Shugoshin

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Shugoshin (meaning "guardian spirit" in Japanese) is a homo-dimeric phospho-protein belonging to the shugoshin protein family. Shugoshin is conserved from single-celled yeast to multicellular mammals including humans. Shugoshin shares several structural features with other members of the shugoshin family, including a basic region at the C-terminus that is essential for centromere binding, chromosome localization, and an N-terminal coiled-coil domain that may regulate its dimerization and interaction with other proteins.

Keywords: shugoshin ; tumor suppressor ; cancer ; oncogene ; tumor-associated gene

1. Introduction

Proper cell division is a foremost requirement for reproduction as well as for the survival and continuity of every species. Mis-segregation of the genome during cell division leads to aneuploidy, which is closely associated with numerous medical consequences ranging from tumorigenesis to sterility, mental retardation, spontaneous abortion, and other birthrelated defects [1][2][3][4][5][6]. To ensure that the genetic blueprint is duplicated and distributed precisely during cell division, cells employ several mechanisms operating either independently or in coordination with one another. Proper and timely removal of cohesin is an example of one such mechanism. Cohesin, a multiprotein complex, holds sister chromatids together from DNA duplication in S-phase until the onset of anaphase. The premature or untimely loss of cohesion as a result of abrupt separase activity leads to chromosome mis-segregation. Hence, cohesin cleavage by separase is kept under tight cellular control [2][8]. Apart from its prime role of holding sister chromatids together, cohesin is also known for its involvement in diverse cellular processes discussed elsewhere [9]. A detailed account of cohesin and separase falls outside the scope of the present review, and these aspects are summarized elsewhere [8][10]. Apart from the timely cleavage of cohesin, several other mechanisms including DNA damage checkpoint (DDC), spindle assembly checkpoint (SAC), separase activation, and centriole duplication (and maybe more which remain unidentified) ensure that the genetic endowment of the cell or organism, i.e., its genome is duplicated and separated properly. A detailed discussion of all such mechanisms is difficult in the present review, may require a separate volume, and can be found elsewhere [8][11][12][13][14] [<u>15][16]</u>

2. Shugoshin Background

Shugoshin (meaning "guardian spirit" in Japanese) is a homo-dimeric phospho-protein belonging to the shugoshin protein family ^{[12][18]}. Shugoshin is conserved from single-celled yeast to multicellular mammals including humans. Shugoshin shares several structural features with other members of the shugoshin family, including a basic region at the C-terminus that is essential for centromere binding, chromosome localization, and an N-terminal coiled-coil domain that may regulate its dimerization and interaction with other proteins ^{[19][20][21][22]}. Initially, shugoshin was discovered in the fruit fly, D. melanogaster , as a peri-centromeric protein (at the time referred to as MEI-S332) required for the protection of Rec8 (meiotic-specific cohesin subunit) from separase action and its persistence during meiosis-I ^{[23][24][25]}. Later, a protein factor with a function equivalent to MEI-S332 was discovered in other eukaryotic species including yeast, insects, vertebrates, and plants ^{[26][27][28][29][30][31]}.

Based on the sequence (at the gene and protein levels) and structural analysis, it has been observed that all eukaryotic species studied to date possess either one or two genes coding for shugoshin (referred to as SGO1 and SGO2), although several splicing isoforms of shugoshin have been reported in higher eukaryotes ^[32]. **Table 1** shows the number of genes coding for shugoshin in different species. The reason why some species (for example, Saccharomyces cerevisiae) possess only one gene for shugoshin and others two (for example, fission yeast, humans) remains elusive. In human cells, a combined total of 10 splicing isoforms (for SGO1 and SGO2) have been identified (http://www.uniprot.org/uniprot/?query=hugoshin%2C+homo+sapiens&sort=score (accessed on 4 March 2021)). Information related to different isoforms of human SGO1 and SGO2, including the number of amino acid residues and

molecular mass, is given in **Table 2**. The size or number of amino acid residues in shugoshin and molecular mass vary significantly across different eukaryotic species ^[31] as well as among different isoforms within the same species (for example, Homo sapiens, **Table 2**). It is important to mention that different shugoshin paralogs are known to exhibit different properties depending on the species under consideration. The expression pattern or profile of shugoshin paralogs may be cell cycle-dependent (i.e., mitosis or meiosis). For example, in fission yeast SGO2 is expressed in both mitosis and meiosis while SGO1 is meiosis-specific ^[26]. Like fission yeast, mouse SGO2 is required for the completion of meiosis but not for mitosis, suggesting its cell cycle-specific expression ^[33].

Species	No. of Genes	Kingdom	References
Saccharomyces cerevisiae	1	Fungi	*
Schizosaccharomyces pombe	2	Fungi	*
Mus musculus	2	Animalia	Uniprot
Arabidopsis thialana	2	Plantae	Uniprot
[§] Homo sapiens	2	Animalia	Uniprot
Drosophila melanogaster	1	Animalia	Uniprot
Caenorhabditis elegence	1	Animalia	Uniprot
Oryza sativa	1	Plantae	Uniprot
Xenopus laevis	1	Animalia	Uniprot
Neurospora crassa	1	Fungi	Uniprot
Danio rerio	1	Animalia	Uniprot
Zea mays	1	Plantae	Uniprot
Rattus norvegicus	1	Animalia	Uniprot
Candida glabrata	1	Fungi	*
Kluyveromyces lactis	1	Fungi	*
Aphis gossypii	1	Fungi	*
Pristionchus pacificus	1	Animalia	Uniprot
Oryzias latipes	1	Animalia	Uniprot
Candida albicans	1	Fungi	*

Table 1. Number of genes coding for shugoshin in different species.

* <u>https://portals.broadinstitute.org/cgibin/regev/orthogroups/show_orthogroup.cgi?orf=YOR073W</u> (accessed on 8 August 2019). Uniprot (www.uniprot.org/uniprot (accessed on 8 August 2019)). [§] Total of ten isoforms have been reported in humans.

Table 2. Size and molecular mass of different isoforms of human SGO1 and SGO2.

Shugoshin	Isoform	Number of Amino Acid Residues	Mol. Mass (in kDa)	Identifier
* SG01	Isoform 1	561	64.19	Q5FBB7-1
	Isoform 2	309	35.344	Q5FBB7-2
	Isoform 3	292	33.501	Q5FBB7-3
	Isoform 4	275	31.276	Q5FBB7-4
	Isoform 5	258	29.433	Q5FBB7-5
	Isoform 6	527	60.122	Q5FBB7-6
	Isoform 7	215	24.646	Q5FBB7-7
[!] SGO2	Isoform 1	1265	144.739	Q562F6-1

Shugoshin	Isoform	Number of Amino Acid Residues	Mol. Mass (in kDa)	Identifier
	Isoform 2	1261	144.181	Q562F6-2
	Isoform 3	247	28.23	Q562F6-3

*https://www.uniprot.org/uniprot/Q5FBB7 (accessed on 4 March 2021). ! https://www.uniprot.org/uniprot/Q562F6

(accessed on 4 March 2021). Shugoshin is present in all the eukaryotic species studied to date, and shugoshin-based protection of centromeric cohesin is conserved across different eukaryotic species. However, the cells of C. elegans use a different strategy that is independent of shugoshin. Unlike other species, chromosome segregation in C. elegans relies on an alternative mechanism that involves LAB-1 (Long Arm of the Bivalent) ^[34]. This study in C. elegans raised the possibility of shugoshin-independent cohesin protection in other species. Why the cells of C. elegans use this alternative mechanism despite the presence of shugoshin remains an open question. Whether shugoshin-independent protection of centromeric cohesin is exclusive to worm species also remains a matter for future investigation.

3. Shugoshin as a Tumor-Associated Gene

A decreased level or complete absence of shugoshin has been observed in head and neck cancer ^[35], nasopharyngeal carcinoma ^[36], neuroblastoma ^[37], and prostate cancer ^{[38][39]}. Homozygous deletion of SGOL2 has been observed in different types of human tumors including head and neck cancer ^[40], small-cell lung carcinoma ^[41], cervical carcinoma ^[42], and neuroblastoma ^[43]. It is important to mention that deletion of either allele of shugoshin (i.e., SGOL1 or SGOL2 for shugoshin in humans) can lead to cancer. Among 46 colorectal cancer cases, hSgo1 mRNA expression was decreased in the tumor tissue compared with the corresponding normal tissue ^[44]. Heterozygous deletion of sgo1 +/- leads to systemic chromosome instability in mice ^[45] and the formation of aberrant crypt foci (ACF) in mice heterozygous for shugoshin-1 ^[46]. Treatment with the carcinogen azoxymethane (oxide of azomethane, a carcinogenic and neurotoxic chemical compound used in biological research) caused sgo1 +/- ME-CIN model mice to develop hepatocellular carcinoma (HCC) within 6 months; in contrast, control mice developed no HCC (p < 0.003) ^[47].

In the last section, we mentioned some of the studies where shugoshin behaved as a tumor suppressor gene. In this section, we will mention some of the studies which showed the oncogenic behavior of shugoshin. Upregulated expression of shugoshin was observed in 82% of hepatocellular carcinoma (HCC) cases and correlated with elevated alphafetoprotein and early disease onset of HCC, while depletion of shugoshin-1 reduced the cell viability of hepatoma cell lines including HuH7, HepG2, Hep3B, and HepaRG due to persistent activation of the spindle assembly checkpoint [48]. Increased expression and level of shugoshin were reported in human leukemia ^[49] and breast cancers ^{[50][51]}. Similarly, overexpression of SGOL1-B1 in a non-small-cell lung carcinoma (NSCLC) cell line induced aberrant chromosome missegregation, precociously separated chromatids, and delayed mitotic progression. A higher level of SGO1-B mRNA was related to taxane (diterpenes, compounds originally identified in the plant genus Taxus (yews), used in cancer chemotherapy, e.g., paclitaxel and docetaxel) resistance, while the forced downregulation of SGO1-B increased the sensitivity to taxane [52]. Expression of SGO1C (a non-functional isoform of shugoshin) alone induced aberrant mitosis similar to depletion of SGO1A, promoting premature sister chromatid separation, activation of the spindle assembly checkpoint, and mitotic arrest, suggesting that the expression of SGO1C is tightly regulated to prevent dominant-negative effects of SGO1A and genome instability [53]. In another clinical study, the expression of SGO1 in human prostate tumors was higher than that of adjacent normal tissues and was positively correlated with the poor prognosis of prostate cancer patients [54]. Some of the studies mentioned above clearly showed the oncogenic nature of shugoshin.

Not only complete loss of shugoshin but also an altered level of shugoshin can lead to cancer. Whether shugoshin's association with cancer is due to chromosome mis-segregation or due to derailment of other cellular pathways resulting from a complete absence or altered level of shugoshin remains a topic for future research. Because an altered shugoshin level is associated with various cancers, and chemicals (for example, BPA or Bisphenol A, used as a plasticizer in plastic industries) can potentially alter its expression, it is possible that increased incidences of tumors and associated altered shugoshin levels may be linked and require further research ^[55]. The identification of chemicals that can modulate the transcription of shugoshin and other tumor-associated genes can be an important field for future research.

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