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Review

Functional roles of Speckle-Type Poz (SPOP) Protein in Genomic stability

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Abstract

Understanding the functional significance of the essential elements in maintaining genomic stability provides insights into the process of tumor initiation and progression, and predicts therapeutic responses. One such element that has recently attracted significant attention is the Speckle-Type Poz Protein (SPOP), an E3 ubiquitin ligase adaptor protein. SPOP is frequently mutated or has altered expression in various cancers, including prostate, renal and endometrial. SPOP is involved in the regulation of proteasome-mediated degradation of several oncoproteins. Moreover, recent data also indicate SPOP's direct involvement in the DNA damage response. SPOP mutants induce alternations in the DNA damage repair pathway by promoting the error-prone Non-homologous end joining (NHEJ) pathway. SPOP has been linked with significant functions in cellular signaling pathways and cancer suppression. This mini-review will discuss recent findings regarding SPOP's role in genomic stability in the pathological setting.

Key words: SPOP, genomic stability, cancer, DNA damage response

Introduction

Cancer initiation and progression are propelled by the malfunctioning of critical cellular processes. These erroneous functions cause oncogenic phenotypes that can be classified into one of several categories, commonly referred to as the "Hallmarks of Cancer" (1). These hallmarks are driven by oncogenic mutations in genes that give rise to altered expression of the associated proteins, which are involved in the regulation of cellular functions. Mutations within the genome of a cellular lineage contribute to genome instability. Of these mutations in cancer, some are more universal; whereas others are unique to or are far more common in certain cancer subtypes.

Accumulating evidence indicates that the gene encoding SPOP is one such frequent mutation in prostate cancer (2). SPOP was discovered in 1997 by Nagai et al and named for the nuclear speckles it formed and its homology to the Poz domain (3). Soon after its discovery SPOP's function as an E3 ubiquitin ligase adaptor protein was elucidated (4, 5). These studies showed that SPOP interacted with CUL3 to mediate ubiquitination of target substrates. Multiple early SPOP publications hinted that it had an anti-tumor function (5-8). Other studies, mostly in drosophila noted that the fly homolog of SPOP played a role in hedgehog signaling (9-11).

The first investigation focusing on SPOP's role in tumor formation and progression was not published until 2009 by Liu et al (12). Beginning with the landmark paper by Barbieri et al in 2012 highlighting both the frequency and uniqueness of SPOP mutation in prostate cancer, interest in the protein rose dramatically. Since then multiple studies have been published focusing on SPOP's role in cancer. Meanwhile, evidence exists in the literature that SPOP can act as either a tumor suppressor or promoter depending on the context. Mutation of the SPOP gene and/or altered expression of the protein are associated with cancer formation and progression of varieties of carcinomas including prostate, breast, gastric, renal, and gliomas. In this review, we provide a look at the SPOP protein, its role in prostate and other cancers, and the potential clinical impact of SPOP mutation.

SPOP gene and protein

A. SPOP structure

In 2009, Zhuang et al purified wild-type SPOP, and found it is composed of 374 amino acids and two domains: an N-terminal part containing residues 28-166 ($SPOP^{MATH}$) and a C-terminal part containing residues172-329 ($SPOP^{BTB}$) (13). The MATH region mediates substrate binding. Intriguingly, in prostate cancer all of the mutations are localized to this domain (2). The BTB domain facilitates the formation of a 2:2 complex with the CUL3 N-terminal domain. Through these interactions, SPOP participates in ubiquitination and protein degradation (14, 15).

Interestingly, the crystallographic and small-angle X-ray scattering analyses (SAXS) data indicate that the most striking feature of the SPOP structure is the dimeric and asymmetric arrangement of substrate-binding MATH domain and a 55° orientation BTB/3-box domain (13). The MATH domain is located in the middle of the V-shaped groove composed by the two protomers in the BTB domain. The dimeric SPOP BTB domain assembles with CUL3, a subtype of the Cullin gene, generating a dimeric ubiquitin ligase composed of two substrate-binding sites and two catalytic cores. Because of this dimeric structure, SPOP domains can recruit substrates and elongate ubiquitin chains to simple various and flexible orientations for higher avidity and more conformational options for mediating ubiquitination (16). However, some substrates, such as DEK and TRIM24, demonstrated a decrease in ubiquitination due to heteromeric complexes of wild-type and mutant SPOP protein (17).

B. SPOP function

SPOP binds to CUL3 via the BTB domain to form a complex for ubiquitinating target proteins (5). **Table 1** lists the published SPOP substrates. Ubiquitin is a small regulatory protein that can attach itself to proteins and label them for proteasomal degradation (18). Ubiquitin ligases play an important role in maintaining genome stability and cell cycle control (19). During the ubiquitination process, a ubiquitin protein interacts with the substrate domain and Ub-E3 ligase, a substrate enzyme, to modulate the Ub system (20). E3 ligases can be grouped into the RING domain or the closely related U-box domain. The RING domain combined with the Cullin family can provide a scaffold for ubiquitin ligases (E3s) to form Cullin-RING ligases (CRLs) (21, 22).

Table 1: List of known SPOP substrates

SPOP Substrates	
Protein Name	**Protein Function**
MacroH2.A	Chromatin Organization / Accessibility
PDX1	Insulin / Glucose Transport
Daxx	Transcription Repression / Apoptosis regulation
ERa	Hormone Signaling / Growth / Development
HHIP	Hedgehog Signaling / Development
Gli2/3	Hedgehog Signaling / Development
SRC3	Hormone Signaling
AR	Hormone Signaling / Growth / Development
SUFU	Hedgehog Signaling / Development
DUSP7	Tyrosine Phosphotase / Multiple Pathways
PTEN	Phosphotase / Metabolism
DDIT3	ER Stress
DEK	mRNA Processing
ERG	Transcription factor Multiple Pathways
SENP7	Senescence
PR	Hormone Signaling / Growth / Development
TRIM24	Transcriptional Control of Nuclear Receptors / Multiple Pathways
SETD2	Epigenetic Regulation
CDC20	Cell Cycle Regulation
Sirt2	Deacetylase
EgIN2	Oxygen Response
C-Myc	Transcription Factor / Multiple Pathways
INF2	Mitochondrial Dynamics
HDAC6	Epigenetic Regulation
BRD4	Chromatin Reader
PDL1	Apoptosis / Immune Response
MMP2	ECM regulation

SPOP in prostate cancer

Two studies published in 2011 and 2012 showed that SPOP is frequently mutated in prostate cancer (2, 23). The 2012 study by Barbieri et al was especially interesting because it showed that prostate tumors with SPOP mutation did not have the very prevalent TMPRSS2 ETS gene fusion event. Data from subsequent sequencing studies have thus far

supported Barbeiri's findings (24-29). Taken together, these findings suggest that SPOP mutation may be an early event in prostate cancer tumorigenesis and is a potential driver mutation of prostate cancer. Indeed, this hypothesis has been supported by *in vivo* data by two investigations showing that mutation or ablation of SPOP protein can lead to mouse prostate neoplasia (30, 31).

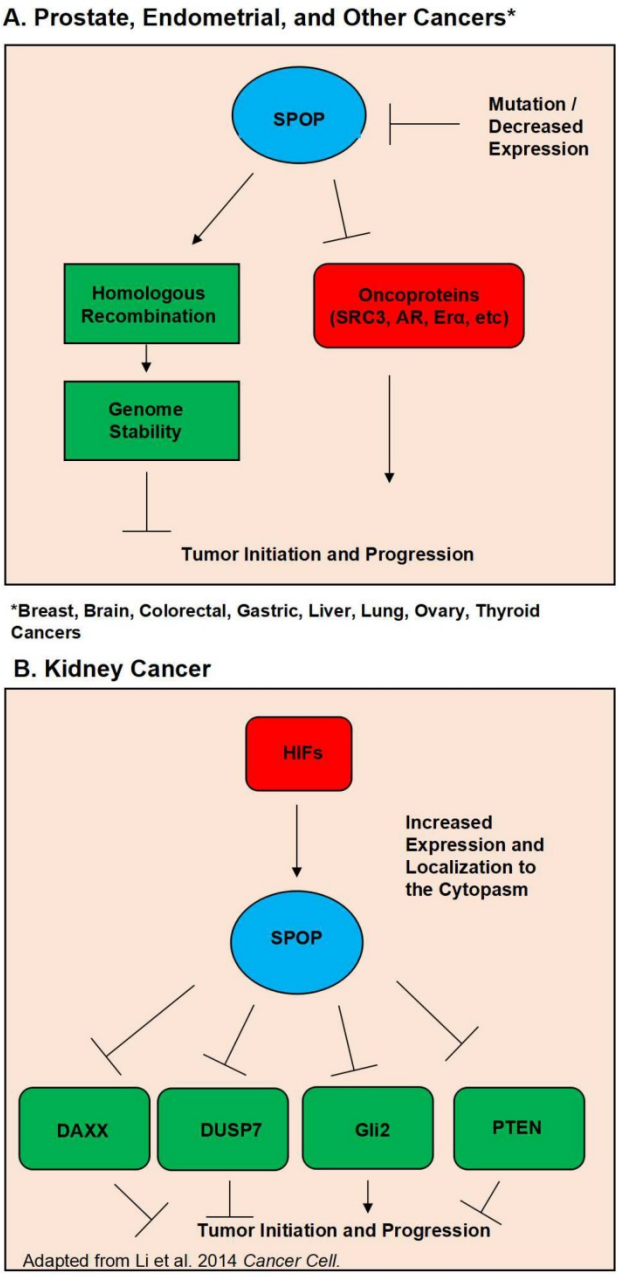

Figure 1: Schematic diagram outlining the functional roles of SPOP. (A). Diagram of the normal functions of SPOP and how these are interrupted by mutations and/or loss of expression in Prostate, Endometrial, Breast, Brain, Colorectal, Gastric, Liver, Lung, Ovary, and Thyroid Cancers. **(B).** Diagram of how overexpression and localization to the cytoplasm alters SPOP function in Kidney Cancer.

Further supporting the evidence of SPOP as a tumor suppressor is the steadily growing list of SPOP substrates, many of which are potent oncogenes. Perhaps foremost among these substrates in prostate cancer is the androgen receptor. In 2013 Geng et al first verified that SRC3 is a SPOP substrate, and that SPOP mutants lost the ability to regulate SRC-3 and thus AR activity (32). Further evidence of SPOP's regulation of AR was then discovered by An et al in 2014 and follow up study by Geng et al showing that SPOP can also directly regulate AR protein levels (33, 34). Another notable SPOP substrate is the ERG oncoprotein. Multiple studies have shown that SPOP regulates ERG protein levels, and that SPOP mutation led to ERG accumulation. This accumulation of ERG then promoted an invasive phenotype (35-37). Additionally, in 2015 An et al. showed that ERG gene fusion events protect ERG protein from regulation by SPOP (38). A study in 2014 by Theurillat et al demonstrated that SPOP, but not its mutants, ubiquitnates and promotes the degradation of a chromatin organizing protein, DEK. The authors also showed that DEK accumulates in mutated SPOP tumor samples (17). Wu et al have also shown that SPOP regulates CDC 20 (39). Trim 24, EgIN2, inF2, Senp7, DDIT3, SETD2, and C-myc have also been demonstrated to be SPOP substrates in prostate cancer (31, 40-45). **Figure 1A** outlines SPOP function in prostate cancer as well as other cancers where wild type SPOP is a tumor suppressor. Considering the vast collection of evidence, it is apparent that SPOP is a potent tumor suppressor in the prostate cancer setting.

SPOP in other cancers

Although a majority of research in SPOP has been in the context of prostate cancer, there are multiple reports of SPOP's anti-tumor effect in other cancer subtypes. **Table 2** summarizes the different SPOP alterations that have been published and the tissue the studies were conducted in. Sequencing studies show that SPOP also has missense mutations in endometrial cancer, similarly to prostate cancer (46-49). However, the residues that are mutated in endometrial cancer are different from prostate cancer. Additionally, two studies have shown that SPOP has variants in ovarian cancer as well as liver cancer (50, 51). Interestingly, liver cancer had the S119N mutant which is also seen in prostate cancer (50). Sequencing studies in thyroid cancer have also found SPOP mutations in (52-54). In 2016 Yoo et al. showed that mutations were present in the MATH domain as in prostate (52). A different investigation by Ye et al in 2017 showed that SPOP mutations were mutually exclusive with alterations in EZH1 and ZNF148 (54). It is interesting to note that although the proteins are different SPOP mutation has mutual exclusivity with aberrations in other proteins as in prostate cancer.

Table 2: List of SPOP alterations

Description of SPOP Alterations in Different Cancer Subtypes	
Organ	**Type(s) of Alteration(s)**
Prostate	Missense Mutations, Loss of Expression
Endometrium	Missense Mutations, Loss of Expression
Breast	Loss of Expression
Brain	Loss of Expression
Colorectal	Loss of Expression
Gastric	Loss of Expression
Kidney	Overexpression, Cytoplasmic Localization
Liver	Missense Mutations
Ovary	Amplification, Deletion
Thyroid	Missense Mutations
Lung	Loss of Expression

Along with missense mutations, multiple cancers have shown loss of SPOP genomic DNA or protein expression. In 2011 Li et al showed that SPOP can have loss of heterozygosity in breast cancer (8). Gao et al found that SPOP is crucial for the regulation of progesterone protein levels in breast cancer (55). This data combined with the data from prostate and endometrial suggest a pattern of SPOP being involved in hormonal regulation. SPOP expression has been found to be lost in colorectal, gastric, lung, and brain tumors (56-61). The researchers from all of these studies reported that loss of SPOP expression has a poor prognosis. Additional SPOP substrates have been discovered using gastric and lung cancer as a model. HDAC6, and MMP2 were found to be regulated by SPOP in the context of colorectal cancer (62, 63), and SIRT2 was found to be regulated by SPOP in non small cell lung cancer (64). Together, it appears that SPOP is a powerful tumor suppressor in solid tumors of a diverse tissue background.

Despite SPOP being almost universally hailed as a tumor suppressor across multiple types of solid cancers, there is evidence that in the context of kidney cancer SPOP acts as a tumor promoter. Liu et al published in 2009 that SPOP is involved in drosophila body segmentation and mediates the phosphorylation of JNK. Additionally they published that SPOP has increased expression in kidney cancer (12). In 2014 the same group released a second study showing that in kidney cancer Hypoxia Inducible Factors (HIF) induce SPOP localization to the cytoplasm instead of the nucleus. In this SPOP promotes tumorigenesis by mediating the degradation of Daxx, Gli2, PTEN and DUSP7 (65). In a follow up study they utilized a small molecule inhibitor targeted to SPOP. Their inhibitor was able to disrupt SPOP binding of substrate and promoted the killing of renal cancer cells. The inhibitor also showed in vivo efficacy in lowering tumor burden (66). A study by a separate group showed that depleting SPOP protein levels via siRNA was able to increase apoptosis in kidney cancer cell lines (67). SPOP's oncogenic function in kidney cancer is shown in **Figure 1B**.

SPOP Clinical Impact

Given the evidence reviewed here it is apparent that aberrations in the SPOP gene and / or protein will have a profound clinical impact. As discussed loss of SPOP or SPOP mutation corresponds with a poor prognosis in most solid tumor subtypes. However, the impact SPOP has on the efficacy of different treatments is still being investigated.

DNA damaging therapies such as radiation and chemotherapeutics have long been standards of cancer treatment. There are currently two studies that suggest SPOP has a role in the DNA damage response, the signaling pathway crucial for maintaining the genome. We have showed that after DNA damage SPOP interacted with ATM, a critical DDR protein, and appeared to co localize with yh2AX. Additionally, depletion of SPOP induced a radiosensitive phenotype (68). A different study by Boysen et al demonstrated that SPOP mutants favor using the relatively error prone non-homologous end joining (NHEJ) DNA damage pathway opposed to the higher fidelity homologous recombination (HR) pathway **(Figure 1A)** (69). Together, these findings suggest SPOP is involved in the DNA damage response although the exact mechanism is not yet understood. These studies also suggest that DNA damaging therapies could potentially have increased efficacy in patients with mutated or depleted SPOP.

BET inhibitors such as JQ1 are another favored treatment modality. As the name implies BET inhibitors impede BET containing proteins, which are epigenetic regulators that promote cell division (70). A trio of studies showed the impact of SPOP mutation on BET inhibitor efficacy. Two of which, using prostate cancer as a model found that Brd4 is substrate of SPOP. As such SPOP mutants had elevated Brd4. The elevated Brd4 resulted in a resistance to BET inhibitors in cells and tumors containing mutations in SPOP (71, 72). Interestingly, the third study by Janouskova et al published in 2017, which instead used endometrial cancer as a model found that SPOP mutation sensitized cells to BET inhibitor treatment (73). Another group investigated the efficacy of epigenetic related drugs on SPOP mutant tumors. In 2018 Yan et al publish that HDAC3 inhibitors blocked mTOR/AKT and AR signaling in tumors harboring SPOP mutations (74).

Immunotherapy has recently become a heavily investigated cancer treatment method. Among the types of immunotherapies used are immune checkpoint inhibitors. Checkpoint inhibitors block the apoptotic signaling proteins on tumor cells and / or immune cells to prevent tumor cells from inducing cell death in immune cells. PDL1 inhibitors are a well-studied treatment gaining use in combination

with current standard therapy. In 2017 Zhang et al published that PDL1 is a SPOP substrate. They also showed that SPOP mutants did not bind to and mediate the ubiquitination of PDL1. Tumors with mutant SPOP had higher PDL1 levels, and a reduction in the number of CD8 tumor infiltrating T-cells (75).

Conclusions and Perspective

As an adapter for CUL3-based ligases, SPOP mediates the degradation of multiple proteins. SPOP mutations have been shown to affect several signaling pathways, such as SRC-3/AR, TNF/JNK and ERG pathways. Studies have provided evidence that SPOP is a tumor suppressor in prostate, endometrial, as well as other solid tumor forming cancers. However, there are reports showing that SPOP promotes tumorigenesis in clear cell renal cell carcinoma. SPOP mutation and loss of expression both can contribute to SPOP losing its tumor suppressor function. Aside from involvement in mediating ubiquitination, there is convincing evidence that SPOP plays a critical role in the DNA damage response, epigenetic regulation, and the immune response against tumors. Further evidence is needed to understand how current cancer therapies affect mutant SPOP tumors versus wild type SPOP tumors. It is clear that SPOP will play an important role in prostate cancer diagnosis, prognosis, and therapy in the future. It is clear SPOP is a critical protein for suppressing tumorigenesis and we are only beginning to understand its clinical impact.

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Competing Interests

The authors have declared that no competing interest exists.

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