Austin Medical Sciences

Open Access

Austin Publishing Group

Review Article

Functional Analysis of SKA Complex and its Family Members

Bastible ST, Golden T and Ning Wu*
Department of Biological Sciences, Southeastern Oklahoma State University, USA

***Corresponding author:** Ning Wu, Department of Biological Sciences, Southeastern Oklahoma State University, Durant, Oklahoma 74701, USA

Received: July 06, 2016; **Accepted:** August 11, 2016; **Published:** August 17, 2016

Abstract

The Spindle- and Kinetochore-Associated (SKA) complex, comprised of subunits SKA1, SKA2, and SKA3, serves an essential role in cell division through the stabilization of interactions between the kinetochore and microtubules and the timely onset of anaphase. Additionally, the SKA complex has also been implicated in the disease pathways of cancer and psychiatric disorders through mechanisms of genetic and epigenetic modulation complex subunit expression. This review focused on the structure and functions of SKA complex and each individual SKA family member to investigate the specific functions of each SKA family member and the potential abnormalities caused by the changes of expression levels of SKA family genes.

Keywords: SKA complex; Spindle microtubules; Kinetochores; Cell division; Anaphase

Introduction

Human cell mitosis is a critical process for normal cell differentiation and is involved in the relocation of duplicated chromosomes into two newly forming daughter cells. Any mistake during this process can lead to cellular functional abnormalities, and therefore, can lead to diseases and even cancers. Previous studies demonstrated that the mitosis of human cells required a group of proteins called the Spindle- and Kinetochore-Associated (SKA) complex to separate and translocate duplicated chromosomes into daughter cells [1,2]. Movement of chromosomes, both their alignment at the metaphase plate and their subsequent separation and regression towards the poles of the cell, is a force-exerting process on Kinetochores (KT), as spindle Microtubules (MT) lengthen and shorten. The way in which KTs remain attached to the + -ends of the polymerizing MTs, despite the forces exerted on them, is through the actions of the SKA complexes, which act with other factors together to power the movement of chromosomes, utilizing energy obtained from depolymerizing MTs [3,4]. The SKA complex is known to be an essential component of mitotic cell division, required for the timely onset of anaphase. Recruitment of the SKA complex to the KT is mediated by the internal loop region of the Ndc80 complex, a large protein machine that accurately segregates chromosomes during cell division, which lies at the heart of the kinetochore, in addition to the conserved KNL-1/Mis12 complex/Ndc80 complex (KMN) network, which is essential for kinetochore-microtubule interactions *in vivo*, as well as Hec1of Ndc80/HEC1 complex [5,6]. Timely anaphase onset is achieved through promoting the proper segregation of chromosomes by stabilizing interactions between the KT and MTs, in addition to the silencing of the mitotic spindle checkpoint [2,7].

SKA Complex Structure and Function

The SKA complex shares many commonalities with the Dam1/DASH complex, a yeast component that can couple the force generated by microtubule depolymerisation to direct chromosome movement *in vivo*, and is composed of two helical SKA1-SKA2 heterodimers, each coiled around a single arm of the helical SKA3 homodimer; creating a W-shaped complex of coiled coils [8]. The MT binding sequence is comprised of residues 132-255, which make up the C-terminal domains of SKA1 and SKA3, protruding at each end of the homodimer and which are a variation of the winged-helix domain [3,8,9]. Additionally, four Aurora B phosphorylation sites are responsible for down regulating the SKA complex's association with the KT through the reduction of SKA1 MT binding activity [9,10]. RNAi knockdown of SKA subunits produces dysfunctional MT attachment slows chromosomal alignment during metaphase, and delays silencing of the Spindle Alignment Checkpoint (SAC) [11-15]. The internal loop region of the Ndc80 complex may also induce aneuploidy and tumorigenesis through sequestration of Ndc80 binding associates such as the SKA complex, among others, when Ndc80 is overproduced through misregulation [16]. In studies of meiosis in mouse oocytes, SKA complex subunit depletion resulted in dysfunction of spindle movement and polar body enlargement, while depletion of the entire complex resulted in instability at the anaphase spindle and extrusion of the first polar body [7,9].

SKA1 Function in Normal and Abnormal Expression

After initial isolation through proteome analysis at the mitotic spindle [17], SKA1 was shown to facilitate spindle dynamics. The SKA complex must track the depolymerizing ends of the MT and does so through the action of SKA1, which in addition to directing Kinesin Heavy Chain Member 2A (Kif2a) to the minus-end of the MT to facilitate spindle dynamics, also assists the Ndc80 complex in doing the same, as the Ndc80 complex does not track depolymerizing MT ends on its own [9,18]. During the course of chromosomal segregation, it is important that the KT maintain stable attachment to MTs, in both their straight configurations, during polymerization, as well as their curved configurations, during depolymerization; after direction from DDA3, a MT-associated protein, the SKA complex provides stabilization for these dynamic configurations through the

Wu et al. © All rights reserved

Citation: Bastible ST, Golden T and Wu N. Functional Analysis of SKA Complex and its Family Members. Austin Med Sci. 2016; 1(2): 1007.

action of the complex's C-terminal winged-helix domain, specifically, at the multiple MT contact sites of SKA1 [18,19]. The onset of anaphase is promoted by the C-terminal domain of SKA1, through the enlistment of Protein Phosphatase 1 (PP1), which acts in opposition of the spindle checkpoint signaling kinases [1]. In contrast to the SKA complex's larger role in mitosis, studies of meiosis in mouse oocytes demonstrate that the complex is only localized on spindle MT from the prophase stage to meiosis I to meiosis II, rather than localizing to the KT from prometaphase to mid-anaphase, as is the case in mitosis [7]. As the SKA complex is an essential component in cell division, consequently, the complex also has been associated with various cancers. Overexpression of SKA1 is known to promote tumorigenesis of the prostate, play an important role in the development of oral adenosquamous carcinoma, and demonstrate utility in the prediction of poor prognosis in papillary thyroid carcinoma [20-22].

SKA2 Function in Normal and Abnormal Expression

In vivo, SKA2 is stabilized through interaction with SKA1, with RNAi silencing experiments of either subunit resulting in the absence of either protein at the KT [14]. It is theorized that stress may be responsible for the activation of behaviorally destructive pathways involving SKA2, among others, with cellular apoptosis serving as the inductive event [23]. As stress is acquired from traumatic events, abnormalities result within the Hypothalamic Pituitary Adrenal (HPA) axis, thereby placing individuals at increased risk for Post-Traumatic Stress Disorder (PTSD), as well as suicidal behaviors. An epigenetic factor involved in this mechanism is the DNA-methylation of SKA2 3'-Untranslated Repeat (UTR), which is reported to hold a predictive validity for suicidal behavior of approximately 80% and suggests the role of SKA2 as a mediator of suicidal behavior through stress-induced epigenetic variation, which in turn contributes to dysregulation of the HPA axis [24]. A significantly reduced expression of SKA2 has been observed in the prefrontal cortex of suicide victims, including those who had been suffering from depression, schizophrenia, substance abuse, and/or conduct disorders; a finding which suggests that the association between the reduction of SKA2 expression and the completion of suicide is not specific to any underlying psychological condition [25]. Increased levels of SKA2 methylation have been identified in the postmortem brain tissue samples taken from suicide decedents and in the blood samples taken from patients with suicidal ideations [26]. Additionally, increased SKA2 methylation has been associated with lower cortisol stress reactivity, with decreases in SKA2 methylation over time being associated with onset of PTSD symptoms, while traumatic stress exposure resulted in gradual increases in SKA2 methylation over time [27]. In addition to the association of increased SKA2 methylation with suicidal behaviors and lower cortisol stress reactivity, such increases in SKA2 methylation have been shown to yield reductions in cortical thickness in the following regions of the brain: frontal pole, superior frontal gyrus, right orbitofrontal cortex, and right inferior frontal gyrus [28]. Along with the decreases in thickness identified in these regions of the brain, negatively correlated with SKA2 methylation, a positive correlation was observed between severity of PTSD symptoms and SKA2 methylation [28].

SKA3 Function in Normal and Abnormal Expression

SKA3, formerly C13orf3 or RAMA1, is a necessary component of cell division through maintaining centrosome integrity and in silencing the spindle checkpoint [13,29,30]. SKA3 is essential for full cooperative MT binding behavior in the SKA complex, as SKA1-SKA2, alone; do not display this behavior [15]. With regard to depletion of individual components of the SKA complex, SKA3 depletion in mitotic cells has been shown to result in the arrest of cell division at metaphase [2]. Silencing of SKA3 *via* RNAi results in metaphase alignment without spindle checkpoint silencing or anaphase entry [11]. In addition to the consequences of SKA gene product depletion, structural abnormalities are also detrimental to dividing cells, as is the case with mutations affecting the coiled central coil or the dimerization of SKA1 and SKA3; both of which result in the failure of chromosomal congression and eventually lead to cell death [8]. Additionally, SKA3 is known to harbor Single Nucleotide Polymorphisms (SNPs) associated with aggressive tumorigenesis in prostate cancer patients .

Conclusion

The site of the KT in cell division remains an important subject of research,with discoveries elucidating not only the understanding of how chromosomes align and divide during cell division, but also the ways in which genetic and epigenetic forces undermine normal physiological function and contribute to the development of disease. Specifically, the SKA complex remains an important area of study, with much more research to be done in order to fully understand the mechanisms at work in the complex's association with the KT, MTs, and various other active protein complexes. With regard to SKA2, the medical potential of the locus is enormous in its potential to change the way in which stress-related mental illnesses are understood, diagnosed, and ultimately treated.

Acknowledgement

This work is supported by Southeastern Faculty Research Grant (A-6-0502-1612-005).

Reference

1. Sivakumar S, Janczyk PL, Qu Q, Brautigam CA, Stukenberg PT, Yu H, et al. The human ska complex drives the metaphase-anaphase cell cycle transition by recruiting protein phosphatase 1 to kinetochores. Elife. 2016; 5.

2. Sivakumar S, Daum JR, Tipton AR, Rankin S, Gorbsky GJ. The spindle and kinetochore-associated (ska) complex enhances binding of the anaphase-promoting complex/cyclosome (apc/c) to chromosomes and promotes mitotic exit. Mol Biol Cell. 2014; 25: 594-605.

3. Boeszoermenyi A, Schmidt JC, Cheeseman IM, Oberer M, Wagner G, Arthanari H. Resonance assignments of the microtubulebindingdomain of the C. Elegans spindle and kinetochore-associated protein1. Biomol NMR Assign. 2014; 8: 275-278.

4. Joglekar AP, Bloom KS, Salmon E. Mechanisms of force generation by end-on kinetochore-microtubule attachments. Current opinion in cell biology. 2010; 22: 57-67.

5. Zhang G, Kelstrup CD, Hu XW, Kaas Hansen MJ, Singleton MR, Olsen JV, et al. The ndc80 internal loop is required for recruitment of the ska complex to establish end-on microtubule attachment to kinetochores. J Cell Sci. 2012; 125: 3243-3253.

6. Chan YW, Jeyaprakash AA, Nigg EA, Santamaria A. Aurorab controls

kinetochore-microtubule attachments by inhibiting ska complex-kmn network interaction. J Cell Biol. 2012; 196: 563-571.

7. Zhang QH, Qi ST, Wang ZB, Yang CR, Wei YC, Chen L, et al. Localization and function of the ska complex during mouse oocyte meiotic maturation. Cell Cycle. 2012; 11: 909-916.

8. Jeyaprakash AA, Santamaria A, Jayachandran U, Chan YW, Benda C, Nigg EA, et al. Structural and functional organization of the ska complex, a key component of the kinetochore-microtubule interface. Mol Cell. 2012; 46: 274-286.

9. Schmidt JC, Arthanari H, Boeszoermenyi A, Dashkevich NM, Wilson-Kubalek EM, Monnier N, et al. The kinetochore-bound ska1 complex tracks depolymerizing microtubules and binds to curved protofilaments. Dev Cell. 2012; 23: 968-980.

10. Daum JR, Wren JD, Daniel JJ, Sivakumar S, McAvoy JN, Potapova TA, et al. Ska3 is required for spindle check point silencing and the maintenance of chromosome cohesion in mitosis. Current Biology. 2009; 19: 1467-1472.

11. Gaitanos TN, Santamaria A, Jeyaprakash AA, Wang B, Conti E, Nigg EA. Stable kinetochore{microtubule interactions dependon the ska complex and its new component ska3/c13orf3. The EMBOjournal. 2009; 28: 1442-1452.

12. Raaijmakers JA, Tanenbaum ME, Maia AF, Medema RH. Rama1 is a novel kinetochore protein involved in kinetochore microtubule attachment. J Cell Sci. 2009; 122: 2436-2445.

13. Hanisch A, Sillje HH, Nigg EA. Timely anaphase onset requires a novel spindle and kinetochore complex comprising ska1 and ska2. The EMBO Journal. 2006; 25: 5504-5515.

14. Welburn JP, Grishchuk EL, Backer CB, Wilson-Kubalek EM, Yates JR, Cheeseman IM. The human kinetochore ska1 complex facilitates microtubule depolymerization-coupled motility. Developmental cell. 2009; 16: 374-385.

15. Tang NH, Toda T. Mapping the ndc80 loop in cancer: A possible link between ndc80/hec1 overproduction and cancer formation. Bioessays. 2015; 37: 248-256.

16. Sauer G, Korner R, Hanisch A, Ries A, Nigg EA, Sillje HH. Proteome analysis of the human mitotic spindle. Molecular & cellular proteomics. 2005; 4: 35-43.

17. Park JE, Song H, Kwon HJ, Jang CY. Ska1 cooperates with dda3 for spindle dynamics and spindle attachment to kinetochore. Biochem Biophys Res Commun. 2016; 470: 586-592.

18. Abad MA, Medina B, Santamaria A, Zou J, Plasberg-Hill C, Madhumalar A, et al. Structural basis for microtubule recognition by the human kinetochore ska complex. Nat Commun. 2014; 5: 2964.

19. Dong C, Wang X, Ma B. Expression of spindle and kinetochore-associated protein 1 is associated with poor prognosis in papillary thyroid carcinoma. Dis Markers. 2015; 2015: 616541.

20. Li J, Xuan JW, Khatamianfar V, Valiyeva F, Moussa M, Sadek A, et al. Ska1 over expression promotes centriole over-duplication, centrosome amplification and prostate tumourigenesis. J Pathol. 2014; 234: 178-189.

21. Zhang B, Li KY, Chen HY, Pan SD, Jiang LC, Wu YP, et al. Spindle and kinetochore associated complex subunit 1regulates the proliferation of oral adenosquamous carcinoma cal-27 cellsin vitro. Cancer Cell Int. 2013; 13: 83.

22. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, et al. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. Mol Psychiatry. 2015; 20: 1266-1285.

23. Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T, et al. Epigenetic and genetic variation at ska2 predict suicidal behavior and post-traumatic stress disorder. Transl Psychiatry. 2015; 5: e627.

24. Pandey GN, Rizavi HS, Zhang H, Bhaumik R, Ren X. The expression of the suicide-associated gene ska2 is decreased in the prefrontal cortex of suicide victims but not of nonsuicidal patients. Int J Neuropsychopharmacol. 2016.

25. Guintivano J, Brown T, Newcomer A, Jones M, Cox O, Maher BS, et al. Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. Am J Psychiatry. 2014; 171: 1287-1296.

26. Boks MP, Rutten BPF, Geuze E, Houtepen LC, Vermetten E, Kaminsky Z, et al. Ska2 methylation is involved in cortisol stress reactivity and predicts the development of Post-Traumatic Stress Disorder (PTSD) after military deployment. Neuropsychopharmacology. 2016; 41: 1350-1356.

27. Sadeh N, Spielberg JM, Logue MW, Wolf EJ, Smith AK, Lusk J, et al. Ska2 methylation is associated with decreased prefrontal cortical thickness and greater PTSD severity among trauma exposed veterans. Mol Psychiatry. 2016; 21: 357-363.

28. Ohta S, Bukowski-Wills JC, Sanchez-Pulido L, de Lima Alves F, Wood L, Chen ZA, et al. The protein composition of mitotic chromosomes determined using multiclassifier combinatorial proteomics. Cell. 2010; 142: 810-821.

29. Theis M, Slabicki M, Junqueira M, Paszkowski-Rogacz M, Sontheimer J, Kittler R, et al. Comparative profiling identifies c13orf3 as a component of the ska complex required for mammalian cell division. The EMBO Journal. 2009; 28: 1453-1465.

30. Lee M, Williams KA, Hu Y, Andreas J, Patel SJ, Zhang S, et al. Gnl3 and ska3 are novel prostate cancer metastasis susceptibility genes. Clin Exp Metastasis. 2015; 32: 769-782.

Austin Med Sci - Volume 1 Issue 2 - 2016
Submit your Manuscript | www.austinpublishinggroup.com
Wu et al. © All rights reserved

Citation: Bastible ST, Golden T and Wu N. Functional Analysis of SKA Complex and its Family Members. Austin Med Sci. 2016; 1(2): 1007.