Role of the Spindle and kinetochore associated (Ska) protein complex in mitotic progression.

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Abstract
The Spindle and Kinetochore Associated (Ska) protein complex is a heterotrimeric complex involved in mitotic progression. Depletion of Ska1, Ska2 or Ska3 by RNAi causes delays in chromosome alignment followed by a long metaphase arrest that results in Cohesion fatigue. Ska1 and Ska3 have been shown to bind microtubules both *in vitro* and *in vivo*. Ska1 directly recruits the protein phosphatase PP1 to kinetochores during mitosis. The Ska complex has also been implicated is regulating the localization of Anaphase promoting complex/cyclosome (APC/C) to chromosomes. Aurora B kinase has been shown to phosphorylate and regulate kinetochore recruitment of Ska proteins. The Ska complex, in addition to being substrate of Aurora B, also directly activates Aurora B and regulates kinetochore microtubule stability to ensure proper chromosome bi-orientation. The master mitotic kinase Cdk1 phosphorylates Ska3 and regulates Ska complex localization to kinetochores. Cdk1 kinase does not affect spindle localization of the Ska complex suggesting that distinct pathways exist to recruit Ska complex to defined mitotic substructures. Herein we discuss these findings and postulate their implications on Ska complex function during mitosis.
Keywords: Mitosis, Ska, spindle checkpoint signaling, APC/C activation.

Mitosis is the process by which cells segregate the replicated DNA equally into two daughter cells. During mitosis, DNA is hyper condensed and a multi protein complex called kinetochore assembles on the centromere region of chromosomes. Kinetochores perform many important roles such as microtubule attachment, spindle checkpoint signaling and chromosome movement. In the last decade, multiple laboratories have embarked on studies to identify new proteins that localize to kinetochores.

In 2009 multiple laboratories concurrently discovered a novel three-member protein complex called Spindle and kinetochore associated protein complex (SKA) (Daum et al., 2009; Gaitanos et al., 2009; Raaijmakers et al., 2009; Theis et al., 2009; Welburn et al., 2009). Individual members of the Ska complex namely Ska1, Ska2 and Ska3 were found to localize to spindle microtubules and kinetochores during mitosis (Gaitanos et al., 2009; Welburn et al., 2009). Depletion of any of the Ska proteins individually or in combination caused chromosome alignment delays, metaphase delays or arrest at metaphase eventually causing cohesion fatigue. Cohesion fatigue is the phenomenon where a prolonged arrest at metaphase causes spindle microtubules to pull chromosomes apart and cause mitotic arrest (Daum et al., 2011). Long-term video microscopy of Ska depleted cells also showed "escaper" phenomenon where chromosomes once aligned would leave metaphase plate in a rapid motion and subsequently realign (Daum et al., 2009; Gaitanos et al., 2009; Raaijmakers et al., 2009; Theis et al., 2009; Welburn et al., 2009). This phenomenon can be interpreted as chromosome alignment defect or can be observed to be a distinct phenomenon that occurs only in Ska depleted cells.

The localization pattern of the Ska proteins and the strong mitotic arrest observed upon protein depletion was unique to this complex. Since its discovery multiple laboratories have strived to understand the role of this complex in mitotic progression. In this review we outline the initial studies that led to the discovery of the Ska complex. We explain how mitotic kinases regulate spindle microtubules or kinetochore localization of the Ska complex. Lastly, we discuss the functional relevance of this protein complex and its role in spindle checkpoint signaling and anaphase onset.

Discovery

In 2006 a proteomic analysis of mitotic spindle associated proteins from vertebrate cells identified Ska1 and Ska2 to be two mitotic proteins that localize to both spindle microtubules and kinetochores (Hanisch et al., 2006). In HeLa cells, the two proteins were found to interact and Ska1 was required for Ska2 stability *in vivo (Hanisch et al., 2006)*. The Ska proteins are conserved in vertebrates and homologs of Ska1 and Ska3 but not Ska2 were identified in C.*elegans* (Schmidt et al., 2012). No obvious homologs of the Ska genes were found in yeast (Hanisch et al., 2006). In addition, loss of Ska1 or Ska2 by siRNA-mediated protein depletion was found to cause metaphase like arrest with the occasional chromosome escaping from the metaphase chromosome alignment. Ska protein depletion was found to cause increased cold-sensitivity to kinetochore fibers suggesting that Ska proteins may function in maintaining stable attachment between kinetochores and microtubules (Hanisch et al., 2006).

Proteins at the kinetochore-microtubule interface couple microtubule attachment to chromosome movement. In budding yeast a protein complex called Dam1 couples microtubule depolymerization with chromosome movement (Cheeseman et al., 2001; Janke et al., 2002; Li et al., 2002). However, in vertebrates, a homologue of Dam1 has not been found. To identify novel proteins at the kinetochore microtubule interface in vertebrates that could function as homologs of the yeast Dam1 protein one group immunoprecipitated Ska1 and Ska2 from mammalian cells and did mass spectrometric analysis. They identified Ska3/C13orf3/RAMA1 as a protein that associated with both Ska1 and Ska2 (Welburn et al., 2009). Concurrently the laboratory that discovered Ska1 and Ska2 identified Ska3 as an interaction partner and the three proteins stably formed the Ska complex (Gaitanos et al., 2009). Additionally, a siRNA screen to identify novel kinetochore proteins led to discovery of Ska3 (Raaijmakers et al., 2009). By combining protein localization with RNAi screening data another group discovered Ska3 (Theis et al., 2009). Finally using bioinformatics to analyze existing microarray data and identify novel genes co-regulated with known mitotic genes one more group discovered Ska3 (Daum et al., 2009). Characterization of the Ska complex found that the Ska proteins localize to the outer kinetochore, centrosomes and the spindle microtubules during mitosis (Daum et al., 2009; Gaitanos et al., 2009; Hanisch et al., 2006; Welburn et al., 2009). Phenotypes observed upon depletion of the Ska proteins include chromosome alignment delays, metaphase delay or arrest, occasional presence of escaper and cohesion fatigue. Reconstitution studies determined the Ska complex to be made of two molecules of each Ska1, Ska2 and Ska3 subunits (Gaitanos et al., 2009; Welburn et al., 2009). Structural analysis showed that the N terminal of Ska proteins forms a W-shaped dimer of coiled coils while the C terminals of Ska1 and Ska3 protrude outside from this structure to bind microtubules (Jeyaprakash et al., 2012). The N termini of Ska1, Ska2 and Ska3 interact

with one another to promote complex formation and the whole Ska complex functions together to promote proper mitosis (Jeyaprakash et al., 2012). Some studies have proposed that the W shaped dimer extends to bind microtubules and promote both microtubule stability and anaphase onset but precise mechanisms are unknown (Daum et al., 2009; Gaitanos et al., 2009; Raaijmakers et al., 2009; Theis et al., 2009; Welburn et al., 2009).

Kinetochore recruitment of Ska complex

Kinetochores have trilaminar architecture with an inner centromeric region, middle linker region and an outer kinetochore domain that is responsible for binding microtubules (Cheeseman and Desai, 2008). The early studies showed that the Ska proteins localize to the outer kinetochore. Ndc80 complex is a stable outer kinetochore protein complex that directly interacts with microtubules (Cheeseman and Desai, 2008). Depletion of Ndc80 by RNAi abolishes kinetochore localization of Ska proteins suggesting that Ndc80 is required for recruitment of Ska proteins to kinetochores (Daum et al., 2009; Gaitanos et al., 2009; Raaijmakers et al., 2009; Welburn et al., 2009). However a direct interaction between Ska proteins and Ndc80 complex has been difficult to observe (Gaitanos et al., 2009; Raaijmakers et al., 2009; Welburn et al., 2009). This could be due to multiple possible reasons such as weak binding affinity, requirement of additional posttranslational modifications or requirement of additional adaptor proteins that facilitate an interaction.

Ska proteins accumulate at kinetochores as chromosomes bi-orient on the mitotic spindle (Chan et al., 2012; Sivakumar et al., 2014). Aurora B kinase was found to negatively regulate localization of Ska proteins to kinetochores (Chan et al., 2012)(Figure 1). Ska1 at T157, S185, T205, S242 and Ska3 at S87, S110 and S159 were directly phosphorylated by Aurora B kinase during mitosis. Expression of phophomimetic mutants ($Ska1^{4D}$ + $Ska3^{3D}$) failed to associate with kinetochores while expression of non-phosphorylatable mutants ($Ska1^{4A}$ + $Ska3^{3A}$) localized similar to wild type (WT) Ska proteins at kinetochores (Chan et al., 2012). Interestingly the phosphomimetic mutants displayed reduced K-fiber stability (similar to Ska depleted cells) while the non-phosphorylatable mutants showed hyperstable K-fiber formation. The authors then tested the mitotic phenotypes by time-lapse imaging and found that neither the phophomimetic nor the nonphosphorylatable mutants rescued the mitotic delays observed upon Ska protein depletion (Chan et al., 2012). This suggests that nonphosphorylatable mutants localize to kinetochores prematurely and hyper stabilize microtubule attachments preventing error-correction and causing delays in chromosome alignment. Thus, phosphorylation by Aurora B regulates Ska complex recruitment to kinetochores. Dynamic phosphorylation and dephosphorylation of Ska by Aurora B ensures that optimum Ska kinetochore localization occurs only after stable microtubule attachments are made (Chan et al., 2012). If true, why are there multiple Aurora B regulated phosphorylation sites on Ska proteins? Does each site contribute to microtubule detachment/attachment cycle and the multiple sites are required for cooperativity to ensure only the most stable and optimum microtubule attachments are maintained?

Ska3 is also phosphorylated by Cdk1 kinase. Two residues in the C terminus of Ska3 (T358 and T360) bear the Cdk1 consensus site (S/TP) and when phosphorylated by Cdk1 are sufficient to promote kinetochore recruitment and direct binding to Ndc80 (Zhang et al., 2017). Ska3 2A (T358A, T360A)

does not localize to kinetochores and is delayed in mitotic progression suggesting that kinetochore recruitment of Ska is required for proper mitotic progression (Figure 1). Additionally, in Ska3 depleted cells, Ska1 and Ska2 fail to localize to kinetochores. Thus, Ska3 binding to Ndc80 recruits Ska1 and Ska2 to kinetochores. Further, Cdk1 regulates only kinetochore recruitment and does not affect spindle localization of Ska complex (Zhang et al., 2017).

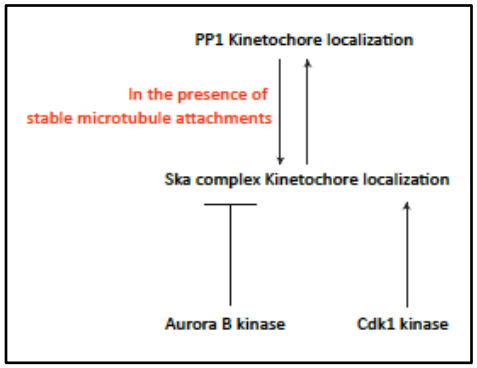

Figure 1: Aurora B kinase inhibits while Cdk1 kinase phosphorylation promotes kinetochore recruitment of Ska proteins. Upon kinetochore localization, Ska recruits PP1 phosphatase to kinetochores. In the presence of stable microtubule attachments, PP1 in turn promotes further recruitment of Ska proteins to kinetochore. This feedback loop strengthens microtubule attachments and promotes rapid and irreversible anaphase onset.

Cdk1 kinase and Aurora B kinases regulate kinetochore recruitment of Ska complex (Chan et al., 2012; Sivakumar et al., 2016). Phosphatases are also required for Ska kinetochore recruitment (Redli et al., 2016). Ska1 recruits phosphatase PP1 to kinetochores once stable microtubule attachments are made (Sivakumar et al., 2016). In Ska depleted cells, PP1 recruitment to kinetochores was diminished and phosphoepitope signals at kinetochores were increased suggesting that Ska recruits PP1 to dephosphorylate kinetochore substrates (Sivakumar et al., 2016). This suggests that there is a feedback loop where Ska increases Aurora B activity to inhibit its own recruitment until proper microtubule attachments are made (Redli et al., 2016). After stable microtubule attachment, Ska1 recruits PP1 and this promotes Ska localization at kinetochores further to promote rapid spindle checkpoint silencing and anaphase onset (Figure 1). We propose that this occurs only in the presence of microtubules to ensure accurate chromatid separation into daughter cells. In the absence of microtubules, Ska and PP1 at kinetochores is decreased and Aurora B activity in high to prevent mitotic exit and the unequal segregation of chromosomes into daughter cells.

During chromosome congression microtubules that are improperly attached to kinetochores are depolymerized by Aurora B activity and this process regulates Ska complex recruitment. Cdk1 activity reaches maximum levels after nuclear envelope breakdown. At this time, chromosomes are trying to align and Aurora B activity is high to facilitate proper microtubule attachments. Ska localization to kinetochores is low during chromosome alignment and reaches maximum at metaphase. What is the mechanism that prevents Cdk1 from recruiting Ska to kinetochores at prometaphase? Is there a crosstalk between Cdk1 and Aurora B regulation of Ska kinetochore localization? If not, are the two pools independent of each other? Future work will shed light on these questions and help understand how these regulatory networks intersect and function during mitosis.

Interaction with microtubules

The Ska complex was found to directly bind microtubules *in vitro* and *in vivo* (Jeyaprakash et al., 2012; Welburn et al., 2009). The C terminus of Ska1 was found to

contain a conserved microtubule-binding domain (Abad et al., 2014; Jeyaprakash et al., 2012; Schmidt et al., 2012). Structural studies identified this region to form a winged helix domain (Abad et al., 2014; Schmidt et al., 2012). Further this C terminal domain (CTD) contained three conserved Arginine residues that formed a basic patch (R141, R225 and R234). One study showed that the mutation of the three residues to Alanine abolished binding to microtubules *in vitro* suggesting that this basic patch binds to the acidic tails of tubulin to promote microtubule binding (Schmidt et al., 2012). Another study showed that multiple positively charged amino acid clusters (including the R141, R225 and R234 residues) identified in the C terminus of Ska1 are involved in binding to microtubules (Abad et al., 2014). *In vivo*, expression of Ska1 deleted of the C terminal microtubule-binding domain caused severe alignment delays and loss of kinetochore oscillation at metaphase (Abad et al., 2014; Schmidt et al., 2012). These data suggest that multiple weak interactions promote binding between microtubules and the C terminus of Ska1.

The Ndc80 complex is a stable kinetochore protein complex that directly binds microtubules. The Aurora B kinase phosphorylates N terminal tail of Ndc80 and regulates microtubule attachments to kinetochores. Dephosphorylation of Ndc80 tail stabilizes microtubule attachments. Recent study shows that Ndc80 directly recruits Ska complex and orients it correctly on microtubules to couple microtubule depolymerization with chromosome movement (Janczyk et al., 2017). Another corroborating study shows that Ska complex is required for microtubule stabilization following Ndc80 tail dephosphorylation in C.*elegans* (Cheerambathur et al., 2017).

To move chromosomes, the Ska complex has to bridge kinetochores to depolymerizing microtubules. In the future, it will be interesting to analyze how exactly the Ska complex maintains interactions with microtubules during chromosome congression. Mitotic kinases such as Aurora B, BubR1 and Cdk1 regulate microtubule binding to kinetochores and further work will help comprehend if the kinases contribute to Ska interaction with microtubules directly.

The C terminus of Ska1 was also shown to directly bind and recruit the protein phosphatase PP1 to kinetochores (Sivakumar et al., 2016). In Ska depleted cells, after metaphase-like chromosome alignment some chromosomes escape from the alignment and subsequently realign (Gaitanos et al., 2009; Hanisch et al., 2006; Sivakumar et al., 2014). The chromosome that escapes the alignment could have suddenly lost attachment to microtubules due to increased Aurora B activity, which is a result of reduced PP1 recruitment. We propose that this could be the cause of the “escaper” phenomenon.

It has not been possible to identify a Ska1 mutant that bound microtubules but abolished PP1 binding or vice versa. In other words, point mutants in the Ska1 CTD that disrupt microtubule binding also inhibited PP1 binding (Sivakumar et al., 2016). It is possible for PP1 binding to be downstream of microtubule binding and future work will have to determine how the same domain can perform two functions to promote anaphase onset.

Metaphase-anaphase transition

Extensive work has been done to understand the role of the Ska complex in microtubule binding and regulation of this interaction by Aurora B kinase. An additional phenotype observed after Ska depletion is delay at metaphase without

anaphase onset or mitotic exit. Two studies suggest that the Ska complex is required for accumulating Anaphase promoting Complex/Cyclosome (APC/C) on chromosomes (Ohta et al., 2010; Sivakumar et al., 2014). It was proposed that Ska complex in the presence of stable microtubule attachments localizes dephosphorylated APC/C to chromosomes so that it can potentiate rapid degradation of Cyclin B1 and Securin for irreversible anaphase onset (Figure 2) (Sivakumar et al., 2014). Another study also suggested that Ska complex recruits PP1 to dephosphorylate mitotic substrates, reduce Bub1 at kinetochores and inactivate spindle checkpoint signaling to promote anaphase onset (Figure 2) (Daum et al., 2009; Sivakumar et al., 2016). Is it possible for Ska complex recruited PP1 to dephosphorylate APC/C and cause anaphase onset? Or are these two roles of the Ska complex independent of each other? It is possible for these two roles to be two parallel yet redundant pathways that promote anaphase onset. Future work will help us understand this better.

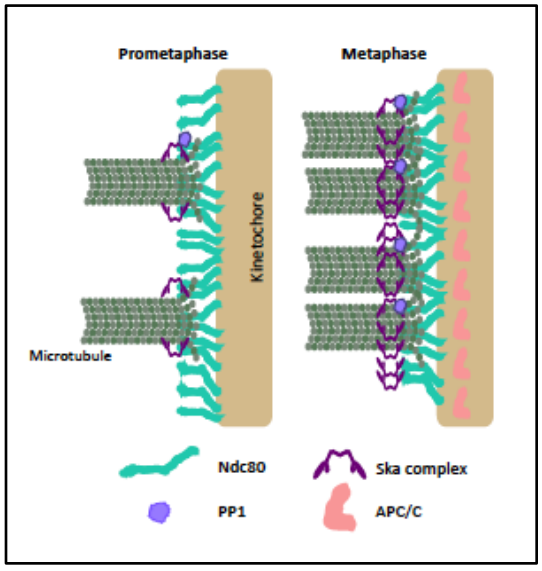

Figure 1: Model for Ska complex function during mitosis. In prometaphase, microtubule attachments are unstable, Ska and PP1 at kinetochores are decreased and APC/C association with chromosomes is inefficient. At metaphase, stable microtubule attachments are made and Ska association with kinetochores increases to maximum levels. Ska recruits PP1 to kinetochores and APC/C to chromosomes thereby promoting rapid anaphase onset.

The Ska complex also promotes Aurora B activity *in vitro* and *in vivo* (Redli et al., 2016). Phosphorylation of kinetochore substrates (Hec1-pS44, KNL1-pS24, Dsn1-pS100, H3-pS10, H3-pS28) was decreased in Ska depleted cells (Redli et al., 2016) suggesting that Ska promotes Aurora B activity to phosphorylate these substrates. The authors suggest that Ska complex regulates microtubule dynamics through Aurora B. Thus, Ska promotes Aurora B activity in early mitosis to limit its own accumulation on kinetochores until stable microtubule attachments are made. This ensures that kinetochore-microtubule dynamics and stability fall within an optimum range for chromosome bi-orientation to occur (Redli et al., 2016).

The Ska complex along with Ndc80 has been proposed to bind and stabilize microtubule attachments to kinetochores. How exactly it does this is not well understood. The Ska complex is a W shaped dimer of coiled coils that is proposed to extend and cover multiple microtubule attachment sites at kinetochores. An early model proposed that Ska physically couples unoccupied microtubule binding sites at a kinetochore with adjacent occupied microtubule binding sites to ensure microtubule attachment status at kinetochore is integrated with spindle checkpoint inactivation (Daum et al., 2009). Another model suggests that Ska complex binds clusters of Ndc80 complexes to stabilize microtubule attachments and hold onto chromosomes as they congress on the mitotic spindle (Janczyk et al., 2017). Yet another study suggests that Ska complex stabilizes microtubules by laterally

crosslinking lattice of individual microtubules at the kinetochore-microtubule interface (Redli et al., 2016). More work is required to tease apart this mechanism and fully comprehend how Ska complex binds and stabilizes microtubule attachments.

Conclusion

The Spindle and kinetochore associated complex was discovered in 2009 to be a novel protein complex that localizes to spindle microtubules and kinetochores during mitosis. Loss of the Ska proteins caused severe mitotic defects and mitotic arrest. Multiple studies over the last few years have elucidated role of this complex in microtubule binding, kinetochore microtubule dynamics and spindle checkpoint signaling. Future work will help elucidate the kinases and phosphatases that regulate this complex and how the complex integrates its many functions to promote proper mitotic progression.

A 2016 study showed that knockdown of Ska proteins in Colorectal cancer cells reduced cell growth and increased apoptosis (Chuang et al., 2016). These results are similar to what is observed with HeLa cells and suggests that development of inhibitors against Ska proteins will be useful in cancer chemotherapy.

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