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ARTÍCULO DE REVISIÓN

Speckle type POZ adaptor protein (SPOP) and its role in cancer

La proteína adaptadora Speckle-type POZ (SPOP) y su papel en cáncer

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Abstract

Proteasomal degradation is an essential regulatory mechanism for cellular homeostasis maintenance. The speckle-type POZ adaptor protein (SPOP) is part of the ubiquitin ligase E3 cullin-3 RING-box1 complex, responsible for the ubiquitination and proteasomal degradation of biomolecules involved in cell cycle control, proliferation, response to DNA damage, epigenetic control, and hormone signaling, among others. Changes in SPOP have been associated with the development of different types of cancer, since it can act as a tumor suppressor mainly in prostate, breast, colorectal, lung cancer and liver cancer, due to point mutations and/or reduced expression, or as an oncogene in kidney cancer by protein overexpression. In endometrial cancer it has a dual role, since it can act as a tumor suppressor or as an oncogene. SPOP is a potential prognostic biomarker and a promising therapeutic target.

Keywords: SPOP, Ubiquitin ligase, Cancer, Biomarker, Oncogene, Tumor suppressor gene, proteasomal degradation.

Resumen

La degradación proteosómica es un mecanismo de regulación esencial para el mantenimiento de la homeostasis celular. La proteína adaptadora Speckle-type POZ (SPOP) hace parte del complejo ubiquitin ligasa E3 cullin-3 RING-box1, encargado de la ubiquitinación y degradación proteosomal de biomoléculas involucradas en el control del ciclo celular, proliferación, respuesta al daño de ADN, control epigenético, señalización hormonal, entre otros. Las alteraciones en SPOP han sido asociadas al desarrollo de diferentes tipos de cáncer, ya que puede actuar como supresor tumoral principalmente en cáncer de próstata, mama, colorrectal y pulmón, debido a mutaciones puntuales y/o expresión reducida o como oncogén en cáncer riñón por sobreexpresión de la proteína. En cáncer endometrial tiene un rol dual, ya que puede actuar como supresor tumoral o como oncogén. SPOP es considerado como un potencial biomarcador pronóstico y un objetivo terapéutico prometedor.

Palabras clave: SPOP, Ubiquitin Ligasa, Cáncer, Biomarcador, Oncogen, Gen supresor tumoral, degradación proteasomal.

Introduction

Degradation of biomolecules is an especially important regulatory mechanism for maintaining cell balance. It may be mediated by the lysosomal or the ubiquitin-proteasome pathways, the latter being responsible for maintaining intracellular levels of proteins involved in many cellular processes such as cell cycle regulation, proliferation, apoptosis, response to DNA damage, and transcriptional activation, among others. Many of the proteins involved in the process of ubiquitination and proteolysis have gained attention because of the effects they can have on the development of cancer (1). One of them is the Speckle-type POZ protein (SPOP), which acts as an adaptor protein in the ubiquitin ligase E3 cullin-3 RING-box1 (Cul3-RING-box1) complex, recruiting substrates for ubiquitination and subsequent degradation in the 26S proteasome (2). Among the SPOP substrates, there are the androgen receptor (AR) (3,4), the estrogen receptor (ER) (5,6), the steroid receptor coactivator 3 (SRC3) (4), the bromodomain and extra-terminal BET domain proteins (7,8), the cell-

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division cycle protein 20 (Cdc20) (9) and the proteins associated with DAXX and FADD death domains (10–12), among other effectors, which show its importance in cell development and growth.

SPOP has recently been found to act as a tumor suppressor gene (TSG) or oncogene in different types of cancer, as shown by findings of mutations, loss in the number of copies and/or reduced expression, gain of function or protein overexpression, and it has been associated with prognosis, which has suggested SPOP as a prognostic biomarker and promising therapeutic goal (13–18). In this review, we will describe the structure of the adaptor protein, its main functions and molecular mechanisms, its relationship with cancer, its usefulness as a prognostic biomarker, and therapeutic advances.

2. Methodology

2.1 Eligible studies

We conducted a search of the literature from the last 16 years (2004 – 2020) using Pubmed (NIH) and Scielo (19,20). The eligibility criteria included original articles that addressed different roles of the SPOP protein, its main functions and molecular mechanisms related to the development of different types of cancer, as well as its usefulness as a prognostic biomarker and cancer treatment. Relevant review articles were consulted as well. Studies written in languages other than English or Spanish, studies that did not describe the topics mentioned and studies whose publications were not accessible were excluded.

2.2 Publication search

An initial search was performed in the PubMed database combining the Medical Subject Headings (MeSH): "SPOP", "SPOP mutation", "SPOP in cancer", "Speckle-type POZ protein" and retrieve 130 publications from which 106 articles were eligible. The last search was carried out on July 29, 2020. We revised manuscripts cited within those studies to identify additional publications that fulfilled our eligibility criteria. A total of 112 unique publications were included in our review.

3. Structure of the SPOP protein

The SPOP protein was first identified in 1997 as a nuclear protein with a speckle-type pattern (21). This protein is encoded by the SPOP gene which is located in locus 17q21.33 and has 16 exons (79280 bp). It has an isoform called SPOPL (SPOP like) that is encoded in locus 2q22.1 and is formed by 12 exons and 71778 bp (Figure 1A) (22). SPOPL shares an overall 85% protein sequence identity with SPOP but has 18 more amino acid residues, suggesting that the isoform could perform similar functions; though, as we will see below, it also seems to play a role in modulating the SPOP function (2,23).

The SPOP protein is made up of 374 amino acid, has a molecular weight of 43.13 kDa, and its secondary structure consists of 18 α-helices and 14 ß sheets, which form three main domains: MATH, BTB, and BACK (Figure 1B). Followed by the BACK domain, in the C-terminal region is the NLS, which allows its location in the nucleus (24). It has been shown that SPOP can be found in a dimeric or oligomeric conformation, which increases binding to substrates (Figure 1C).

MATH (Meprin and TRAF-C homology) is the N-terminal domain, which function is to recruit substrates to the ubiquitin ligase complex by forming a cleft surrounding the hydrophobic side chain of the substrate (Figure 1D) (2,24–26).

BTB (Bric-a-brac/Tamtrack/Broad), is an internal domain known as POZ (zinc finger and poxvirus protein) that allows SPOP binding to the ubiquitin ligase complex via Cullin3 (Figure 1D), and also allows the formation of SPOP-SPOP homodimers or SPOP-SPOPL heterodimers (2).

BACK (BTB with Kelch repeats) is a carboxyterminal domain that allows a greater interaction surface between BTB and Cul3, besides the formation of oligomers through interaction with other SPOP BACK domains (Figure 1C); this allows recruiting multivalent substrates, and significantly increases their degradation (Figure 1D) (2,14). The interaction between SPOP oligomers and substrates generates membraneless "organelles" formed by liquid–liquid phase separation (LLPS), as nuclear speckles (Figure 1E) (14,27). The creation of these complexes is dependent on the concentration of SPOPL since, by lacking 18 residues in the BACK domain, it is not possible to form oligomers, suggesting SPOPL as a regulator in the ubiquitination process (28). Formation of these LLPS enhances binding of enzymes and substrates, and it is suggested that the organelles that are created could be involved in cell proteostasis processes such as location, control, and balance of different proteins. Perturbations in proteostasis, leads to an accumulation of damaged and misfolded proteins (14).

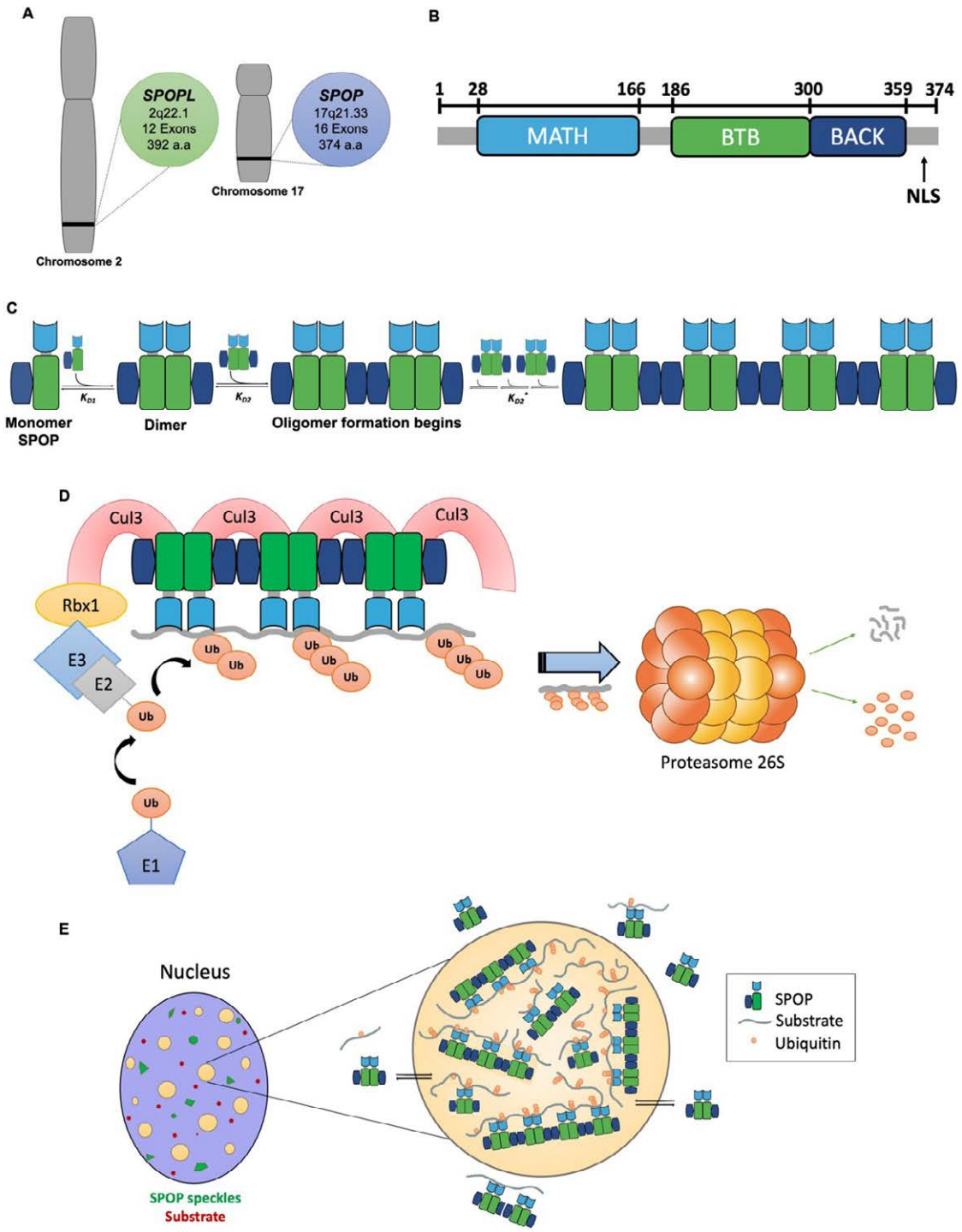

Figure 1. **Structure and function of the SPOP protein. A.** *SPOP and SPOPL locus.* ***B****. SPOP domains: MATH (light blue), BTB (green), BACK (dark blue), and nuclear localization sequence (NLS)* ***C****. Dimeric and oligomeric association of SPOP.* ***D****. Cul3-Rbx1 E3 ubiquitin ligase complex, showing the adapter role of a SPOP oligomer for substrate ubiquitination (gray wavy line) and subsequent degradation in the 26S proteasome.* ***E****. In the nucleus, SPOP is observed in higher-order oligomers as small green nuclear speckles, and the substrate available to be ubiquitinated is shown in red. Increase in substrate concentration generates SPOP-substrate localization foci that form membraneless liquid organelles (yellow), which favors SPOP oligomerization and location of the mono or multivalent substrate for its ubiquitination.*

4. Functions of SPOP

4.1 Regulation of substrates by proteasomal degradation

Approximately 20% of protein degradation in the cell is mediated by Ubiquitin ligases E3 CRL-RING complexes. Specifically, Cul3 uses proprietary substrate adaptors such as SPOP (29). Figure 1D shows the interaction of a SPOP oligomer with the Ubiquitin ligase E3 Cul3-RING-box1 complex. The ubiquitinated substrate is targeted to the 26S proteasome for degradation (29).

More than 33 substrates of SPOP have been described, whose functions vary and involve regulating important processes at the cellular level (Table 1) (3,4,5,7,8,9-12,14,22,28-36,37-46,47-56,57). It is interesting to see that most of these substrates have been associated with a particular type of cancer, and this may be due to the impact that a substrate can have on a given tissue, and causes different SPOP mutations to affect the degradation of said substrates, therefore being associated with a specific type of cancer.

Table 1. SPOP substrates classified by function and type of cancer.

Type of cancer	Function	Substrate	Reference
SPOP as a tumor suppressor gene (TSG)			
Mutations in the MATH domain with loss-of-function: Increased effect on the substrate			
Prostate	Steroid hormone receptor	Androgen receptor (AR)	(3),(4)
	Transcriptional regulation	Tripartite motif-containing 24 (TRIM24)	(38),(39)
		Steroid receptor coactivator 3 (SRC3)	(4),(14)
		ETS transcription factor (ERG)	(40),(41)
		Activating transcription factor-2 (ATF2)	(28)
		SR-related CTD associated factor 1 (SCAF1)	(30)
		Proto-oncogene c-Myc	(8),(29)
		Homeobox transcription factor NANOG	(32-34)
		Hedgehog pathway proteins: glioma-associated oncogene Gli2	(25)
	Cell cycle regulation	Cell division cycle protein 20 (Cdc20)	(9)
		Cyclin E1	(44)
		Cell cycle associated protein 1 (CAPRIN1)	(45)
	Cell cycle regulation, transcription, and apoptosis	Death domain-associated protein (DAXX)	(10),(11), (14)
	Epigenetic regulation / Chromatin remodeling and transcription regulation	Proto-oncogene DEK	(40)
		Zinc finger protein WIZ	(30)
		Bromodomain and extra-terminal (BET) protein family (BRD2/3/4)	(7),(8),(23) (78),(103),(107)
	Immune system suppression	Programmed death-ligand 1 (PDL1)	(50)
	SUMO removal	Sentrin-specific protease 7 (SENP7)	(18)
	Regulation of actin polymerization, maintenance of Golgi structure, and mitochondrial fission	Inverted formin 2 (INF2)	(109)
Lung	Cell cycle regulation and apoptosis	FAS-associated protein with death domain (FADD)	(12)
	DNA repair and transcription regulation	NAD-dependent deacetylase sirtuin 2 (SIRT2)	(49)

Endometrial	Steroid hormone receptor	Estrogen receptor (ER)	(5)
	Transcription regulation	Zinc finger and BTB domain containing 3 (ZBTB3)	(43)
		Steroid receptor coactivator 3 (SRC3)	(5)
Low SPOP expression levels: Increased effect on the substrate			
Breast	Steroid hormone receptor	Progesterone receptor (PR)	(37)
	Epigenetic and transcriptional regulation	Breast cancer metastasis suppressor 1 (BRMS1)	(31)
	Cell cycle regulation, transcription, and apoptosis	Death domain-associated protein (DAXX)	(10),(11), (14)
Colorectal	Transcription regulation	Interleukin enhancer binding factor 3 (ILF3)	(110)
		Hedgehog pathway proteins: glioma-associated oncogene Gli2	(86)
	Cell cycle regulation, transcription, and apoptosis	Death domain-associated protein (DAXX)	(10),(11), (14)
Liver	SUMO removal	Sentrin-specific protease 7 (SENP7)	(51)
SPOP overexpression: Decreasing effect on the substrate			
Gastric	Transcription regulation	Hedgehog pathway proteins: glioma-associated oncogenes Gli2/Gli3	(35),(42)
SPOP as an oncogene			
Mutations in the MATH domain with gain-of-function: Decreasing effect on the substrate			
Endometrial	Chromatin remodeling and transcription regulation	Bromodomain and extra-terminal (BET) protein family (BRD2/3/4)	(7),(78)
SPOP overexpression: Decreasing effect on the substrate			
Kidney	Regulation of signaling pathways with phosphatase activity	Dual-specificity phosphatase 6/7 (DUSP6/7)	(93),(102)
	Phosphatase, tumor suppressor	*Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase (PTEN)	(102)
	Cell cycle regulation, transcription, and apoptosis	Death domain-associated protein (DAXX)	(10),(11), (14)
	Transcription regulation	Hedgehog pathway proteins: glioma-associated oncogene Gli2	(93)
	Chromatin remodeling	SET domain containing 2, histone lysine methyltransferase (SETD2)	(48)
	Cell cycle regulation and apoptosis	Large tumor suppressor kinase 1 (LATS1)	(56)
CL myeloid (K562-HPC7) and animal model (mouse)	Signal transduction to IL-1R-associated kinases (IRAK)	Myeloid differentiation primary response 88 (MYD88)	(54),(55), (57)
CL osteosarcoma (U2OS)	Epigenetic regulation /Chromatin remodeling	**B Lymphoma Mo-MLV insertion region 1 homolog (BMI1)	(53)
		**Histone variant macroH2	(47),(53)

CL: Cell line. *PTEN phosphatase is a SPOP substrate only in kidney cancer, in which SPOP is in the cytoplasm.
** Substrates with poor location.

4.2 Role in the response to DNA damage

It has been proposed that SPOP modulates transcriptional repression activities and participates in the repair of double-stranded DNA ruptures (DSB) (60), where it is recruited forming nuclear foci, which depend on the kinase activity of the ataxia-telangiectasia (ATM) protein, and are colocalized with histone γ-H2AX foci in response to damage. Depletion or decrease in SPOP has been shown to generate impaired DNA damage response (DDR) and high sensitivity to ionizing radiation; however, the mechanism has not yet been determined, but it could be associated with the regulation it exerts on the levels of expression of Rad51 and Ku80 factors, which are important in DSB repair by homologous recombination (HR) (17,61). In addition, an interactome analysis showed that SPOP is associated with multiple proteins involved in the transcription, splicing, and export of the mRNA molecules (62).

4.3. Function of SPOPL

Besides being a regulator of SPOP, one study found that SPOPL is involved in the regulation of endosome maturation and traffic of endosome load to lysosomes and that this depended on ubiquitination and degradation of the EPS15 endocytic adapter, which according to the study, is a SPOPL substrate, not a SPOP substrate (63).

5. Relationship of SPOP with cancer: a view from protein structure and function

SPOP plays a key role in maintaining cell development and growth by controlling the degradation of proteins that regulate important processes for cell homeostasis (Table 1). However, it is striking that, apart from cancer, just a few functions of SPOP have been described, such as regulation of fetal hemoglobin expression (64), regulation of insulin and glucose homeostasis and having the pancreatic and duodenal homeobox transcription factor (PDX1) as a substrate (54,55). SPOP is also believed to have a role in the development of neurological disorders, as “de novo” genetic variants have been found in one study (65).

Given its functions, SPOP can act as a tumor suppressor gene (TSG), by regulating processes of cell division, repair and apoptosis, or as an oncogene, inducing proliferation, through different mechanisms as shown by findings of reduced expression or overexpression of the protein, loss of copy number, or mutations in the gene in different types of cancer (13–18).

5.1 SPOP as a tumor suppressor gene

5.1.1 Mutations in the MATH domain with loss-of-function

Missense mutations with loss of function have been found in prostate cancer (PCa), endometrial cancer (EC), and lung cancer (LC) (Figure 2A); however, mutation hot spots are different. In PCa, they are located in the substrate-binding cleft, in EC they are outside the cleft, and in LC they are both inside and outside this site (Figure 2B); these differences could be related to the role of SPOP in each of these malignancies, since SPOP substrates in PCa and LC are overexpressed, whereas in EC some of the substrates are overexpressed but others are underexpressed (38,66–71).

SPOP mutation in PCa is frequent and is taken as one of the molecular subtypes identified by the TCGA. Although a germline mutation in the BTB domain (N296I), associated with hereditary PCa has been described in a family of European ancestry (72), the remaining mutations found are somatic in the MATH domain (Figure 2). In localized PCa, the mutation frequency is between 6% and 15%, and between 15% and 25% in advanced PCa. A frequency of 20% has been reported in patients with African ancestry, while in those with European ancestry it ranges between 6% and 10%, between 7% and 12% in Asians, and between 5% and 14% in North Americans (24,38,69,73–76).

The frequency of SPOP mutations described in EC ranges between 6% and 10%, mainly in serous tumors and clear cell carcinoma (5,66,70,77,78), and 6% in non-small cell LC (NSCLC) (Figure 2) (70,71). Not all SPOP mutations in these cancers have been associated with an effect on protein function.

These loss-of-function mutations prevent SPOP from binding to its substrates, increasing their quantity. Figure 3 shows some SPOP substrates, by type of cancer, that participate in signaling pathways that could be deregulated and associated with tumor progression processes. In PCa, the overexpression of AR is associated with increased proliferation and survival (4,14). Another SPOP substrate found in EC and PCa is SRC3, which is found overexpressed in these tumors and activates the PI3K/mTOR and AKT signaling pathways (Figure 3), causing a higher cell growth and proliferation rate (3,4,66,79).

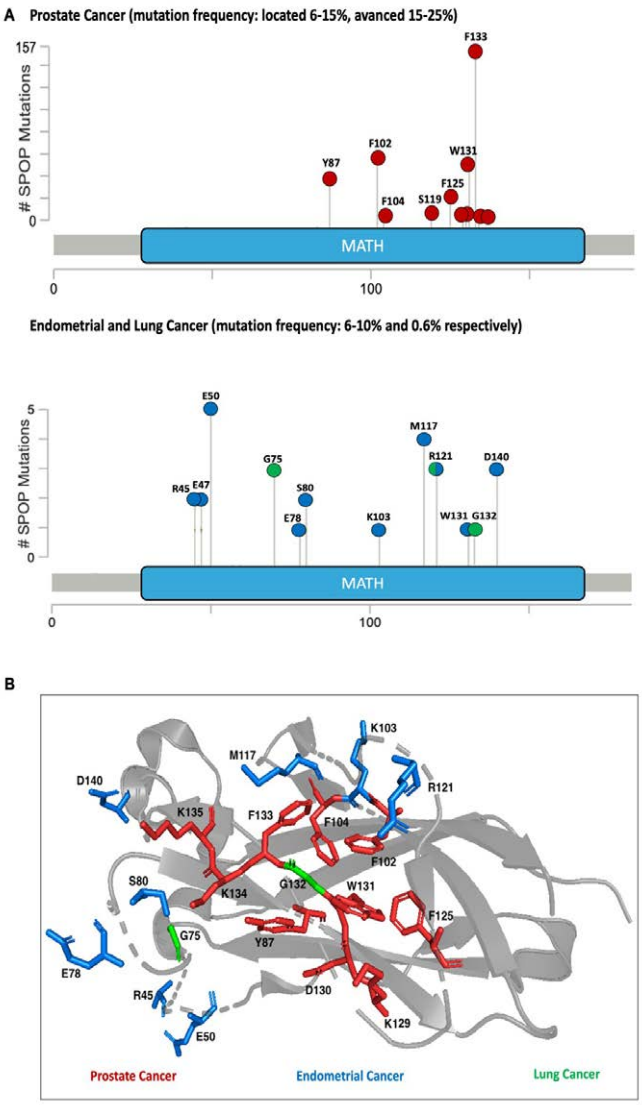

Figure 2. ***Point mutations of the MATH domain in SPOP in prostate, endometrial, and lung cancer. A****. Mutation frequency, mutation hot spots, and number of mutations reported in prostate cancer (top), and endometrial and lung cancer (bottom) with clinical impact on the disease.* ***B****. Crystal structure of the MATH domain with missense point mutations, relevant in different types of cancer. Residues are marked with different colors depending on the type of cancer: prostate cancer (red), endometrial cancer (blue), and lung cancer (green). Endometrial cancer mutations include loss and gain of function.*

Other substrates are also increased in EC, such as the estrogen receptor alpha (ERα), which increases its transactivation (5), and the expression of the transcription factor ZBTB3, a substrate that accumulates and generates a positive regulation on Sonic hedgehog (SHH), which in turn promotes tumor proliferation and survival (Figure 3) (45).

Proteins from the bromodomain family and the extraterminal BET domain, such as BDR2, BDR3, and BDR4, have also been related to PCa and EC. These proteins increase their stability by mutations in some SPOP residues in PCa, while in EC their amount decreases due to the role of SPOP as an oncogene, which will be discussed later (80).

In the case of NSCLC, an increase in two substrates has been observed: NAD-dependent deacetylase sirtuin 2 (SIRT2), which favors tumor proliferation (51) and FADD, which regulates the NF-kβ activity and is associated with an unfavorable prognosis (Figure 3) (12).

There are other genetic changes in PCa related to mutated SPOP, such as somatic deletions in 5q21 and 6q21 (60,81). Locus 5q21 contains the CHD1 gene, which encodes for helicase with DNA-binding chromodomain, involved in regulating gene transcription through chromatin interaction and remodeling (38), and in genomic stability (82). Moreover, locus 6q21 contains the forkhead box O3 gene (FOXO3), which acts as a regulatory transcription factor of genes necessary for cell death, so its loss is related to PCa carcinogenesis and progression (38). This could mean that the effects of SPOP mutations are synergetic with those of these genes or others located in these regions.

Loss of SPOP function also affects DNA repair (62). In LC and PCa, a high genomic instability has been found, related to a deficiency in HR, a decrease in the recruitment of RAD51, and an increase in NHEJ (60–62). In LC, the decrease in SPOP expression also affects DDR, increases apoptosis, and activates cell cycle control points induced by ionizing radiation (61), and in PCa leads to replicative stress and cell cycle deregulation. In PCa, the F133V mutant generates a deficiency in the expression of BRCA2, ATR, CHK1, RAD51, TDP1, TDP2, and MRE11, which are essential enzymes for DNA repair (62,83,84).

5.1.2 Low levels of SPOP expression

Low SPOP expression has been found in breast cancer (BC), colorectal cancer (CRC) and liver cancer (HCC), associated with increased substrate expression (Figure 3), and even though point mutations have also been found, these have not been associated with loss of function or changes in SPOP expression (33,39,53,70,85,86).

In BC, low SPOP levels cause overexpression of the progesterone receptor (PR), favoring cell cycle progression and activation of ERK1/2 (39) and breast

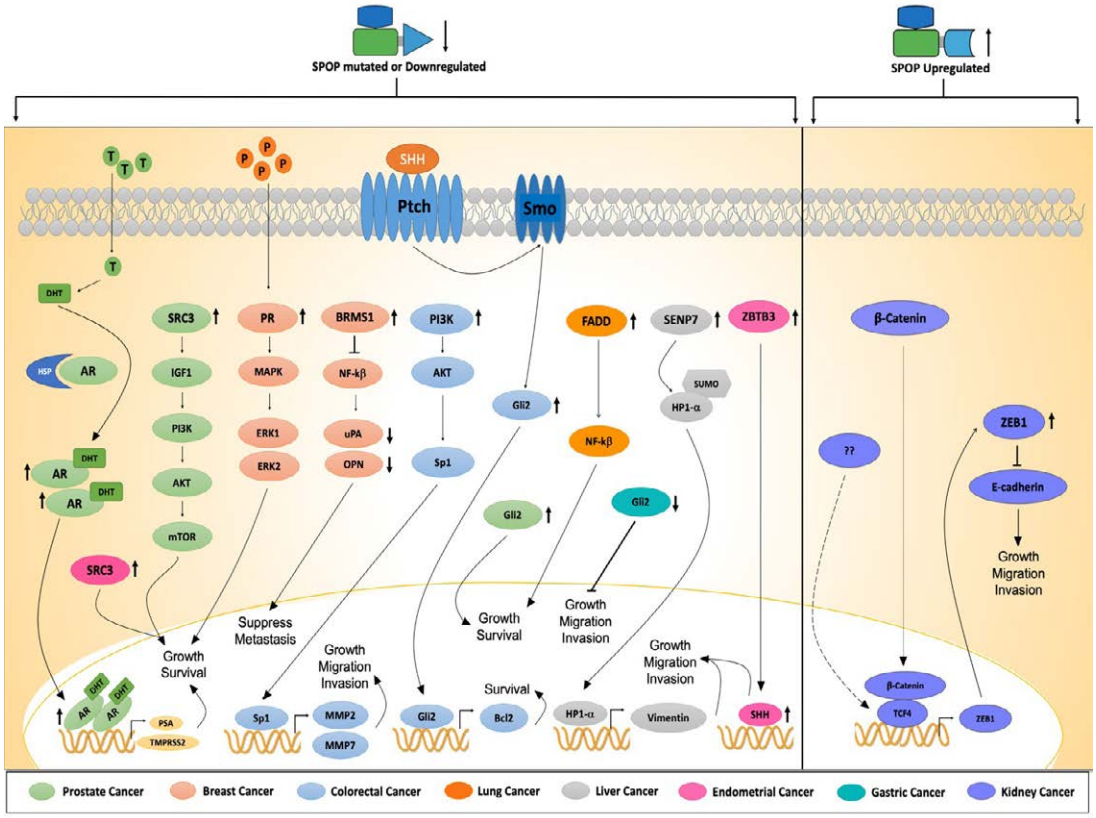

Figure 3. ***Signaling pathways compromised by SPOP alterations in different types of cancer.*** *The signaling pathways presented here involve proteins that are SPOP substrates and are associated with increased or decreased growth, survival, migration, and invasion. The arrows next to these proteins indicate the following: upward arrows show overexpression and downward arrows show low expression. Pathway components are marked in colors according to the type of cancer in which their involvement has been demonstrated. Prostate cancer: AR pathway and SRC3/PI3K/Akt pathway. Breast cancer: PR pathway and metastasis suppressor 1 (BRMS1) pathway. Colorectal cancer: PI3K/Akt/Sp1 and Hedgehog pathways. Lung cancer: FAS-associated protein with death domain (FADD)/NF-kβ pathway. Liver cancer: SENP7 pathway. Endometrial cancer: Pathway associated with ZBTB3 and increase in SRC3. Gastric cancer: Hedgehog pathway. Kidney cancer: Pathway associated with ZEB1. T (testosterone), DHT (dihydrotestosterone), SRC3 (steroid receptor coactivator 3), IGF-1 (insulin growth factor type 1), P (progesterone), MAPK (mitogen-activated protein kinase), uPA (urokinase-type plasminogen activator), OPN (osteopontin), MMP2/7 (metalloproteinases 2/7), SHH (Sonic hedgehog protein), Ptch (Patched), Smo (Smoothened), Gli2 (glioma-associated oncogene 2), SUMO (small ubiquitin-like modifier), HP1-α (heterochromatin protein 1 alpha), TCF4 (transcription factor 4).*

cancer metastasis suppressor 1 (BRMS1), which inhibits activation of urokinase-type plasminogen activator (uPA) and osteopontin (OPN), promoting the onset and progression of this type of cancer (Figure 3) (33).

In CRC, the PI3K/Akt pathway that increases the levels of metalloproteinases is activated, promoting tumor proliferation and migration (86,87). Furthermore, Gli2 is also overexpressed causing an increase in the levels of the anti-apoptotic protein Bcl-2, which favors the inhibition of cell death (Figure 3) (88).

In HCC, SENP7 is increased, which in turn, induced by HP1-α, rises vimentin levels, and this triggers processes of migration, invasion, and metastasis (Figure 3) (53). SENP7 is responsible for mediating epigenetic silencing in PCa (18), and invasion in BC (89).

5.1.3 SPOP overexpression

SPOP protein has been found highly expressed in gastric cancer (GC), and in this model acts as a TSG, since it has been related to the inhibition of the Hedgehog signaling pathway through the accelerated degradation of its Gli2 substrate (Figure 3), decreasing the processes of tumor proliferation, migration, and invasion (37); in addition, it has been found that SPOP suppresses the growth of cancer stem cells and reduces their power (90).

5.2 SPOP as an oncogene

5.2.1 SPOP overexpression

In clear cell renal cell carcinoma (ccRCC), SPOP is overexpressed and accumulates in the cytoplasm and increases degradation of PTEN, DUSP6, DUSP7, DAXX, Gli2, and LATS1 proteins, leading to a higher proliferation, survival, invasion, and apoptosis processes (24,58,91) and it can also increase the expression of ß-catenin and transcription Factor 4 (TCF4), which positively regulate transcription factor ZEB1, an inducer of mesenchymal-epithelial transition (MET), favoring migration and invasion (Figure 3) (92).

BET proteins are underexpressed in EC as a result of the gain of function of SPOP due to mutations in residues E47, E50, E78, S80, M117, and D140 (Figure 2) (80). On the other hand, BET proteins are overexpressed in PCa. This shows how complex the role of SPOP in carcinogenesis is. Moreover, there are reports about the dual role of SPOP in the endometrium, since both loss of function and gain of function mutations has been described.

5.3 Regulation of SPOP expression

The decrease in SPOP expression in CRC and LC has been associated with hypermethylation of the SPOP promoter or binding sites close to the SPOP promoter (Figures 4A and 4B) (88,93) and to the binding of SMAD2/3 to the same promoter (Figure 4C) (94). In GC, regulation in SPOP expression appears to be mediated by long non-coding RNA (LncRNA) ADAMTS9-AS2 (90). In ccRCC, SPOP regulation could be mediated by hypoxia-inducible factors 1 and 2 (HIF1/2), which increase SPOP levels, generating accumulation in cells (Figure 4D) (91). It has also been identified that the miR-520/372/373 family joins a 3'-UTR region of SPOP by

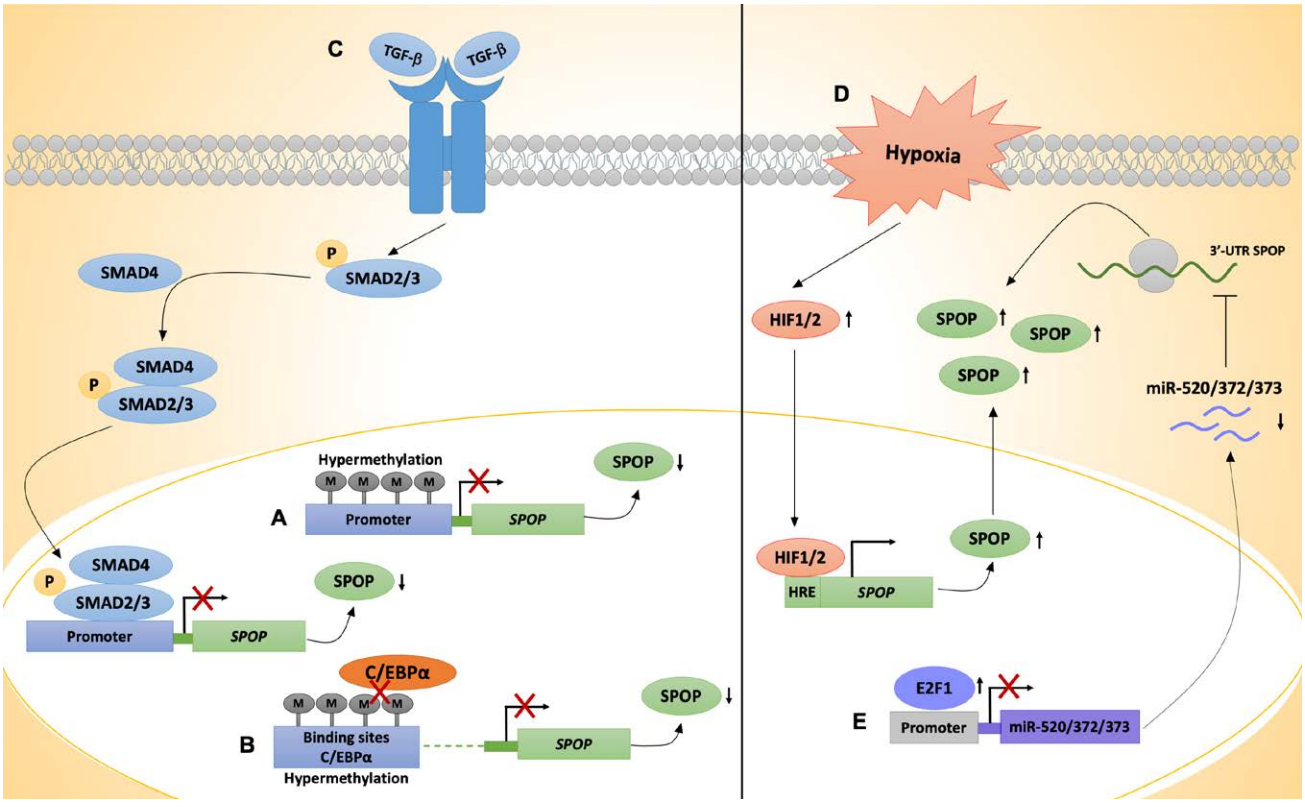

Figure 4. ***Regulatory mechanisms of SPOP expression.*** ***A.*** *Hypermethylation in the SPOP promoter region.* ***B.*** *Hypermethylation at C/EBP∝ binding sites close to the SPOP promoter.* ***C.*** *Binding of TGF-ß to its receptor leads to the binding of phosphorylated SMAD2/3 and SMAD4 to the SPOP promoter. Mechanisms A, B, and C decrease or inhibit SPOP expression.* ***D.*** *Hypoxia causes an increase in hypoxia-inducible factors HIF1/2, which are attached to a hypoxia-response element (HRE) located in the SPOP sequence. E. The overexpressed E2F1 transcription factor binds to the promoter regions of miR-520/372/373, blocking their expression, preventing these miRNAs from binding to the 3'UTR SPOP sequence, preventing their negative regulation on the protein. Mechanisms D and E increase SPOP expression.*

suppressing its expression; these miRNA are regulated downwards in ccRCC (Figure 4E) (95). More studies are required to know the precise mechanisms of regulation in each of these processes.

5.4 Usefulness of SPOP as a prognostic biomarker in cancer

It has been proposed that SPOP could be a prognostic biomarker in some types of cancer. Its role in PCa is controversial, some studies reveal that patients with mutated SPOP or with low protein expression have shorter biochemical and clinical progression free survival, compared to patients without the mutation (27,69,96); however, in other studies mutated SPOP has been associated with a favorable prognosis, finding a lower frequency of positive margins, extraprostatic extension, and invasion of seminal vesicles in radical prostatectomy, in addition to higher metastatic-free survival, particularly in high preoperative PSA patients (67,68,97). More PCa studies are needed to analyze the effect of other variables, such as age, pathological condition, Gleason score, or ethnicity, in the prognosis when the mutation is present.

In CRC, HCC, and NSCLC, the decrease in SPOP levels seems to be involved in a worse prognosis of the disease associated with poor cell differentiation, distant metastasis, advanced TNM and shorter overall survival (53,86–88,98). In the same sense, SPOP overexpression in patients with GC is associated with a good prognosis, given that less metastasis in lymph nodes, greater histological differentiation, and less advanced TNM staging are evident (37,99). In contrast, in ccRCC, SPOP overexpression is related to a high histological grade and tumors with local invasion or metastasis, as well as with a shorter recurrence-free survival and advanced stage of the disease (92,100,101).

5.5 SPOP as a potential therapeutic target

In ccRCC, characterized with an overexpression of SPOP, therapeutic modulators such as miR-520/372/373, could be implemented as pharmacological agents for patients with this type of cancer, since it inhibits SPOP translation and decrease tumor size and metastasis (91,95). Also, other small molecules has been proposed to bind to cytoplasmic SPOP, preventing its interaction with substrates such as PTEN or DUSP7 in ccRCC and increasing the cell viability (Figure 5A) (102–104).

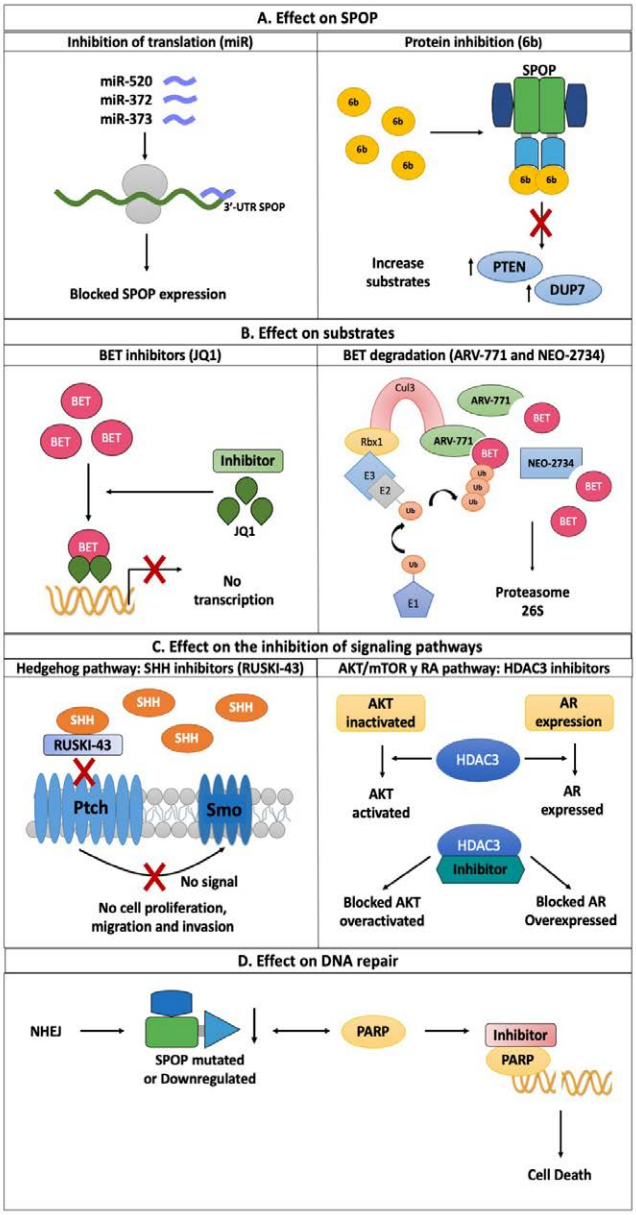

Figure 5. ***Possible therapeutic interventions in tumors with SPOP alterations, according to action mechanisms. A.*** *Inhibition of SPOP expression by miRNAs or small molecules (6b) that bind to the MATH (light blue) domain of SPOP and prevent substrate degradation. B. Effect on SPOP substrates: Inhibitors of its function (JQ1 inhibits BET proteins) or molecules that promote its degradation (PROTAC ARV-771 and NEO2734 promote BET degradation). C. Inhibition of signaling pathways activated by alteration in SPOP (RUSKI-43 inhibits the Hedgehog pathway and the AKT/mTOR and AR pathways by using HDAC3 inhibitors. D. Because of the effect of SPOP on DNA damage, PARP inhibitors may be used to generate effects on DNA repair, inducing cell death.*

In those cases, in which mutations or underexpressed SPOP leads to increased substrates levels, as in EC, inhibitors of BET proteins, such as JQ1 or small molecules called proteolysis targeting chimeras (PROTAC) has been used and may favor patients with overexpressed AR or BET proteins. The designed chimera, ARV-771, has been showing great efficacy against BRD4 with suppression of AR levels and its signaling, leading to tumor regression; also the agent NEO2734, has been proposed as a new BET inhibitor, but its anticancer efficacy on patients is still under study (Figure 5B) (105–109).

It is also possible to block signaling pathways by inhibiting effectors such as the SHH protein by using the RUSKI-43 inhibitor as a therapeutic agent in EC, which suppresses proliferation, migration, and invasion (45,80). In the case of patients with aberrant activation of the AKT/mTOR and AR pathways in PCa, it was found that inhibition of histone deacetylase 3 (HDAC3) can target these pathways, decreasing their activation and suppressing tumor growth in organoids of patients with these characteristics (Figure 5C) (110).

Therapies that affect DNA repair, such as poly (ADP-ribose) polymerase (PARP) inhibitors, could benefit patients with PCa and LC, in which repair has also been affected with SPOP mutations (Figure 5D) (60).

Another study showed that patients with metastatic castration-resistant PCa (mCRPC) with SPOP mutations and/or CHD1 deletions, have a higher response rate to treatment with abiraterone, an androgen synthesis inhibitor, as compared to cases lacking these alterations; however, prospective clinical trials are required to validate this response to treatment (76).

6. SPOPL and cancer

Association and clinical relevance of SPOPL in medulloblastoma have been found. The expression of this isoform is reduced in 75% of biopsies analyzed, and this expression can be related to the level of cell differentiation and the 5-year cumulative survival when compared to patients with increased expression. This suggests that SPOPL could function as a biomarker of poor prognosis in patients with medulloblastoma (23).

Conclusion

Evidence shows that SPOP is a multifunctional adaptor protein, which plays a very important role in maintaining and regulating cell cycle, cell proliferation, response to DNA damage, epigenetic control, and transcriptional control, among others, through ubiquitination and degradation of a large number of substrates. Mutations or changes in the expression of the protein, which trigger tumor progression are evident in different types of cancer, showing the role of SPOP as a tumor suppressor gene or oncogene, and this has been associated with clinicopathological characteristics, which allows considering SPOP as a prognostic biomarker with potential targeted therapies. Given that the adapter protein acts differently in different types of cancer, also depending on the substrates, it is important to do further research on the molecular and biochemical mechanisms involved in carcinogenesis generated by SPOP, to improve understanding of its role in each of these malignancies, aiming at a better classification and association with outcomes.

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