Elledge, 2007), raising the possibility that substrate priming by different kinases could spatiotemporally control Dma1 activity. CK1 is required for the FHA-mediated recruitment of Dma1 to SPBs upon

checkpoint activation (Johnson et al., 2013), and CK1 or other kinases could have additional effects on Dma1 dynamics at other times.

CK1 is the upstream regulator of the Dma1-mediated checkpoint

Understanding whether CK1 functions beyond phosphorylating Thr275 and Ser278 of Sid4 in the Dma1-mediated mitotic checkpoint, or has roles in cell division outside of the checkpoint, is still an open area. CK1 enzymes have diverse cellular functions, including DNA damage repair (Dhillon and Hoekstra, 1994), maintenance of circadian rhythms (Eng et al., 2017; Fan et al., 2008; Meng et al., 2008; Narasimamurthy et al., 2018; Yang et al., 2017), regulation of Wnt signaling (Bernatik et al., 2011; Bryja et al., 2007; Casagolda et al., 2010; Cruciat et al., 2013; Greer and Rubin, 2011; Morgenstern et al., 2017; Peters et al., 1999; del Valle-Perez et al., 2011; Vinyoles et al., 2017), initiation of endocytosis (Peng et al., 2015; Wang et al., 2015), and neurodegenerative disease progression (Kuret et al., 2002; Li et al., 2004). For other multifunctional kinases (e.g. Plk1, see Botchkarev and Haber, 2018; Kettenbach et al., 2011; Lera and Burkard, 2012; Takaki et al., 2008), extensive lists of substrates have been identified, and there is mechanistic detail describing the regulated changes in localization, kinase activity, and interaction partners that determine which subsets of substrates are phosphorylated at a given place and time. In contrast, regulation of CK1 activity and the identification of CK1 substrates remains largely unexplored.

The *S. pombe* CK1 family members Hhp1 and Hhp2 are ubiquitous throughout the cell; there is a substantial cytoplasmic pool, as well as more concentrated populations in the nucleus, cell tips, division site, and SPBs (Elmore et al., 2018). Human CK1 δ and CK1 ϵ localize in a similar manner (Elmore et al., 2018; Greer and Rubin, 2011; Milne et al., 2001). When the Dma1-dependent checkpoint is activated, SPB localization is enhanced, and this is required for CK1 to perform its mitotic checkpoint function (Elmore et al., 2018; Johnson et al., 2013). It is still unclear what drives the accumulation of Hhp1/2 at SPBs during the checkpoint and what serves as the localization cue(s) that direct Hhp1/2 to the division site and cell tips. These signals appear to be distinct from the mechanism of SPB targeting, as Hhp1 mutants deficient in SPB localization are still detected at other subcellular compartments (Elmore et al., 2018). This indicates that CK1 signaling can be compartmentalized via different localization mechanisms, which have yet to be elucidated but would likely be important for regulating a multifunctional kinase like CK1.

Surprisingly, the non-catalytic C-terminus of CK1 is dispensable for spindle pole targeting in both humans and yeast, and we have pinpointed basic residues within the C-lobe of the Hhp1 kinase domain that interact with the SPB scaffold Ppc89 (Elmore et al., 2018). Similarly, human CK1 δ localizes to the centrosome via an interaction with the scaffolding protein AKAP450 (Sillibourne et al., 2002); thus, binding to scaffolds may be a general mechanism to direct CK1 to specific substrates, and it will be interesting to test this further and to identify other potential CK1 interacting partners. The participation of the CK1 kinase domain in docking interactions has also been observed in *S. cerevisiae* Hrr25, which interacts with the monopolin subunit Mam1 via the N-lobe and the central domain, and this interaction promotes phosphorylation of Dsn1, the kinetochore receptor for monopolin (Petronczki et al., 2006; Ye et al., 2016). Whether the interactions of Hhp1/2 with Ppc89, or

other scaffolds that have yet to be identified, affects Hhp1/2 kinase activity remains to be seen.

In general, CK1 enzymes are thought to be constitutively active, but they can be inhibited by autophosphorylation of their C-termini (Carmel et al., 1994; Cegielska et al., 1998; Gietzen and Virshup, 1999; Graves and Roach, 1995; Hoekstra et al., 1994; Rivers et al., 1998; Venerando et al., 2014). The current model of autoinhibition asserts that once phosphorylated, the C-terminus interacts with the kinase domain, blocking substrate access to the active site and decreasing kinase activity (Cegielska et al., 1998; Graves and Roach, 1995; Knippschild et al., 2014; Longenecker et al., 1996, 1998). However, several implications of this model have not been tested: First, the full complement of autophosphorylation sites has never been identified in any CK1 enzyme, and the high degree of sequence divergence between the C-termini of CK1 family members may indicate that each kinase has distinct autophosphorylation sites. Furthermore, autophosphorylation sites in the kinase domain have been noted in addition to those in the C-terminus (Cegielska et al., 1998), but whether kinase domain autophosphorylation also inhibits catalytic activity remains unclear. Second, an intramolecular interaction between the C-terminus and the kinase domain has not been confirmed, though anion binding pockets observed in crystal structures of CK1 kinase domains have led to the hypothesis that the C-terminus may interact with these sites (Longenecker et al., 1996; Xu et al., 1995; Ye et al., 2016). Finally, the physiological consequences of CK1 autoinhibition have never been evaluated *in vivo* in any organism.

Conclusion

As the most upstream members of the Dma1-mediated mitotic checkpoint, the mechanisms that regulate Hhp1/2 activity directly influence checkpoint signaling, and they may also provide insight into the connection between spindle stress and checkpoint activation. Reciprocally, Sid4 phosphorylation could serve as a useful readout of CK1 activity *in vivo*, allowing different regulatory mechanisms to be tested so that we can better understand this conserved family of essential kinases. The mitotic checkpoint is activated following Sid4 phosphorylation by CK1 and ubiquitination by Dma1, but once chromosomes have successfully segregated, the checkpoint can be resolved by switching Dma1's substrate preference to itself. In response to a transient and reversible signal, Dma1 autoubiquitinates and leaves the SPB to allow SIN activation, and then maximal SIN activity causes relocalization of Dma1 to the SPB as cytokinesis completes, in preparation for the next cell cycle. These dynamic changes in protein phosphorylation, ubiquitination, and subcellular localization coordinate mitosis with cytokinesis in *S. pombe* and provide insight as a model for cell cycle regulation in other organisms.

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