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The effects of mutations on pericentromeric localization of shugoshin

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Abstract

Elucidating the effects of mutations on protein-protein interactions can be useful for detecting damaged biological functions like chromosome segregations, because cellular structure and functions are mainly built on concerted interactions of proteins. Shugoshin (Sgo1) is one of those proteins that has many roles in correct chromosome segregation during mitosis and meiosis. One of the important aspects about Sgo1, to function properly, is the fact that it has to be on the chromosomal region surrounding the centromere (the pericentromere). However, some mutations can directly or indirectly affect the localization of Sgo1 and result in chromosomal instability which is known as the occasional gain/loss of chromosomes resulting in aneuploidy, cancer and other diseases. Therefore, this review focuses on the mutations that affect the pericentromeric localization of Sgo1.

Keywords: *Shugoshin, pericentromere, mutation, chromosomal instability, aneuploidy.*

Mutasyonların şugoşinin perisentromerik lokalizasyonu üzerindeki etkileri

Öz

Mutasyonların protein-protein etkileşimleri üzerindeki etkilerinin aydınlatılması, kromozom segregasyonları gibi biyolojik fonksiyonlardaki hasarların tespiti için faydalı olabilir, çünkü hücresel yapı ve fonksiyonlar esas olarak proteinlerin uyumlu etkileşimleri üzerine kuruludur. Shugoshin (Sgo1), mitoz ve mayoz bölünme sırasında doğru kromozom ayrımında birçok rolü olan proteinlerden biridir. Sgo1'in düzgün çalışması için gerekli olan faktörlerden biri, bu proteinin sentromeri çevreleyen

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(perisentromer) kromozomal bölgede bulunması gerekliliğidir. Bununla birlikte, bazı mutasyonlar Sgo1'in lokalizasyonunu doğrudan veya dolaylı olarak etkileyebilir ve anöploidi, kanser ve diğer hastalıklarla sonuçlanabilen kromozom kazanımı/kaybı olarak bilinen kromozomal kararsızlığa neden olabilir. Bu nedenle, bu makale Sgo1'in perisentromerik lokalizasyonunu etkileyen mutasyonlara odaklanmaktadır.

Anahtar kelimeler: *Şugoşin, perisentromer, mutasyon, kromozomal instabilite, anöploidi*

1. Introduction

Cellular structure and function are mainly built on protein-protein interactions and investigations of the protein interactions can be useful to find out damaged biological functions for therapeutic purposes [1]. Mutations of a single gene can lead to multiple different diseases because proteins can have several functions in different cellular events. Therefore, the impact of a disease related mutation may affect all of the protein activities in a functional biological pathway [2]. The chromosome segregation events are also the result of concerted actions of many proteins and their functions are not only determined by their own biochemical properties but also depend on those of other molecules that contribute to the biological process [3]. Mutations in any of the regulatory mechanisms of chromosome segregation can lead to reproduction of cells with genetic mutations or abnormal chromosome numbers which result in genomic instability and diseases [4].

Shugoshin (Sgo1 in *Saccharomyces cerevisiae*, Sgo1 in *Schizosaccharomyces pombe*, Sgo1 and Sgo2 in *Arabidopsis thaliana*, Sgo1 in *Oryza sativa*, Sgo1 in *Zea mays*, Mei-S332 in *Drosophila melanogaster*, Sgo2 in *Mus musculus*, Sgo1 and Sgo2 in *Homo sapiens*) is an important protein that has many roles in correct chromosome segregation during both mitosis and meiosis [5]. It is present in all of the eukaryotic species and its role in protection of centromeric cohesin is conserved among different eukaryotic species [6].

The role of shugoshins in cohesion enables the chromosomal stability during nuclear divisions [7]. However, some mutations in *SGO1* can result in disruption of this stability and lead to chromosomal instability which is known as the occasional gain/loss of whole chromosomes resulting in aneuploidy [8]. Chromosomal instability is the main reason of karyotypic instability and observed in many cancer types [9]. According to the previous findings, *SGO1* downregulation/knockdown related chromosomal instabilities were observed in colorectal/colon cancers and non-functional Sgo1 led to aneuploidy, micronuclei and aberrant chromosome segregations [10-12]. In addition, it was shown that a tumor specific variant of *SGO1* (variant *B*) caused resistance to anticancer drug taxane in nonsmall cell lung cancers [10, 13]. A frameshift mutation of Sgo1 (*SGO1-P1*) which results in the shortening of *SGO1* sequence to 177 base pairs was also responsible for the chromosomal instabilities in colon cancer [10, 14].

Cancers are not the only clinical conditions related to mutations of Sgo1 and subsequent chromosomal instabilities. For example, a genetic disorder called Perrault syndrome is known to be resulted from the mutations of *SGO2* (frameshift, p.Glu485Lysfs *5) and *CLDN14* causing ovarian dysfunction in females and sensorineural hearing loss in males

and females [6, 15, 16]. Chromosomal instabilities are also reported in the normal and pathogenic aging of the human brain [17-22]. The studies showed that Sgo1 is involved in neurological disorders such as late-onset Alzheimer's disease characterized by high rates of chromosomal instability [6, 22].

One of the important aspects about Sgo1, to function properly, is the fact that it has to be on the chromosomal region surrounding the centromere (the pericentromere) [5, 23, 24]. The centromeres have critical roles in equal distribution of the genome between daughter cells during cell division with the help of biorientation process performed by kinetochores and an error in kinetochore assembly can lead to aneuploid cells that contain abnormal number of chromosomes [25]. Therefore, this review focuses on the mutations that affect the pericentromeric localization of Sgo1.

1.1 Importance of pericentromeric localization of sgo1

The reason that chromosomes do not separate randomly and aneuploidy doesn't occur is because of the resistance created by cohesins around sister chromatids against the force created by mitotic spindles [26]. Cohesins bind to the chromosomes of budding yeast at the end of G1 phase but they hold sister chromatids only after the replication of sister chromatids at S phase [27, 28]. In the pericentromere high amounts of cohesin and another protein called condensin, which gives a compact rod shape of the chromosomes, are found and their presence is very important for protection of pericentromeric chromatin structure which is exposed to the highest level of tension created by mitotic spindles. Pericentromere stays resistant against spindle forces by the help of condensin and cohesins by keeping the pericentromeric chromatin compact in correct direction with spindles and preventing it to spread in wrong directions [26, 29-33]. In all eukaryotes, before the anaphase starts, the chromosomes meet on the central metaphase plate, which is equidistant from both poles. In order to do this, microtubules from opposite poles must be attached to the kinetochore protein in the centromere [34]. The correct binding of microtubules to the kinetochores depends on both the structural feature of the chromosome (provided by the cohesin and condensin) and the resulting tension [26]. If sufficient tension is not provided, the link between microtubule and kinetochore is destabilized and another chance is given to ensure correct attachment. The proteins involved in this error correction pathway are Sgo1 and Aurora B kinase (Ipl1), a member of the chromosomal passenger complex (CPC). If a tensionless connection has occurred, Sgo1 ensures that Ipl1 remains in the centromere, while Ipl1 breaks the connection with the microtubule by phosphorylating many substrates in the outer kinetochore [23, 35]. In order to perform those functions, Sgo1 is known to be localized to the pericentromere and cohesin (with other factors required for cohesin loading) is required for the proper association of Sgo1 with the pericentromere [23, 24].

1.2 Effects of mutations on pericentromeric localization of sgo1

Sgo1 has important regions with specific functions. Firstly, it has a coiled coil domain close to N terminal (between 40^{th} and 84^{th} amino acids) responsible for binding of another adaptor protein called PP21A- Rts1 [24, 36-40]. Secondly, it has a basic region (between 366^{th} and 390^{th} amino acids) close to C terminal where it binds to histone H2A (phosphorylated on serine 121 by a protein kinase called Bub1) in order to be localized on the centromeric chromatin [5, 41]. Thirdly, there is a region called destruction box (between 494^{th} and 498^{th} amino acids) where Sgo1 binds to the anaphase promoting complex/ cyclosome (APC/C) to be degraded at the end of anaphase [5, 36]. In order to determine the effects on pericentromeric localization of Sgo1, some mutations were

analyzed previously [23, 37, 39, 42, 43]. For example, it was shown that an allele called *sgo1-700* having two point mutations ("Pro^{390} to His (P390H)" and "Asp^{519} to Asn (D519N)" together) caused a weak localization of Sgo1 on centromere and damaged interaction with condensin and Aurora B [23, 43]. Another study also investigated the effects of some mutations on localization of Sgo1 with *sgo1-100* (Sgo1-T379I), *sgo1-700* (Sgo1-P390H-D519N) and *sgo1-3A* (*sgo1-Y47A;Q50A;S52A*) strains [23]. The researchers showed that in budding yeast, *sgo1-3A* didn't cause Sgo1 delocalization but *sgo1-100* and *sgo1-700* did [23]. One of the possible explanations of these results is the fact that the D519N mutation (which is close to the destruction box) might have caused a damage in tension sensing capacity of Sgo1 which could result in abnormal cell cycle behavior. It is known that the duration of mitosis is determined by the APC/C complex which is bound to its activator Cdc20 and if there is a problem in kinetochore-microtubule interaction, the APC/C is inhibited to block mitotic exit [44]. In fact, it is known that the cells with high chromosomal imbalances like cancer cells can also decrease the APC/C activities in order to use this as a strategy for tumor development [45]. Moreover, Pro^{390} residue is in the C- terminal region of Sgo1 which is in a site of H2A-S121 phosphorylation known to be an essential event for centromeric recruitment of Sgo1, so this could be the reason of the Sgo1 delocalization in strains with P390H mutation. In another study with *Drosophila*, "Asn^{61} to Ile (N61I)" mutation on MEI-S332 caused a loss in centromeric localization of shugoshin in addition to the defect on interaction between PP2A and shugoshin [39]. Peplowska et al. compared the intensities of GFP signals observed by fluorescent microscope with wild type strains in order to determine the effects of "Asn^{51} to Ile (Sgo1-N51I)" mutation on Sgo1- Rts1 interactions and they found that Sgo1-N51I-GFP signal had the same intensity with wild type Sgo1-GFP while the Rts1 GFP intensity in cells with Sgo1-N51I mutation was significantly weaker than the wild type and they concluded that the mutation they studied didn't affect localization of Sgo1 at centromere but gave damage to its interaction with Rts1 [37]. The latest work with *S. cerevisiae* also showed that deletion of the sequence between 137^{th} and 163^{rd} aminoacids significantly reduced the interaction of Sgo1 with condensin subunits by impairing the localization of condensin to the centromeres and it was a serine rich motif ($Sgo1^{137}$LKRTSSRSRSCSLSSPTYSKSYTRLSN^{163}) [42]. Although deletion of the sequence between 137^{th} and 163^{rd} aminoacids significantly reduced the interaction of Sgo1 with condensin subunits, it didn't affect the localization of Sgo1 [42]. However, it was clearly seen that the Sgo1 mutations that couldn't recruit condensin to the centromeres caused disrupted sister chromatid biorientation and segregation, too [42].

1.3 Other modifications affecting pericentromeric localization of sgo1

Histones (H2A, H2B, H3, H4 and a linker histone H1) are the proteins that wrap the DNA helix to create chromatin structure [46]. Histone proteins are subject to various posttranslational modifications (like phosphorylation, acetylation, methylation, ubiquitination, ADP-ribosylation, SUMOylation etc.) and these modifications have important functions in cellular processes like regulation of gene expression/chromatin structure, DNA damage response and chromosome segregation [47]. Various residues in the histone tails can be the targets of post translational modifications. For example, the ε-amino groups of lysine residues at the N-termini are known as the sites of histone acetylations while the the side chains of lysines and arginines can be the targets of methylations [48]. Moreover, serine, threonine and tyrosine residues of histones are often exposed to phosphorylations which are known to give negative charges to the

histones resulting in open chromatin conformations that can dramatically affect gene expression, DNA damage repair and chromatin remodelling mechanisms [48].

Sgo1 localization at centromeres is known to depend on the phosphorylation of H2A by Bub1 [41]. Therefore, researchers questioned different histone modifications with a potential to affect pericentromeric localization of Sgo1 and found that the malonylation as a post translational modification of Lys^{119} (K119) prevented the phosphorylation of S121 which in turn caused Sgo1 delocalization both in *S. cerevisiae* and *S. pombe* [49]. It is suggested that non-functional malonyl-CoA decarboxylase may prevent malonyl-CoA to be broken down into acetyl-CoA and carbon dioxide so the resulting accumulation of cellular malonyl-CoA may cause excess histone malonylations [49].

The mutations in chromatin remodelers may also indirectly affect the Sgo1 localization at centromeres. The chromatin remodelers are the group of enzymes that can mediate posttranslational modifications on histones and change the connection between histones and DNA in the nucleosome by ATP hydrolysis [50]. Thus, they have important roles in transcription, chromatin compaction and accessibility, replication, histone variant deposition, DNA repair and chromatin maintenance [50]. Remodeling and spacing factor 1 (Rsf1) is a chromatin-remodeling factor that regulates Sgo1 localization at centromeres by maintaining a crosstalk of histone acetylation with phosphorylation [51, 52]. Rsf1 is known to enable deacetylation of H2A by counteracting TIP60-mediated acetylation and this leads to the phosphorylation of H2A by Bub1 which is a process needed for Sgo1 localization at centromere [52]. Therefore, damaged Rsf1 causes delocalization of Sgo1. It was also reported that overexpressions of Rsf1 cause cell cycle checkpoint inhibitions leading to cancer proliferation and survival [53]. It is showed that RSF1 is overexpressed in cholangiocarcinoma, head-neck squamous cell carcinoma, liver hepatocellular carcinoma and stomach adenocarcinoma tissues [53]. Deletions/mutations of chromatin remodelers are known to result in apoptosis or tumorigenesis because of the dysregulated cell cycle control [54]. In addition, oxidative stress is a well known inducer of the alterations in histone modifier enzymes. Reactive oxygen species can affect the enzymatic activities of the epigenetic regulators and change the nature of histone residues. In fact, reactive aldehydes are known to be formed in cysteines of class I histone deacetylases (HDAC1, HDAC2 and HDAC3) because of the free radicals [46]. In future, other potential post translational modifications and mutations in modifiers should be analyzed in detail to understand the molecular mechanisms of metabolic diseases and their relationship with chromosome segregations.

2. Conclusions

Sgo1, an important protein to prevent improper chromosomal segregation and aneuploidy, must be localized to the pericentromere in order to perform its functions [24], so the effector proteins should also be recruited to the pericentromere to help Sgo1. However, some mutations in the amino acid sequences may effect this recruitment process because they can modify protein interaction interfaces causing a gain or loss of protein-protein interactions [55], so these mutations can cause damages in protein networks responsible for chromosome segregation and correct segregation can be prevented. Dysregulation of correct segregation mechanisms can result in genomic instability which is a distinct characteristic of cancer and can be lethal [4]. Validation of

functional mechanisms of gene mutations and their effects on cellular mechanisms are the valuable sources for precision medicine because therapeutic strategies are determined by them [56]. Therefore, specific mutations affecting pericentromeric localization of Sgo1 were compiled in this paper.

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