Role of Sam68 in different types of cancer (Review)

CARLOS JIMÉNEZ-CORTEGANA[1], FLORA SÁNCHEZ-JIMÉNEZ[1,2], LUIS DE LA CRUZ-MERINO[3-5] and VÍCTOR SÁNCHEZ-MARGALET[1,2,5]

[1]Department of Medical Biochemistry, Molecular Biology and Immunology, School of Medicine, University of Seville, 41009 Seville, Spain; [2]Department of Laboratory Medicine, Virgen Macarena University Hospital, 41009 Seville, Spain; [3]Department of Medicine, School of Medicine, University of Seville, 41009 Seville, Spain; [4]Medical Oncology Service, Virgen Macarena University Hospital, 41009 Seville, Spain; [5]Institute of Biomedicine of Seville, Virgen Macarena University Hospital, Consejo Superior de Investigaciones Científicas, University of Seville, 41013 Seville, Spain

Received July 8, 2024; Accepted September 24, 2024

DOI: 10.3892/ijmm.2024.5444

Abstract. Src-associated in mitosis 68 kDa protein (Sam68) is a protein encoded by the heteronuclear ribonucleoprotein particle K homology (KH) single domain-containing, RNA-binding, signal transduction-associated protein 1 (known as *KHDRBS1*) gene in humans. This protein contains binding sites for critical components in a variety of cellular processes, including the regulation of gene expression, RNA processing and cell signaling. Thus, Sam68 may play a role in a variety of diseases, including cancer. Sam68 has been widely demonstrated to participate in tumor cell proliferation, progression and metastasis to be involved in the regulation of cancer stem cell self-renewal. Based on the body of evidence available, Sam68 emerges as a promising target for this disease. The objectives of the present included summarizing the role of Sam68 in cancer murine models and cancer patients, unraveling the molecular mechanisms underlying its oncogenic potential and discussing the effectiveness of antitumor agents in reducing the malignant effects of Sam68 during tumorigenesis.

Contents

Correspondence to: Dr Luis de la Cruz-Merino, Medical Oncology Service, Virgen Macarena University Hospital, Av. Dr Fedriani 3, 41009 Seville, Spain
E-mail: ldelacruzmerino@gmail.com

Professsor Víctor Sánchez-Margalet, Department of Laboratory Medicine, Virgen Macarena University Hospital, Av. Dr Fedriani 3, 41009 Seville, Spain
E-mail: margalet@us.es

Key words: Sam68, KHDRBS1, cancer, RNA-binding protein, tumorigenesis, cancer-stem cells

1. Introduction

The Src-associated in mitosis 68 kDa (Sam68) protein, also known as KH domain-containing, RNA-binding, signal transduction-associated protein 1 (KHDRBS1) due to the gene encoding this protein in humans, was first identified as a molecule phosphorylated by the tyrosine kinase c-SRC during mitosis (1). Sam68 belongs to the signal transduction and activation of RNA metabolism family of RNA-binding proteins (RBPs). This group of proteins contains a glycine-rich protein 33/SAM68/GermLine development defective 1 (also known as GSG) domain for RNA binding and homodimerization (2). Sam68 contains a set of protein domains that allow protein-protein interactions and modifications via multiple pathways. These pathways include six proline-rich sequences enabling interaction with signaling molecules through SRC homology (SH)3 and WW domains, and a tyrosine-rich region at the C-terminus, which form docking sites for signaling proteins that contain SH2 and/or SH3 domains (2).

Due to its high RNA-binding activity and protein-protein interaction domains, Sam68 is considered a multifunctional protein. Sam68 is found in a variety of tissues and cells and has a key role not only in cytosolic cell signaling (3), but also in numerous other processes. These processes include both pre-mRNA and microRNA (miRNA) processing [e.g., spinal muscular atrophy or spermatogenesis, respectively (4,5)]; RNA transport [e.g., human immunodeficiency virus type 1 (6)]; signal transduction [e.g., polycystic ovary syndrome (7)]; alternative splicing [e.g., multiple sclerosis (8)]; and cell cycle progression [e.g., ovarian or prostate cancers (PC) (9,10)]. On another note, Sam68 is also a component of structures such as ribonucleoprotein complexes or subnuclear organelles (11,12). In this sense, Sam68 has a key role in a variety of cellular events, including cell proliferation and growth, be it as a tumor suppressor or as a proto-oncogene regulating cell-cycle

progression and apoptosis through RNA-dependent and RNA-independent mechanisms (11-13). Accordingly, Sam68 overexpression has been found in different types of cancer, which may ultimately promote disease progression and metastasis.

2. Post-transcriptional modifications of Sam68 in cancer

The activity of Sam68 in cellular processes is regulated by post-transcriptional modifications, including tyrosine, serine and threonine phosphorylation mechanisms (Fig. 1), as well as (de)acetylation, arginine methylation and ubiquitination (Fig. 2) (12). During oncogenesis, these mechanisms have been shown to ultimately promote the development and proliferation of malignant cells.

Sam68 phosphorylation. Sam68 seems to play a critical role in cancer, particularly by tyrosine phosphorylation-mediated mechanisms. In 1994, phosphoprotein Sam68 was first identified and described as a mitotic target for tyrosine kinase Src, a mediator of epidermal growth factor (EGF) receptor signaling in breast cancer (BC) cells (14). A variety of studies have demonstrated tyrosine phosphorylation of Sam68 by the Src protein family in numerous settings, including cancer (15-22). The breast tumor kinase (BRK) is an intracellular tyrosine kinase that is overexpressed in BC and boosts EGF response. This kinase was shown to phosphorylate Sam68 on all three tyrosine residues in the nuclear localization signal, with tyrosine 440 being the main Sam68 modulator in BC cells *in vitro* (23). In the same sense, Sam68 tyrosine phosphorylation was found to be augmented in cholangiocarcinoma (CC) livers and CC cell lines, as compared to normal livers and human cholangiocyte cells. Elevated Sam68 tyrosine phosphorylation was also associated with elevated levels of BRK protein and tumor cell proliferation (24). Of note, a study demonstrated that BRK remains in the cytoplasm of PC cells. However, while Sam68 phosphorylation remained intact, BRK overexpression was not sufficient to transport BRK into the nucleus, its most frequent location in normal prostatic epithelial cells (25). Another study examining prostate tumors reported that Sam68 was only phosphorylated in those tumors that expressed a truncated form of the c-Kit tyrosine kinase, which is found in high-grade tumors (26-28).

Hyperleptinemia and hyperinsulinemia induce a proinflammatory state in obesity that increases BC risk (29). As Sam68 has been found to be tyrosine-phosphorylated in BC (27,28), its phosphorylation has also been investigated in patients with these disorders. It was found that insulin receptor (IR) tyrosine phosphorylates Sam68, which allows it to interact with the SH2 domains of p85, the regulatory subunit of phosphoinositide 3-kinase (PI3K) (30). Leptin has been demonstrated to increase Sam68 tyrosine phosphorylation via Janus kinase/IR substrate (IRS-1)/p85/PI3K signaling; consequently, leptin decreases the ability of Sam68 to bind RNA, while it mediates the survival, growth and proliferation of BC cell lines (31) and JEG-3 choriocarcinoma cells (32). Finally, these changes may ultimately promote abnormal placental development and tumor growth (32,33). Under insulin conditions, IRS-1, which has been found in the nucleus of BC cells (34), binds Sam68 following tyrosine phosphorylation by IR in BC cells *in vitro* (31). However, it remains elusive whether Sam68 is directly tyrosine-phosphorylated by IR, as suggested by the results obtained in HTC hepatoma cells (35), and whether Sam68 binds intracellular or nuclear IRS-1.

Serine/threonine phosphorylation of Sam68 has also been studied in cancer. Sam68 has been shown to be threonine-followed-by-proline phosphorylated by the RAS-MAPK/ERK kinase (MEK)1/2-ERK1/2 pathway in mouse EL4 T-lymphoma cells to enhance Sam68-dependent exon v5 inclusion in *CD44* pre-mRNA (36). In addition, serine/threonine has been demonstrated to be phosphorylated by cyclin-dependent kinase (CDK)1 at T33 and T317. Furthermore, there is evidence that this protein kinase reduces the ability of Sam68 to bind RNA, as it downregulates its alternative splicing activity, thus limiting apoptosis and promoting the proliferation of HCT116 colon cells (37).

Sam68 (de)acetylation. Protein acetylation is a reversible post-transcriptional modification involved in a variety of cellular processes. Its abnormal action has been associated with multiple disorders, including cancer (38). Acetylation is widely known to influence the activity of DNA-binding proteins. Of note, Sam68 was the first RBP reported to be also acetylated (28). Histone deacetylase (HDAC) inhibition and the overexpression of the acetyltransferase CREB binding protein (also known as CBP) promote Sam68 acetylation in renal and, most frequently, in BC cell lines. Hence, CREB-mediated Sam68 acetylation enhances the ability of Sam68 to bind RNA for these cell lines, although other acetyltransferases may be involved in this process (28). CBP also takes part in mixed-lineage leukemia (MLL) gene translocations (39,40) and interacts with the extra eleven-nineteen gene-MLL complex via Sam68 (41,42). Sam68 has been demonstrated to be acetylated in a p300-dependent manner (43). In colorectal cancer (CRC) cell lines, butyrate resistance-associated p300 deficiency has been shown to favor CBP-induced acetylation. Consequently, acetylation added to Sam68 activity may affect gene expression and carcinogenesis in CRC cell lines (44).

Of note, ERK-1/2-mediated phosphorylation of the Scaffold/matrix-associated region-binding protein 1 (SMAR1) releases the inhibitory SMAR1-HDAC6-Sam68 complex, facilitating Sam68 acetylation and alternative splicing in BC cells (45).

Sam68 arginine methylation. Protein methylation is involved in a variety of cellular processes and its aberrant action is implicated in cancer. Therefore, protein arginine methyltransferases (PRMTs) have gained interest in numerous tumors as a therapeutic target (46). Sam68 has been shown to independently recruit PRMT1 and promote RNA splicing (41). By contrast, loss of PRMT1 in mouse embryonic fibroblasts led to the downregulation of Sam68 arginine methylation (47). It has also been demonstrated that PRMT1-mediated methylation may be modulated by the silencing of the human CCR4-associated factor 1 in human MCF7 BC cells, which also regulated Sam68 methylation (48). Of note, the protein PRMT2 has been shown to interact with both Sam68 and PRMT1 to boost its activity. In

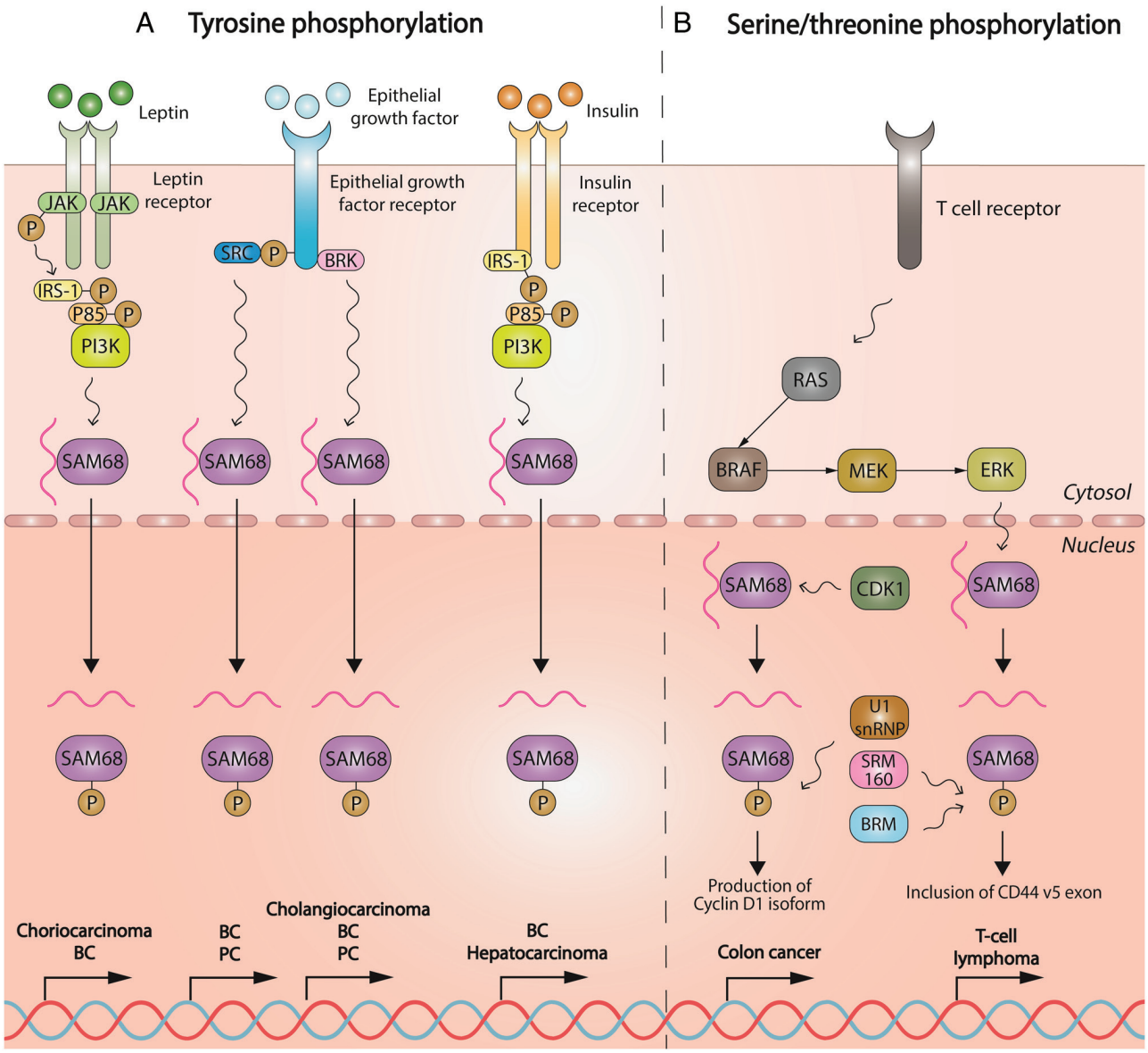

Figure 1. Sam68 phosphorylation in cancer. (A) Tyrosine phosphorylation mechanisms can be driven by i) the Src family kinases and BRK, which mediate epidermal growth factor receptor signaling, and ii) the IRS-1/PI3K pathway, which is promoted under hyperleptinemia and hyperinsulinemia. (B) Serine/threonine phosphorylation mechanisms can be driven by i) T-cell receptor via RAS/BRAF/MEK/ERK signaling to induce the inclusion of the CD44 v5 exon, and ii) CDK1 migrating into the nucleus, which finally promote the production of the cyclin D1 isoform. These mechanisms reduce the ability of Sam68 to bind RNA and promote the transcription of multiple genes involved in oncogenesis. BC, breast cancer; CDK1, cyclin-dependent kinase 1; JAK, Janus kinase; IRS-1, insulin receptor-1; PC, prostate cancer; PI3K, phosphoinositide 3-kinase; Sam68, Src-associated in mitosis 68 kDa; BRK, breast tumor kinase; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; BRAF, B-Raf proto-oncogene.

addition, Sam68 regulates subcellular PRMT2 localization via the SH3 domain in HeLa cells. These findings suggest a role of PRMT2 during inflammation in Sam68-mediated alternative splicing regulation (49).

Sam68 ubiquitination. Aberrant protein ubiquitination also has a crucial role in tumorigenesis (50). Specifically, the ubiquitin-like protein small ubiquitin-related modifier (SUMO) may be a regulator of Sam68 in cancer development. SUMO-1 protein levels have been found to be elevated in acute myeloid leukemia cells and to transform human pluripotent stem cells. This activity may affect nuclear abundance of Sam68 (51). Also, Sam68 was modified by SUMOylation at its first lysine at the amino-terminal region to repress cyclin D1 expression, ultimately inhibiting its ability to induce apoptosis of human renal 293T cells (42,52).

3. Role of Sam68 in preclinical tumor models and cancer patients

As shown in Tables I and II, the role of Sam68 has been studied in a variety of cancer mouse models and cancer patients, respectively. There is evidence that Sam68 plays a critical role by not only promoting tumor cell development and proliferation, but also by regulating self-renewal in cancer stem cells (CSCs). Consistently, Sam68 regulated the self-renewal of

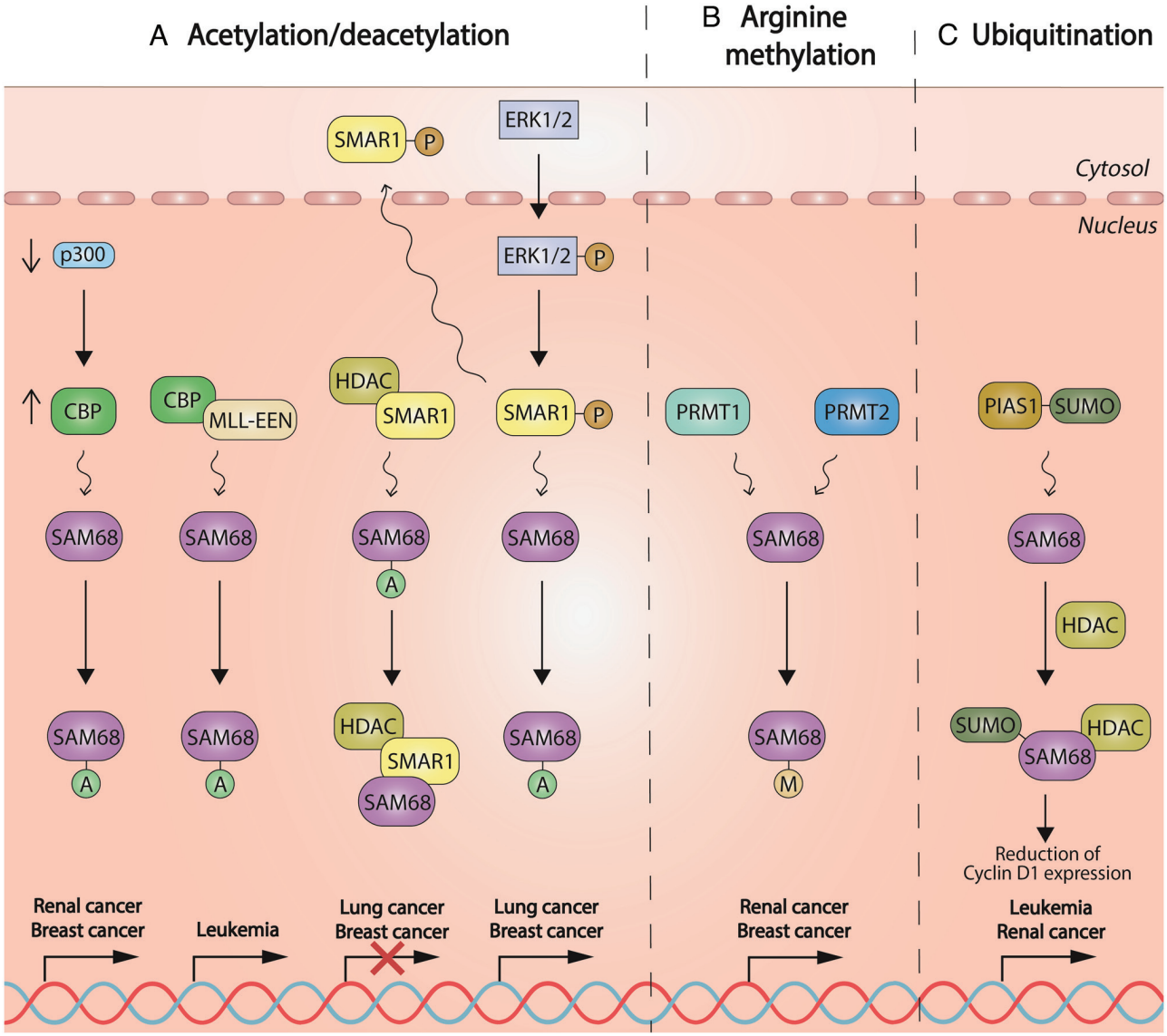

Figure 2. Sam68 acetylation, arginine methylation and ubiquitination in cancer. (A Acetylation is mediated by i) *CBP* overexpression, which may be produced via p300 deficiency, ii) interactions between CBP and the EEN-MLL complex, or iii) ERK-1/2-mediated phosphorylation of SMAR1 to release this protein into the cytoplasm. On the contrary, the SMAR1-HDAC6 complex binds Sam68 to promote its deacetylation. (B) PRMTs interact with Sam68 to induce its arginine methylation. (C) Ubiquitination is mainly produced by the SUMO protein (SUMOylation) via interaction with PIAS-1 and HDAC to repress cyclin D1 expression. These mechanisms finally promote the transcription of multiple genes involved in oncogenesis. CBP, CREB binding protein; ERK, extracellular signal-regulated kinase; HDAC, histone deacetylase; MLL-EEN, mixed lineage leukemia-extra eleven nineteen complex; PIAS, protein inhibitor of activated STAT1; PRMT, protein arginine methyltransferase; SMAR1, scaffold/matrix-associated region-binding protein 1; SUMO, small ubiquitin-related modifier; Sam68, Src-associated in mitosis 68 kDa.

neural stem/progenitor cells via the modulation of the aldehyde dehydrogenase 1 family member A3 (ALDH1A3) (53). ALDH1A3 is a protein that promotes self-renewal and clonogenicity in glioma stem cells (54). This finding implies that the Sam68/ALDH1A3 pathway may be involved in the stemness of cancer cells, although the evidence available is not sufficient.

Sam68 in BC. Sam68 has been demonstrated to be involved in tumorigenesis by modulating CSC self-renewal. NF-κB, a DNA transcription factor acting as a key regulator during oncogenesis (55,56), is involved in the underlying mechanism (57).

Other studies have shown the influence of Sam68 in the self-renewal capacity of breast CSCs; these studies focused on the tumor-derived spheroids responsible for the enrichment of CSCs or cells with stem cell-related characteristics (58,59). Investigation of mammosphere formation in NOD/SCID mice revealed that SKBR-3-Sam68 BC cells had a significantly higher weight compared to SKBR-3-vector tumor cells. In addition, Sam68 activated the Wnt/β-catenin pathway and Sam68 protein expression was negatively correlated with miRNA-204 expression (60). MiRNA-204 is a tumor suppressor miRNA that inhibits cancer cell proliferation and invasion in multiple types of cancer (61-63), which may be useful for diagnosis (64). In the same sense, the Wnt/β-catenin signaling pathway has been found to be activated by Sam68 in MDA-MB-231 BC-bearing mice (a breast CSC-like model), compared to MCF-7 BC-bearing mice (a breast non-CSC-like

Table I. Impact of Sam68 expression and protein levels in murine tumor models.

Type of cancer	Mouse model	Impact of Sam68 expression/protein level	(Refs.)
Breast	DB7 and Met-1 cells	• Sam68 may be involved in the epithelial-mesenchymal transition to promote altered cellular morphology, loss of cell adhesion and gain of migratory ability • Sam68 haploinsufficiency delayed mammary tumor onset • Sam68 may be a modulator of tyrosine kinase activity to promote tumorigenesis and metastasis	(13)
	MDA-MB-231 and MCF7 cells	Sam68 was overexpressed in mouse models, particularly in those bearing the CSC-like population (MDA-MB-231) compared with the non-CSC-like population (MCF7)	(51)
	MDA-MB-231 cells	Sam68 deficiency inhibited tumor growth and metastasis	(69)
	$BRCA^{mut}$ and BCSphCs	• Sam68 silencing delayed tumor growth in xenograft mice • Sam68 knockout mice experienced delayed tumor growth and improved survival	(65)
	SKBR-3 cells	Mammosphere formation assays in NOD/SCID mice demonstrated significant tumor weights from inoculated SKBR-3-Sam68 cells compared to tumors from injected SKBR-3-vector cells	(60)
Colorectal	$Apcmin^{716/+}$	• Sam68 expression was higher in tumors compared to adjacent normal tissue • Sam68 expression promoted tumor growth and reduced survival rates	(86)
	AOM	p53 status may influence the role of Sam68 during tumorigenesis, since Sam68 deficiency enhanced AOM tumors in wild-type mice, whereas Sam68-haploinsufficiency delayed the onset of spontaneous tumors in p53-deficient mice	(90)
	HT29 and SW480 cells	Sam68 expression was markedly higher in the CSC-like mouse model (HT29 tumor-bearing mice) compared with the non-CSC-like mouse model (SW480 colon cancer cells)	(51)
Gastric	EBVaGC	Sam68 expression levels were positively correlated with the expression of cancer-related proteins, such as METTL3 and Ki-67	(93)
	AGS cells	Sam68 overexpression promoted cell growth and lung metastasis in the mouse model, particularly its transcript with a shorter 3'UTR	(91)
Glioblastoma	T98G cells	• Sam68 deficiency was associated with tumorigenesis • Decrease of Sam68 protein levels was a feature of cell mitosis	(113)
Lung	NCI-H1975 cells	The Sam68 knockout NCI-H1975 model had a lower risk of cancer-related death compared to control mice	(82)
Prostate	PC3 y LNCaP cells	Sam68 was found in high-grade prostate tumors and its localization was unchanged compared with its expression pattern in normal tissues, whereas breast tumor kinase showed loss of nuclear localization in the less-differentiated tumors	(74)
	PC3 cells	Disruption of Sam68 revealed disorganization of cancer cell-specific perinucleolar bodies that suggested nonapoptotic cancer cell death together with the downregulation of c-Myc expression	(78)
Renal	NC-65 cells	Downregulation of Sam68 reduced sunitinib sensitivity, which weakened tumor growth inhibition by inhibiting cell apoptosis	(111)
Skin	$Gli2^{tg/+}$	• Sam68 was elevated in skin lesions of Gli-2 transgenic mice • Sam68 participated in regulating DNA damage responses to promote growth and survival of non-melanoma skin cancer	(96)
Testicular	$Sam68^{-/-}$	Sam68-deficiency mouse testis were found to havedownregulation of numerous genes, including those involved in cancer	(97)
Tongue	SCC-9 cells	• Upregulation of Sam68 inhibited cisplatin-induced apoptosis in mice bearing oral tongue squamous cell carcinoma cells, associated with the induction of anti-apoptotic proteins caspase-9, caspase-3 and PARP • Sam68 silencing enhanced the sensitivity of cancer cells to apoptosis induced by cisplatin	(95)

CSC, cancer stem cell; AOM, azoxymethane; Sam68, Src-associated in mitosis 68 kDa; METTL3, m6A methyltransferase; Gli-2, glioma-associated oncogene family zinc finger 2; PARP, poly(ADP-ribose) polymerase.

Table II. Impact of Sam68 expression and protein levels in oncological patients.

Type of cancer	Impact of Sam68 expression/protein level	(Refs.)
Bladder	• Sam68 expression was elevated in muscle invasive bladder cancer compared to normal urothelium and non-invasive tumors	(104)
	• Sam68 may be a promising prognostic marker for muscle invasive bladder cancer	
Breast	• Sam68 was overexpressed in 52% of tumors	(70)
	• Not only Sam68 but also PTEN, MAPK and p-MAPK were significantly correlated with PTK6 expression and poor outcomes	
	• Sam68 expression was overexpressed in cancer tissue and associated with lymph node metastasis	(69)
	• MMP-9 was also found overexpressed and associated with Sam68 expression	
	• Different levels Sam68 expression were found in cancer cells but barely found in normal/adjacent healthy tissue	(65)
	• There was a negative correlation between Sam68 expression and distant relapse-free survival probability in luminal A and triple-negative breast cancer	
	• Association between Sam68 and β-catenin nuclear expression in cancer tissue	(60)
	• miR-204 was significantly reduced in cancer tissue and may boost *Sam68* 3'-UTR activity	
	Sam68 expression was positively correlated with clinical stage, tumor-nodes-metastasis, histological grade and estrogen receptor expression	(71)
Cervical	Sam68 may induce early-stage cervical cancer lymph node metastasis via epithelial-mesenchymal transition	(103)
Colorectal	• Sam68 levels were significantly increased in 94.1% of patients compared to adjacent healthy tissue from the same patient	(86)
	• Sam68 expression was positively correlated with increased PAR and phospho-p65 levels	
	Sam68 affected cell growth and glycolysis pathway by regulating the alternative splicing and expression of PKM2 in colorectal cancer	(87)
	Sam68/Set7/9 co-expression was positively associated with better survival rates	(88)
	Sam68 expression was higher in cancer stem cell-enriched spheroids derived from patients with colorectal cancer	(85)
Endometrial	Sam68 expression positively correlated with the FIGO stage and deep myometrial invasion compared to superficial myometrial invasion	(105)
Esophageal squamous cell carcinoma	Sam68 may activate the Akt/GSK-3β pathway to promote tumor cell proliferation and progression	(106)
Gastric	Sam68 expression was associated with poor prognosis	(92)
	Sam68 expression was significantly correlated with the Lauren classification, lymph node metastasis and distant metastasis in EBV-associated gastric cancer	(93)
	Sam68 expression was markedly increased in cancer tissue compared to paracancer tissue	(91)
Glioblastoma	• Sam68 expression was upregulated in tumor tissue	(112)
	• High Sam68 expression was correlated with an unfavorable prognosis	
Hepatocellular	Sam68 expression was significantly increased in cancer patients and positively correlated with the Edmondson grade, tumor size, tumor nodule number, HBsAg status and Ki-67 expression, and associated with poor prognosis	(109)
Kidney	• Sam68 expression was similar in normal and cancer tissue from patients with kidney renal papillary cell carcinoma	(84)
	• However, Sam68 was significantly spliced by the uc001bub isoform compared with the uc001bua and uc001buc isoforms in cancer tissue, suggesting that Sam68 may be a prognostic marker	
Leukemia	Sam68 expression was upregulated in patients with T-cell acute lymphoblastic leukemia	(98)
	• Sam68 was highly overexpressed in blood cancer stem cells	(51)
	• Sam68 may alter transcription in the interaction between cancer stem cells and CBP	
Lung	High Sam68 expression was found to predict poor prognosis of non-small cell lung cancer	(80)
	• High Sam68 expression resulted in poor prognosis in non-small cell lung cancer	(83)
	• Sam68 promoted cell proliferation via activating the Wnt/β-catenin signaling pathway	

Table II. Continued.

Type of cancer	Impact of Sam68 expression/protein level	(Refs.)
	Patients with higher Sam68 expression exhibited higher death rates and shorter survival times compared with their low-Sam68-expression counterparts	(82)
	Patients with high OGT and high Sam68 expression had poorer overall survival compared to those with low OGT and low Sam68 expression	(81)
	• Sam68 was associated with poor survival rates • An electrochemical immunosensor for the detection of Sam68 was developed for the first time and exhibited an excellent analytical performance to predict the pathological state	(79)
	• Sam68 expression was similar in normal and cancer tissue from patients with lung squamous cell carcinoma • However, Sam68 was significantly spliced by the uc001bub isoform compared with the uc001bua and uc001buc isoforms in cancer tissue, suggesting that Sam68 may be a prognostic marker	(84)
Neuroblastoma	• Sam68 expression was significantly higher in cancer tissues compared to their matched adjacent healthy tissues • Sam68 knockdown reduced the proliferation, migration and invasion of human neuroblastoma cells *in vitro*	(99)
	Sam68 expression was positively correlated with age, clinical stage, tumor histology and distant metastasis, and associated with shorter survival time	(100)
Non-Hodgkin lymphoma	• Sam68 expression was found to be increased in diffuse large B-cell lymphomas and four reactive lymphoid hyperplasia tissues • Sam68 expression was correlated with poor clinical outcomes and positively associated with tumor cell proliferation	(107)
Oral squamous cell carcinoma	• Nuclear Sam68 expression was significantly observed in cancer cells, whereas its expression in adjacent healthy mucosal epithelium was mainly moderate • Cytoplasmic Sam68 expression was mostly negative • High Sam68 expression was notably correlated with advanced pathological T stage, positive lymphovascular invasion and pathological cervical lymph node metastasis	(94)
Ovarian	• Sam68 was overexpressed at the mRNA and protein levels in epithelial ovarian tumor tissue • Sam68 may accelerate cell cycle progression, since its expression was associated with the FIGO stage, residual tumor size, histological grade and lymph node metastasis	(101)
	High Sam68 expression was correlated with poor prognosis in patients with epithelial ovarian cancer	(9)
Pancreatic	Sam68 was required by Fyn and hnRNPA2B1 to regulate apoptosis, induce the proliferation of pancreatic cancer cells and promote metastasis	(102)
Prostate	Sam68 was found in high-grade prostate tumors and its localization was unchanged compared with its expression pattern in normal tissues	(74)
	Sam68 was detected in all grade 7-9 hypertrophic prostate tumors that expressed tr-Kit	(26)
	Sam68 expression promoted cancer cell proliferation and resistance to cytotoxic agents	(75)
	Sam68 was significantly overexpressed in prostate cancer biopsies	(76)
	Sam68 expression was significantly associated with XRN2 and a high Gleason score, which indicates disease progression in prostate cancer	(10)
	Positive correlation between Sam68 expression and the Cyclin D1 proto-oncogene in cancer tissue	(72)
	Correlations between Sam68 expression and the transcription factor c-MYC in cancer patients	(73)
Renal	• Sam68 was notably overexpressed in cancer tissues at both the transcriptional and translational levels • Patients with high Sam68 expression had shorter overall survival rates compared to those with low SAM68 expression • Cytoplasmic Sam68 was significantly correlated with the clinicopathologic grade and outcomes	(110)
	• Sam68 expression was significantly higher in sunitinib-sensitive tumors than in sunitinib-resistant tumors • Sam68 was mostly located in the nucleus in sunitinib-sensitive tumors	(111)

Table II. Continued.

Type of cancer	Impact of Sam68 expression/protein level	(Refs.)
Sacral chordoma	• Sam68 had a positive correlation with time to progression in clear-cell renal cell carcinoma • Sam68 was significantly upregulated in cancer tissues compared with normal tissues • Sam68 was significantly associated with surrounding muscle invasion and shorter local recurrence-free survival time	(108)
Thyroid	Variable Sam68 and Sam68DKH isoform expression in not only thyroid cancer tissue (depending on the subtype: Follicular or papillary), but also normal thyroid tissue	(21)

FIGO, International Federation of Gynecology and Obstetrics; Sam68, Src-associated in mitosis 68 kDa; XRN2, 5'-3'exoribonuclease 2; hnRNPA2B1, heterogenous nuclear ribonucleoprotein A2/B1; CBG, corticosteroid-binding globulin; OGT, O-linked N-acetylglucosamine (GlcNAc) transferase; HBsAg, Hepatitis B surface antigen; EBV, Epstein-Barr virus; GSK-3β, glycogen synthase kinase 3β; PKM2, pyruvate kinase muscle 2; PAR, polymers of ADP-ribose; PTK6, protein tyrosine kinase 6; p-MAPK, phosphorylated MAPK; PTEN, phosphatase and tensin homolog.

model) (51). This finding suggests a stronger role of Sam68 during tumor initiation.

Similarly, stem-like cells from spheroids in triple-negative BC-bearing mice expressed high levels of Myc, which required the presence of Sam68 for DNA-damage repair (65). Also, Sam68 gene inhibition caused defects in the poly(ADP-ribose) polymerase (PARP)-induced PAR chain synthesis upon DNA damage. This resulted in cancer cell death, delayed tumor growth and improved survival rates (65), thus demonstrating a key role of Sam68 in CSC-mediated oncogenesis.

Sam68 was also shown to be a regulator of tyrosine kinase activity *in vivo* and essential in mammary tumorigenesis and metastasis. In a study in nude mice, Sam68 haploinsufficiency delayed tumor progression and metastasis formation driven by the polyoma middle T-antigen (PyMT) oncogene. Furthermore, Sam68 knockdown limited the tumor burden in PyMT-transformed cell lines (13). Similarly, matrix metalloproteinase (MMP)-9, mainly produced by BC cells for invasion and metastasis (66), has been found to be overexpressed in mouse cancer tissue. In addition, MMP-9 correlated with Sam68 expression, which, in turn, upregulated the pro-tumorigenic ephrin tyrosine kinase a3 (EPHA3) gene (67,68) to boost metastasis (69).

Of note, certain proteins with tumor-promoting properties have been found to be associated with Sam68 in patients with BC but not in BC murine models. In this sense, disease-free survival of patients with BC has been associated with BRK6 expression in tumor tissue. In turn, BRK6 expression was significantly correlated with the expression of Sam68 and other signaling proteins such as phosphatase and tensin homolog, ERK and p-ERK (70). MMP-9 has been proven to correlate with Sam68 expression along with lymph node metastasis, suggesting a role in epithelial-mesenchymal transition (69).

In light of the evidence available, Sam68 plays a major role in all stages of oncogenesis. Indeed, Sam68 has been identified as an independent negative prognostic factor for BC (71), particularly in luminal A and triple-negative BC (65), and emerges as a promising therapeutic target in this disease.

Sam68 in PC. The association between Sam68 overexpression and PC cell proliferation and poor outcomes has been consistently demonstrated in different clinical settings (72,73). However, there is a paucity of data from murine models as compared to patients (10,26,74-76). Sam68 has been documented to be phosphorylated by BRK in PC-bearing mice to inhibit the Sam68 RNA-binding capacity and lead to uncontrolled cell cycle progression (74). Of note, Sam68 has been detected in the nuclei of luminal epithelial cells and to be unaltered in high-grade prostate tumors. By contrast, nuclear localization of BRK correlated with higher BRK activity in a more differentiated prostate tumor cell line (LNCaP, poorly differentiated tumorigenic cells), whereas cytoplasmic localization of BRK correlated with decreased BRK activity in a poorly differentiated prostate tumor cell line (PC3, more aggressive cell line) (74).

Regarding LNCaP PC cells, Sam68 has been phosphorylated and detected in grade 7-9 hypertrophic prostate tumors that expressed a truncated form of the c-Kit tyrosine kinase receptor (26). Of note, Sam68 may also interact with the androgen receptor (AR) to co-regulate AR-dependent transcription and modulate AR-dependent alternative splicing. These effects are exerted by enhancing the recruitment of a Sam68-responsive exon transcribed to androgen response elements within the promoter region of the prostate-specific antigen gene (76). This activity ultimately promotes cancer development and progression. In fact, downregulation of Sam68 has resulted in the reduction of both cell cycle progression and PC cell proliferation (75,77).

Similarly, in a PC3 murine model, an antitumor hemisynthetic cardenolide called UNBS1450 showed effectiveness *in vitro* and *in vivo* in impairing c-Myc expression and disrupting Sam68 nuclear bodies. These nuclear bodies consisted of Sam68 protein, nucleolar proteins and nucleic acids. According to the authors, Sam68 nuclear bodies delayed the proliferation of PC3 cells but not of normal cells *in vitro* (78). These findings suggest a critical role of Sam68 in PC, emerging as a promising therapeutic target in the disease.

Sam68 in lung cancer. High Sam68 expression has been shown to be protumorigenic in lung cancer (79) and has been suggested as an independent prognostic marker for overall survival (80). In lung adenocarcinoma (LUAD) cells, Sam68

undergoes *O*-GlcNAcylation, a post-translational protein modification catalyzed by *O*-GlcNAc transferase associated with LUAD aggressiveness and poor survival rates (81). In the same sense, Sam68 was demonstrated to switch the metabolism of glucose from oxidative phosphorylation to glycolysis in LUAD cells. Sam68 activity promoted LUAD cell proliferation by regulating the alternative splicing of pyruvate kinase muscle (PKM)2, a key enzyme in glycolysis-dominant energy metabolism in tumor cells (82). This means that patients with elevated Sam68 expression are at a higher risk of tumor recurrence and cancer-related death and shorter overall survival rates, as compared to patients with reduced Sam68 expression (82).

High Sam68 expression has also been found in non-small cell lung cancer (NSCLC) tissue compared to adjacent non-cancerous tissue. In addition, Sam68 expression correlated with lymph node metastasis, advanced tumor grade and poor prognosis (80,83). Similarly, NSCLC cell lines show high Sam68 expression and its knockdown inhibited tumor cell proliferation, colony formation and cell cycle progression via Wnt/β-catenin pathway inhibition (83). By contrast, in lung squamous cell carcinoma, a type of NSCLC, Sam68 expression was similar in normal and tumor tissue; however, Sam68 was spliced by the uc001bub isoform in normal tissue, whereas it was spliced by the uc001bua and uc001buc isoforms in tumor tissue, suggesting a potential role for Sam68 as a prognostic marker in this disease (84).

Of note, an electrochemical immunosensor has been developed for Sam68 protein quantification. The sensor was successfully tested in lung cancer patients, showing a good analytical performance and sensitivity, as compared to ELISA kits (79). This means that Sam68 protein can be tested and quickly quantified in other types of tumors.

Sam68 in CRC. As in BC, Wnt/β-catenin signaling has been demonstrated to be involved in CSC-mediated tumor initiation via Sam68 in patients with colon cancer (85). This signaling pathway was found to be strongly activated by Sam68 in the HT29 colon CSC-like model, as compared to the SW480 non-CSC-like model (51). In line with these results, Sam68 upregulation was correlated with both increased PAR production and NF-κB-mediated anti-apoptotic transcription. Furthermore, Sam68 genetic deletion limited the tumor burden. These results suggest a novel role for this RBP in genotoxic stress-initiated nuclear signaling, which is crucial for colon tumorigenesis (86). Consistently with those notions and similarly to LUAD (see above), Sam68 drove glycolysis in CRC cells via alternative splicing of PKM2, which resulted in CRC cell proliferation (87).

However, the protumoral role of Sam68 in CRC and colon tumors may not be as evident as in other types of cancer. In a study, the lysine-specific methyltransferase Set7/9 methylated Sam68 and its knockout reduced the levels of Sam68 protein in human colon cancer cells. This activity resulted in an altered regulation of the cell cycle and apoptosis, which explains the association between high levels of Sam68-Set7/9 co-expression and improved survival rates (88). On another note, it should be taken into account that the p53 status may influence the role of Sam68 in tumor development (89). At least in colon cancer *in vivo*, Sam68 may not only have a tumor-promoting role in p53-deficient mice, but also a tumor-suppressive role in mice expressing wild-type p53 (90).

Sam68 in other types of tumor. To a lesser extent, Sam68 has also been studied in other types of tumors in both mice and humans, and its expression has been unfailingly associated with cell proliferation, transformation, tumorigenesis and metastasis.

There is evidence of a high expression of the Sam68 isoform with a shortened 3'untranslated region (3'UTRs) due to alternative polyadenylation in gastric cancer tissue, as compared to paracancer tissue. Overexpression of Sam68 3'UTRs drives tumor progression, as it helps Sam68 miRNA escape from miRNA-mediated gene inhibition (91). Therefore, Sam68 3'UTR expression is elevated in gastric cancer, being associated with a higher grade of malignancy and, ultimately, with poor prognosis (92). Of note, *in vitro* Sam68 knockdown reduced cell cycle progression and gastric cancer cell migration and invasion (92). The circular RNA Epstein-Barr virus (ebv)-circular RNA ribosomal protein S13 (circRPMS1) was overexpressed in EBV-associated gastric carcinoma (EBVaGC). In addition, the binding of ebv-circRPMS1 to Sam68 activated m6A methyltransferase (METTL3) transcription, resulting in EBVaGC cell proliferation, migration and invasion. This mechanism was ultimately associated with distant metastasis and poor prognosis in clinical EBVaGC samples (93).

In oral tongue squamous cell carcinoma (OTSCC), Sam68 overexpression was significantly associated with lymphovascular invasion and pathological cervical lymph node metastasis in cancer patients (94). Sam68 was also shown to play a role in an OTSCC murine model. According to a study, high Sam68 expression significantly inhibited cisplatin-induced apoptosis. This resulted in the induction of anti-apoptotic proteins such as caspase-9, caspase-3 and PARP, whereas Sam68 silencing markedly boosted the sensitivity of cancer cells to apoptosis (95).

Sam68 has also been found to be highly expressed in skin lesions from glioma-associated oncogene family zinc finger 2-transgenic mice with nonmelanoma skin cancer. A study suggested that Sam68 regulates discoidin domain receptor in keratinocytes and promotes the growth and survival of cancer cells via the NF-κB signaling pathway (96). In addition, Sam68 deficiency in mouse testis has been associated with infertility and defects in spermatogenesis due to the downregulation of genes involved in the cell cycle, cell death, cell-to-cell signaling and interaction, and cancer. This evidence suggests that Sam68 not only plays a role in the development of functional male gametes, but it may also be involved in testis cancer (97). However, the role of Sam68 in skin and testis cancer has not yet been assessed in clinical patients.

Sam68 expression has also been analyzed in certain types of human tumors rather than murine tumors. In these studies, Sam68 was shown to act as a regulator of human CSC vulnerability and increase tumor cell proliferation, migration and invasion. Thus, Sam68 has been identified as a promising prognostic factor for leukemia (51,98); neuroblastoma (99,100); epithelial ovarian cancer (9,101); PC (102); cervical cancer lymph node metastasis (103); muscle invasive bladder cancer (104); endometrial carcinoma (105);

esophageal squamous cell carcinoma (106); non-Hodgkin's lymphoma (107); sacral chordoma (108); and hepatocellular carcinoma (109).

Sam68 also plays a key role in the development of renal cell carcinoma (RCC). Evidence suggests that Sam68 is overexpressed in RCC cell lines and cancer tissue, is positively associated with disease stage and severity, and is linked to shorter overall survival rates (110). Sunitinib downregulated phosphorylated Sam68 expression and, in turn, inhibited RCC cell apoptosis in murine models (111). Similarly, Sam68 has been found to be upregulated in human glioblastoma tumor tissue, and its expression was associated with poor prognosis; therefore, it has been suggested as a therapeutic target in this disease (112). By contrast, Sam68 deficiency has been associated with neoplastic transformation of murine NIH3T3 fibroblasts, defective contact inhibition and the development of metastatic tumors in glioblastoma-bearing nude mice after tyrosine phosphorylation (113).

4. Sam68 as a therapeutic target in cancer

As outlined in section 2, Sam68 is regulated post-translationally via multiple pathways, including tyrosine phosphorylation by the Src tyrosine kinase (114), or SUMOylation by the SUMO-1 protein (51). This regulation provides Sam68 with oncogenic properties that regulate cell cycle and promote tumor cell survival, growth, proliferation and metastasis. Thus, Sam68 has been suggested as a promising therapeutic target in different types of tumors.

From a traditional perspective, chemotherapy (CT) is very effective in increasing the immunogenicity of malignant cells and inhibiting immunosuppressive pathways in cancer (115). However, tumor cell eradication by CT was not as effective as initially expected. Later, combinatorial regimens were developed and successfully tested, with improved clinical safety and efficacy (115,116). On another note, certain tumors do not respond properly to CT due to the development of drug resistance. Resistance may be induced either by pharmacological and physiological factors, such as drug metabolism or inadequate drug access to tumor sites, or by cell- and tissue-specific factors, including gene overexpression and phosphorylation (117,118). In this sense, Sam68 phosphorylation was shown to induce CT resistance *in vitro* and *in vivo* in a variety of tumors, including OTSCC and prostate, breast and colon cancer. Thus, silencing of Sam68 phosphorylation enhanced the sensitivity of tumor cells to apoptosis induced by chemotherapeutic agents such as cisplatin, etoposide or camptothecin (65,75,86,95). This evidence suggests that Sam68 knockdown may improve the cytotoxic effects of CT.

Similar results have been obtained in BC using the small molecule dinaciclib (65), a CDK inhibitor (119). Of note, small molecules have been increasingly used as therapeutic targets for two decades due their advantages over CT (120,121). The small molecule B02 has been proven to inhibit RAD51 recombinase, a critical effector of homologous recombination that is upregulated in cancer (122) and in BC xenograft models (123). In these settings, the combination of B02 and downregulation of Sam68, rather than silencing, boosted the reduction of tumor size (65). Intriguingly, other small molecules directly promoted the downregulation of Sam68. Doxycycline, which inhibits CSC phenotypes and epithelial-to-mesenchymal transition (124), reduced Sam68 expression *in vitro* at the protein and mRNA level in Jurkat and CCRF-CEM T-cell acute lymphoblastic leukemia cells (98). In line with this, Sam68-mediated drug resistance was inhibited in OCI-Ly8 and Jeko-1 non-Hodgkin lymphoma cell lines after treatment with MK2206 (107), an Akt inhibitor (125). Of note, the sodium pump inhibitor UNBS1450 induced the disruption of the Sam68 body in human PC3 prostate cancer cells *in vitro*, which significantly reduced tumor cell proliferation (78). Based on evidence on the role of Sam68 in the regulation of CSCs via Wnt/β-catenin (51,85), different Wnt/β-catenin inhibitors have been tested. Inhibitors included YB-0158, which disrupted Sam68-Src interactions in CRC cells and significantly inhibited tumorigenesis (85). Other inhibitors included ICG-001 or its analog CWP, which induced the formation of a Sam68/CBP complex to inhibit Wnt/β-catenin in leukemia, colon cancer and BC (51).

5. Conclusions and future perspectives

In most types of tumors, there is strong evidence that elevated levels of the protein Sam68, along with Sam68 gene overexpression, play a major role in oncogenesis. Thus, Sam68 has been proven to promote tumor cell development, proliferation, progression and metastasis *in vitro* and *in vivo*. These findings identify Sam68 as a key regulator in cancer that should be considered as a clinical biomarker and a promising therapeutic target. This conclusion is also supported by the fact that this RBP is directly involved in the self-renewal and survival capacity of CSCs, which are essential for the activation of tumor growth and promote treatment failure and tumor relapse (126).

Of note, post-transcriptional modifications, added to Sam68's characteristics, lead to an increased number of interactions with multiple genes involved in cancer. Some of these genes include (but are not limited to) NIMA related kinase 2 or EPHA3 in BC (69,127); Rad51 in acute myeloid leukemia (123); lysine-specific methyltransferase Set7/9 in colon cancer (88); or METTL3 in gastric carcinoma (88). Thus, the evidence available suggests that Sam68 may also need the involvement of other actors with specific roles in these diseases.

The regulation of cancer driven by Sam68 may depend, at least in part, on i) the type of tissue in which the tumor develops; ii) the tumor niche; and iii) the interactions between Sam68 with different RNAs or other proteins via different signaling pathways, as previously suggested (114). For these reasons, further research is needed to elucidate the potential role of Sam68 and its interactions in these settings *in vivo* and *in vitro*.

Based on previous experience of our group with Sam68, it is strongly suggested that high levels/expression of Sam68 have an important role not only in cancer (31-33,128), but also in other diseases (7,129,130). There is cumulative evidence supporting this idea, which has been particularly evaluated in BC; CRC (85-88); gastric cancer (91-93); lung cancer (79-84); and PC (10,26,72-76) tumors, among many others (Table II). Different mechanisms of the role of Sam68 on tumorigenesis in these tumors have been found, such as regulation

of alternative splicing of glycolytic enzymes (82,87) and proto-oncogenes (72,73,76), the Wnt/β-catenin pathway (83), genotoxic stress-induced NF-κB activation (86), DNA methylation (93) and modification of miRNAs (91). However, no meta-analyses or clinical trials have been developed to elucidate the exact mechanism of Sam68 mediated tumorigenesis. Meta-analyses may be useful to synthesize the existing data for diseases in which Sam68 is involved, including cancer. On the other hand, there is only one clinical trial, carried out by Awe *et al* (131), who reported in 2020 that Sam68 is a key determinant of vascular endothelial growth factor receptor 1 isoform expression, extensively found in cancer (132). In light of the cumulative evidence available on the potential role of Sam68 as a therapeutic target in cancer, further studies are needed to provide conclusive evidence.

Acknowledgements

Not applicable.

Funding

CJ-C is supported by a Margarita Salas fellowship, granted by the University of Seville (Seville, Spain). The group is supported by Plan Andaluz Investigación y Desarrollo, Junta de Andalucia, Spain (grant no. CTS-151 to VS-M).

Availability of data and materials

Not applicable.

Authors' contributions

CJ-C, FS-J, LC-M and VS-M contributed to the conceptualization, literature search and reviewing of the draft. CJ-C wrote the draft. All authors have read and agreed to the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Courtneidge SA and Fumagalli S: A mitotic function for Src? Trends Cell Biol 4: 345-347, 1994.
2. Frisone P, Pradella D, Di Matteo A, Belloni E, Ghigna C and Paronetto MP: SAM68: Signal transduction and RNA metabolism in human cancer. Biomed Res Int 2015: 528954, 2015.
3. Najib S, Martín-Romero C, González-Yanes C and Sánchez-Margalet V: Role of Sam68 as an adaptor protein in signal transduction. Cell Mol Life Sci 62: 36-43, 2005.
4. Pagliarini V, Jolly A, Bielli P, Di Rosa V, De la Grange P and Sette C: Sam68 binds Alu-rich introns in SMN and promotes pre-mRNA circularization. Nucleic Acids Res 48: 633-645, 2020.
5. Messina V, Meikar O, Paronetto MP, Calabretta S, Geremia R, Kotaja N and Sette C: The RNA binding protein SAM68 transiently localizes in the chromatoid body of male germ cells and influences expression of select microRNAs. PLoS One 7: e39729, 2012.
6. Li J, Liu Y, Kim BO and He JJ: Direct participation of Sam68, the 68-kilodalton Src-associated protein in mitosis, in the CRM1-mediated Rev nuclear export pathway. J Virol 76: 8374-8382, 2002.
7. Vilariño-García T, Pérez-Pérez A, Santamaría-López E, Prados N, Fernández-Sánchez M and Sánchez-Margalet V: Sam68 mediates leptin signaling and action in human granulosa cells: Possible role in leptin resistance in PCOS. Endocr Connect 9: 479-488, 2020.
8. Adinolfi A, Di Sante G, Rivignani Vaccari L, Tredicine M, Ria F, Bonvissuto D, Corvino V, Sette C and Geloso MC: Regionally restricted modulation of Sam68 expression and Arhgef9 alternative splicing in the hippocampus of a murine model of multiple sclerosis. Front Mol Neurosci 15: 1073627, 2022.
9. Wang Y, Zhang W, Wang X, Wang D, Xie J, Tang C, Xi Q, Zhong J and Deng Y: Expression of Sam68 correlates with cell proliferation and survival in epithelial ovarian cancer. Reprod Sci 24: 97-108, 2017.
10. 10. Pieraccioli M, Caggiano C, Mignini L, Zhong C, Babini G, Lattanzio R, Di Stasi S, Tian B, Sette C and Bielli P: The transcriptional terminator XRN2 and the RNA-binding protein Sam68 link alternative polyadenylation to cell cycle progression in prostate cancer. Nat Struct Mol Biol 29: 1101-1112, 2022.
11. Taylor SJ, Resnick RJ and Shalloway D: Sam68 exerts separable effects on cell cycle progression and apoptosis. BMC Cell Biol 5: 5, 2004.
12. Sanchez-Jimenez F and Sanchez-Margalet V: Role of Sam68 in post-transcriptional gene regulation. Int J Mol Sci 14: 23402-23419, 2013.
13. Richard S, Vogel G, Huot ME, Guo T, Muller WJ and Lukong KE: Sam68 haploinsufficiency delays onset of mammary tumorigenesis and metastasis. Oncogene 27: 548-556, 2008.
14. Irwin ME, Bohin N and Boerner JL: Src family kinases mediate epidermal growth factor receptor signaling from lipid rafts in breast cancer cells, Cancer Biol Ther 12: 718-726, 2011.
15. Pillay I, Nakano H and Sharma SV: Radicicol inhibits tyrosine phosphorylation of the mitotic Src substrate Sam68 and retards subsequent exit from mitosis of Src-transformed cells, Cell Growth Differ 7: 1487-1499, 1996.
16. Barlat I, Maurier F, Duchesne M, Guitard E, Tocque B and Schweighoffer F: A role for Sam68 in cell cycle progression antagonized by a spliced variant within the KH domain. J Biol Chem 272: 3129-3132, 1997.
17. Paronetto MP, Achsel T, Massiello A, Chalfant CE and Sette C: The RNA-binding protein Sam68 modulates the alternative splicing of Bcl-x. J Cell Biol 176: 929-939, 2007.
18. Zambuzzi WF, Granjeiro JM, Parikh K, Yuvaraj S, Peppelenbosch MP and Ferreira CV: Modulation of Src activity by low molecular weight protein tyrosine phosphatase during osteoblast differentiation. Cell Physiol Biochem 22: 497-506, 2008.
19. Horn S, Meyer J, Stocking C, Ostertag W and Jücker M: An increase in the expression and total activity of endogenous p60(c-Src) in several factor-independent mutants of a human GM-CSF-dependent leukemia cell line (TF-1). Oncogene 22: 7170-7180, 2003.
20. Brignatz C, Paronetto MP, Opi S, Cappellari M, Audebert S, Feuillet V, Bismuth G, Roche S, Arold ST, Sette C and Collette Y: Alternative splicing modulates autoinhibition and SH3 accessibility in the Src kinase Fyn. Mol Cell Biol 29: 6438-48, 2009.
21. Gorla L, Cantù M, Miccichè F, Patelli C, Mondellini P, Pierotti MA and Bongarzone I: RET oncoproteins induce tyrosine phosphorylation changes of proteins involved in RNA metabolism. Cell Signal 18: 2272-2282, 2006.
22. Mamidipudi V, Dhillon NK, Parman T, Miller LD, Lee KC and Cartwright CA: RACK1 inhibits colonic cell growth by regulating Src activity at cell cycle checkpoints. Oncogene 26: 2914-2924, 2007.
23. Lukong KE, Larocque D, Tyner AL and Richard S: Tyrosine phosphorylation of sam68 by breast tumor kinase regulates intranuclear localization and cell cycle progression. J Biol Chem 280: 38639-38647, 2005.
24. Mizuguchi Y, Specht S, Isse K, Sasatomi E, Lunz JG III, Takizawa T and Demetris AJ: Breast tumor kinase/protein tyrosine kinase 6 (Brk/PTK6) activity in normal and neoplastic biliary epithelia. J Hepatol 63: 399-407, 2015.

25. Brauer PM, Zheng Y, Wang L and Tyner AL: Cytoplasmic retention of protein tyrosine kinase 6 promotes growth of prostate tumor cells. Cell Cycle 9: 4190-4199, 2010.
26. Paronetto MP, Farini D, Sammarco I, Maturo G, Vespasiani G, Geremia R, Rossi P and Sette C: Expression of a truncated form of the c-Kit tyrosine kinase receptor and activation of Src kinase in human prostatic cancer. Am J Pathol 164: 1243-1251, 2004.
27. Locatelli A and Lange CA: Met receptors induce Sam68-dependent cell migration by activation of alternate extracellular signal-regulated kinase family members. J Biol Chem 286: 21062-21072, 2011.
28. Babic I, Jakymiw A and Fujita DJ: The RNA binding protein Sam68 is acetylated in tumor cell lines, and its acetylation correlates with enhanced RNA binding activity. Oncogene 23: 3781-3789, 2004.
29. Sánchez-Jiménez F, Pérez-Pérez A, de la Cruz-Merino L and Sánchez-Margalet V: Obesity and breast cancer: Role of leptin. Front Oncol 9: 596, 2019.
30. Sanchez-Margalet V and Najib S: p68 Sam is a substrate of the insulin receptor and associates with the SH2 domains of p85 PI3K. FEBS Lett 455: 307-310, 1999.
31. Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, de la Cruz L, Virizuela JA and Sánchez-Margalet V: Sam68 mediates the activation of insulin and leptin signalling in breast cancer cells. PLoS One 11: e0158218, 2016.
32. Sánchez-Jiménez F, Pérez-Pérez A, González-Yanes C, Najib S, Varone CL and Sánchez-Margalet V: Leptin receptor activation increases Sam68 tyrosine phosphorylation and expression in human trophoblastic cells. Mol Cell Endocrinol 332: 221-227, 2011.
33. Sánchez-Jiménez F, Pérez-Pérez A, González-Yanes C, Varone CL and Sánchez-Margalet V: Sam68 mediates leptin-stimulated growth by modulating leptin receptor signaling in human trophoblastic JEG-3 cells. Hum Reprod 26: 2306-2315, 2011.
34. Reiss K, Del Valle L, Lassak A and Trojanek J: Nuclear IRS-1 and cancer. J Cell Physiol 227: 2992-3000, 2012.
35. Sung CK, Choi WS and Sanchez-Margalet V: Guanosine triphosphatase-activating protein-associated protein, but not src-associated protein p68 in mitosis, is a part of insulin signaling complexes. Endocrinology 139: 2392-2398, 1998.
36. Matter N, Herrlich P and König H: Signal-dependent regulation of splicing via phosphorylation of Sam68. Nature 420: 691-695, 2002.
37. Malki I, Liepina I, Kogelnik N, Watmuff H, Robinson S, Lightfoot A, Gonchar O, Bottrill A, Fry AM and Dominguez C: Cdk1-mediated threonine phosphorylation of Sam68 modulates its RNA binding, alternative splicing activity and cellular functions. Nucleic Acids Res 50: 13045-13062, 2022.
38. Yang J, Song C and Zhan X: The role of protein acetylation in carcinogenesis and targeted drug discovery. Front Endocrinol (Lausanne) 13: 972312, 2022.
39. Sobulo OM, Borrow J, Tomek R, Reshmi S, Harden A, Schlegelberger B, Housman D, Doggett NA, Rowley JD and Zeleznik-Le NJ: MLL is fused to CBP, a histone acetyltransferase, in therapy-related acute myeloid leukemia with a t(11;16)(q23;p13.3). Proc Natl Acad Sci USA 94: 8732-8737, 1997.
40. Lavau C, Du C, Thirman M and Zeleznik-Le N: Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia. EMBO J 19: 4655-4664, 2000.
41. Cheung N, Chan LC, Thompson A, Cleary ML and So CW: Protein arginine-methyltransferase-dependent oncogenesis, Nat Cell Biol 9: 1208-1215, 2007.
42. Bielli P, Busà R, Paronetto MP and Sette C: The RNA-binding protein Sam68 is a multifunctional player in human cancer. Endocr Relat Cancer 18: R91-R102, 2011.
43. Siam A, Baker M, Amit L, Regev G, Rabner A, Najar RA, Bentata M, Dahan S, Cohen K, Araten S, *et al*: Regulation of alternative splicing by p300-mediated acetylation of splicing factors. RNA 25: 813-824, 2019.
44. Bordonaro M: Hypothesis: Sam68 and Pygo2 mediate cell type-specific effects of the modulation of CBP-Wnt and p300-Wnt activities in colorectal cancer cells. J Cancer 12: 5046-5052, 2021.
45. Nakka KK, Chaudhary N, Joshi S, Bhat J, Singh K, Chatterjee S, Malhotra R, De A, Santra MK, Dilworth FJ and Chattopadhyay S: Nuclear matrix-associated protein SMAR1 regulates alternative splicing via HDAC6-mediated deacetylation of Sam68. Proc Natl Acad Sci USA 112: E3374-E3383, 2015.
46. Hwang JW, Cho Y, Bae GU, Kim SN and Kim YK: Protein arginine methyltransferases: Promising targets for cancer therapy. Exp Mol Med 53: 788-808, 2021.
47. Yu Z, Chen T, Hébert J, Li E and Richard S: A mouse PRMT1 null allele defines an essential role for arginine methylation in genome maintenance and cell proliferation. Mol Cell Biol 29: 2982-2996, 2009.
48. Robin-Lespinasse Y, Sentis S, Kolytcheff C, Rostan MC, Corbo L and Le Romancer M: hCAF1, a new regulator of PRMT1-dependent arginine methylation. J Cell Sci 120: 638-647, 2007.
49. Vhuiyan MI, Pak ML, Park MA, Thomas D, Lakowski TM, Chalfant CE and Frankel A: PRMT2 interacts with splicing factors and regulates the alternative splicing of BCL-X. J Biochem 162: 17-25, 2017.
50. Deng L, Meng T, Chen L, Wei W and Wang P: The role of ubiquitination in tumorigenesis and targeted drug discovery. Signal Transduct Target Ther 5: 11, 2020.
51. Benoit YD, Mitchell RR, Risueño RM, Orlando L, Tanasijevic B, Boyd AL, Aslostovar L, Salci KR, Shapovalova Z, Russell J, *et al*: Sam68 allows selective targeting of human cancer stem cells. Cell Chem Biol 24: 833-844.e9, 2017.
52. Babic I, Cherry E and Fujita DJ: SUMO modification of Sam68 enhances its ability to repress cyclin D1 expression and inhibits its ability to induce apoptosis. Oncogene 25: 4955-4964, 2006.
53. La Rosa P, Bielli P, Compagnucci C, Cesari E, Volpe E, Farioli Vecchioli S and Sette C: Sam68 promotes self-renewal and glycolytic metabolism in mouse neural progenitor cells by modulating Aldh1a3 pre-mRNA 3'-end processing. Elife 5: e20750, 2016.
54. Mao P, Joshi K, Li J, Kim SH, Li P, Santana-Santos L, Luthra S, Chandran UR, Benos PV, Smith L, *et al*: Mesenchymal glioma stem cells are maintained by activated glycolytic metabolism involving aldehyde dehydrogenase 1A3. Proc Natl Acad Sci USA 110: 8644-8649, 2013.
55. Rinkenbaugh AL and Baldwin AS: The NF-κB pathway and cancer stem cells. Cells 5: 16, 2016.
56. Vazquez-Santillan K, Melendez-Zajgla J, Jimenez-Hernandez L, Martínez-Ruiz G and Maldonado V: NF-κB signaling in cancer stem cells: A promising therapeutic target? Cell Oncol (Dordr) 38: 327-339, 2015.
57. Vazquez-Santillan K, Melendez-Zajgla J, Jimenez-Hernandez LE, Gaytan-Cervantes J, Muñoz-Galindo L, Piña-Sanchez P, Martinez-Ruiz G, Torres J, Garcia-Lopez P, Gonzalez-Torres C, *et al*: NF-kappaB-inducing kinase regulates stem cell phenotype in breast cancer. Sci Rep 6: 37340, 2016.
58. Ishiguro T, Ohata H, Sato A, Yamawaki K, Enomoto T and Okamoto K: Tumor-derived spheroids: Relevance to cancer stem cells and clinical applications. Cancer Sci 108: 283-289, 2017.
59. Manuel Iglesias J, Beloqui I, Garcia-Garcia F, Leis O, Vazquez-Martin A, Eguiara A, Cufi S, Pavon A, Menendez JA, Dopazo J and Martin AG: Mammosphere formation in breast carcinoma cell lines depends upon expression of E-cadherin. PLoS One 8: e77281, 2013.
60. Wang L, Tian H, Yuan J, Wu H, Wu J and Zhu X: CONSORT: Sam68 is directly regulated by MiR-204 and promotes the Self-renewal potential of breast cancer cells by activating the Wnt/beta-catenin signaling pathway. Medicine (Baltimore) 94: e2228, 2015.
61. Hong BS, Ryu HS, Kim N, Kim J, Lee E, Moon H, Kim KH, Jin MS, Kwon NH, Kim S, *et al*: Tumor suppressor miRNA-204-5p regulates growth, metastasis, and immune microenvironment remodeling in breast cancer. Cancer Res 79: 1520-1534, 2019.
62. Li P, Wang Q and Wang H: MicroRNA-204 inhibits the proliferation, migration and invasion of human lung cancer cells by targeting PCNA-1 and inhibits tumor growth *in vivo*. Int J Mol Med 43: 1149-1156, 2019.
63. Imam JS, Plyler JR, Bansal H, Prajapati S, Bansal S, Rebeles J, Chen HI, Chang YF, Panneerdoss S, Zoghi B, *et al*: Genomic loss of tumor suppressor miRNA-204 promotes cancer cell migration and invasion by activating AKT/mTOR/Rac1 signaling and actin reorganization. PLoS One 7: e52397, 2012.
64. Liang CY, Li ZY, Gan TQ, Fang YY, Gan BL, Chen WJ, Dang YW, Shi K, Feng ZB and Chen G: Downregulation of hsa-microRNA-204-5p and identification of its potential regulatory network in non-small cell lung cancer: RT-qPCR, bioinformatic- and meta-analyses. Respir Res 21: 60, 2020.
65. Turdo A, Gaggianesi M, Di Franco S, Veschi V, D'Accardo C, Porcelli G, Lo Iacono M, Pillitteri I, Verona F, Militello G, *et al*: Effective targeting of breast cancer stem cells by combined inhibition of Sam68 and Rad51. Oncogene 41: 2196-2209, 2022.

66. Mehner C, Hockla A, Miller E, Ran S, Radisky DC and Radisky ES: Tumor cell-produced matrix metalloproteinase 9 (MMP-9) drives malignant progression and metastasis of basal-like triple negative breast cancer. Oncotarget 5: 2736-2749, 2014.
67. London M and Gallo E: Critical role of EphA3 in cancer and current state of EphA3 drug therapeutics. Mol Biol Rep 47: 5523-5533, 2020.
68. Lv XY, Wang J, Huang F, Wang P, Zhou JG, Wei B and Li SH: EphA3 contributes to tumor growth and angiogenesis in human gastric cancer cells. Oncol Rep 40: 2408-2416, 2018.
69. Chen X, Zhang L, Yuan M, Kuang Z, Zou Y, Tang T, Zhang W, Hu X, Xia T, Cao T and Jia H: Sam68 Promotes the progression of human breast cancer through inducing activation of EphA3. Curr Cancer Drug Targets 20: 76-83, 2020.
70. Aubele M, Walch AK, Ludyga N, Braselmann H, Atkinson MJ, Luber B, Auer G, Tapio S, Cooke T and Bartlett JM: Prognostic value of protein tyrosine kinase 6 (PTK6) for long-term survival of breast cancer patients. Br J Cancer 99: 1089-1095, 2008.
71. Song L, Wang L, Li Y, Xiong H, Wu J, Li J and Li M: Sam68 up-regulation correlates with, and its down-regulation inhibits, proliferation and tumourigenicity of breast cancer cells. J Pathol 222: 227-237, 2010.
72. Paronetto MP, Cappellari M, Busà R, Pedrotti S, Vitali R, Comstock C, Hyslop T, Knudsen KE and Sette C: Alternative splicing of the cyclin D1 proto-oncogene is regulated by the RNA-binding protein Sam68. Cancer Res 70: 229-239, 2010.
73. Caggiano C, Pieraccioli M, Panzeri V, Sette C and Bielli P: c-MYC empowers transcription and productive splicing of the oncogenic splicing factor Sam68 in cancer. Nucleic Acids Res 47: 6160-6171, 2019.
74. Derry JJ, Prins GS, Ray V and Tyner AL: Altered localization and activity of the intracellular tyrosine kinase BRK/Sik in prostate tumor cells. Oncogene 22: 4212-4220, 2003.
75. Busà R, Paronetto MP, Farini D, Pierantozzi E, Botti F, Angelini DF, Attisani F, Vespasiani G and Sette C: The RNA-binding protein Sam68 contributes to proliferation and survival of human prostate cancer cells. Oncogene 26: 4372-4382, 2007.
76. Rajan P, Gaughan L, Dalgliesh C, El-Sherif A, Robson CN, Leung HY and Elliott DJ: The RNA-binding and adaptor protein Sam68 modulates signal-dependent splicing and transcriptional activity of the androgen receptor. J Pathol 215: 67-77, 2008.
77. Uddin MH, Li Y, Khan HY, Muqbil I, Aboukameel A, Sexton RE, Reddy S, Landesman Y, Kashyap T, Azmi AS and Heath EI: Nuclear export inhibitor KPT-8602 synergizes with PARP inhibitors in escalating apoptosis in castration resistant cancer cells. Int J Mol Sci 22: 6676, 2021.
78. Mijatovic T, De Nève N, Gailly P, Mathieu V, Haibe-Kains B, Bontempi G, Lapeira J, Decaestecker C, Facchini V and Kiss R: Nucleolus and c-Myc: Potential targets of cardenolide-mediated antitumor activity. Mol Cancer Ther 7: 1285-1296, 2008.
79. Sumithra B, Jayanthi VSPKSA, Manne HC, Gunda R, Saxena U and Das AB: Antibody-based biosensor to detect oncogenic splicing factor Sam68 for the diagnosis of lung cancer. Biotechnol Lett 42: 2501-2509, 2020.
80. Zhang Z, Xu Y, Sun N, Zhang M, Xie J and Jiang Z: High Sam68 expression predicts poor prognosis in Non-small cell lung cancer. Clin Transl Oncol 16: 886-891, 2014.
81. Lin CH, Liao CC, Wang SY, Peng CY, Yeh YC, Chen MY and Chou TY: Comparative O-GlcNAc proteomic analysis reveals a role of O-GlcNAcylated SAM68 in lung cancer aggressiveness. Cancers (Basel) 14: 243, 2022.
82. Zhu S, Chen W, Wang J, Qi L, Pan H, Feng Z and Tian D: SAM68 promotes tumorigenesis in lung adenocarcinoma by regulating metabolic conversion via PKM alternative splicing. Theranostics 11: 3359-3375, 2021.
83. Li X, Zhou X, Hua F, Fan Y, Zu L, Wang Y, Shen W, Pan H and Zhou Q: The RNA-binding protein Sam68 is critical for non-small cell lung cancer cell proliferation by regulating Wnt/β-catenin pathway. Int J Clin Exp Pathol 10: 8281-8291, 2017.
84. Sumithra B, Saxena U and Das AB: A comprehensive study on genome-wide coexpression network of KHDRBS1/Sam68 reveals its cancer and Patient-specific association. Sci Rep 9: 11083, 2019.
85. Masibag AN, Bergin CJ, Haebe JR, Zouggar A, Shah MS, Sandouka T, Mendes da Silva A, Desrochers FM, Fournier-Morin A and Benoit YD: Pharmacological targeting of Sam68 functions in colorectal cancer stem cells. iScience 24: 103442, 2021.
86. Fu K, Sun X, Wier EM, Hodgson A, Liu Y, Sears CL and Wan F: Sam68/KHDRBS1 is critical for colon tumorigenesis by regulating genotoxic stress-induced NF-κB activation. Elife 5: e15018, 2016.
87. Zhao J, Li J, Hassan W, Xu D, Wang X and Huang Z: Huang, Sam68 promotes aerobic glycolysis in colorectal cancer by regulating PKM2 alternative splicing. Ann Transl Med 8: 459, 2020.
88. Vasileva E, Shuvalov O, Petukhov A, Fedorova O, Daks A, Nader R and Barlev N: KMT Set7/9 is a new regulator of Sam68 STAR-protein. Biochem Biophys Res Commun 525: 1018-1024, 2020.
89. Li N and Richard S: Sam68 functions as a transcriptional coactivator of the p53 tumor suppressor. Nucleic Acids Res 44: 8726-8741, 2016.
90. Li N, Ngo CT, Aleynikova O, Beauchemin N and Richard S: The p53 status can influence the role of Sam68 in tumorigenesis. Oncotarget 7: 71651-71659, 2016.
91. Yu X, Kang W, Zhang J, Chen C and Liu Y: Shortening of the KHDRBS1 3'UTR by alternative cleavage and polyadenylation alters miRNA-mediated regulation and promotes gastric cancer progression. Am J Transl Res 14: 6574-6585, 2022.
92. Xiao J, Wang Q, Yang Q, Wang H, Qiang F, He S, Cai J, Yang L and Wang Y: Clinical significance and effect of Sam68 expression in gastric cancer. Oncol Lett 15: 4745-4752, 2018.
93. Zhang JY, Du Y, Gong LP, Shao YT, Pan LJ, Feng ZY, Pan YH, Huang JT, Wen JY, Sun LP, *et al*: ebv-circRPMS1 promotes the progression of EBV-associated gastric carcinoma via Sam68-dependent activation of METTL3. Cancer Lett 535: 215646, 2022.
94. Komiyama T, Kuroshima T, Sugasawa T, Fujita SI, Ikami Y, Hirai H, Tsushima F, Michi Y, Kayamori K, Higashino F and Harada H: High expression of Sam68 contributes to metastasis by regulating vimentin expression and a motile phenotype in oral squamous cell carcinoma. Oncol Rep 48: 183, 2022.
95. Chen S, Li H, Zhuang S, Zhang J, Gao F, Wang X, Chen W and Song M: Sam68 reduces Cisplatin-induced apoptosis in tongue carcinoma. J Exp Clin Cancer Res 35: 123, 2016.
96. Fu K, Sun X, Xia X, Hobbs RP, Guo Y, Coulombe PA and Wan F: Sam68 is required for the growth and survival of nonmelanoma skin cancer. Cancer Med 8: 6106-6113, 2019.
97. Paronetto MP, Messina V, Bianchi E, Barchi M, Vogel G, Moretti C, Palombi F, Stefanini M, Geremia R, Richard S and Sette C: Sam68 regulates translation of target mRNAs in male germ cells, necessary for mouse spermatogenesis. J Cell Biol 185: 235-249, 2009.
98. Wang Q, Li Y, Cheng J, Chen L, Xu H, Li Q and Pang T: Sam68 affects cell proliferation and apoptosis of human adult T-acute lymphoblastic leukemia cells via AKT/mTOR signal pathway. Leuk Res 46: 1-9, 2016.
99. Zhao D, Tian Y, Li P, Wang L, Xiao A, Zhang M and Shi T: MicroRNA-203 inhibits the malignant progression of neuroblastoma by targeting Sam68. Mol Med Rep 12: 5554-5560, 2015.
100. Zhao X, Li Z, He B, Liu J, Li S, Zhou L, Pan C, Yu Z and Xu Z: Sam68 is a novel marker for aggressive neuroblastoma. Onco Targets Ther 6: 1751-1760, 2013.
101. Dong L, Che H, Li M and Li X: Sam68 is overexpressed in epithelial ovarian cancer and promotes tumor cell proliferation. Med Sci Monit 22: 3248-3256, 2016.
102. Chen ZY, Cai L, Zhu J, Chen M, Chen J, Li ZH, Liu XD, Wang SG, Bie P, Jiang P, *et al*: Fyn requires HnRNPA2B1 and Sam68 to synergistically regulate apoptosis in pancreatic cancer. Carcinogenesis 32: 1419-1426, 2011.
103. Li Z, Yu CP, Zhong Y, Liu TJ, Huang QD, Zhao XH, Huang H, Tu H, Jiang S, Zhang Y, *et al*: Sam68 expression and cytoplasmic localization is correlated with lymph node metastasis as well as prognosis in patients with Early-stage cervical cancer. Ann Oncol 23: 638-646, 2012.
104. Zhang Z, Yu C, Li Y, Jiang L and Zhou F: Utility of SAM68 in the progression and prognosis for bladder cancer. BMC Cancer 15: 364, 2015.
105. Wang Q, Li Y, Zhou J, Liu J, Qin J, Xing F, Zhang J and Cheng J: Clinical significance of Sam68 expression in endometrial carcinoma. Tumour Biol 36: 4509-4518, 2015.
106. Wang Y, Liang L, Zhang J, Li M, Zhu J, Gong C, Yang L, Zhu J, Chen L and Ni R: Sam68 promotes cellular proliferation and predicts poor prognosis in esophageal squamous cell carcinoma. Tumour Biol 36: 8735-8745, 2015.

107. Wu Y, Xu X, Miao X, Zhu X, Yin H, He Y, Li C, Liu Y, Chen Y, Lu X, *et al*: Sam68 regulates cell proliferation and cell adhesion-mediated drug resistance (CAM-DR) via the AKT pathway in non-Hodgkin's lymphoma. Cell Prolif 48: 682-690, 2015.
108. Wen H, Li P, Ma H, Zheng J, Yu Y and Lv G: High expression of Sam68 in sacral chordomas is associated with worse clinical outcomes. Onco Targets Ther 10: 4691-4700, 2017.
109. Zhang T, Wan C, Shi W, Xu J, Fan H, Zhang S, Lin Z, Ni R and Zhang X: The RNA-binding protein Sam68 regulates tumor cell viability and hepatic carcinogenesis by inhibiting the transcriptional activity of FOXOs. J Mol Histol 46: 485-497, 2015.
110. Zhang Z, Li J, Zheng H, Yu C, Chen J, Liu Z, Li M, Zeng M, Zhou F and Song L: Expression and cytoplasmic localization of SAM68 is a significant and independent prognostic marker for renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 18: 2685-2693, 2009.
111. Wu Z, Peng Y, Xiong L, Wang J, Li Z, Ning K, Deng M, Wang N, Wei W, Li Z, *et al*: Role of Sam68 in Sunitinib induced renal cell carcinoma apoptosis. Cancer Med 11: 3674-3686, 2022.
112. Feng J, Ren X, Fu H, Li D, Chen X, Zu X, Liu Q and Wu M: LRRC4 mediates the formation of circular RNA CD44 to inhibitGBM cell proliferation. Mol Ther Nucleic Acids 26: 473-487, 2021.
113. Liu K, Li L, Nisson PE, Gruber C, Jessee J and Cohen SN: Neoplastic transformation and tumorigenesis associated with sam68 protein deficiency in cultured murine fibroblasts. J Biol Chem 275: 40195-40201, 2000.
114. Lukong KE and Richard S: Targeting the RNA-binding protein Sam68 as a treatment for cancer? Future Oncol 3: 539-544, 2007.
115. Galluzzi L, Buqué A, Kepp O, Zitvogel L and Kroemer G: Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 28: 690-714, 2015.
116. Behranvand N, Nasri F, Zolfaghari Emameh R, Khani P, Hosseini A, Garssen J and Falak R: Chemotherapy: A double-edged sword in cancer treatment. Cancer Immunol Immunother 71: 507-526, 2022.
117. Raguz S and Yagüe E: Resistance to chemotherapy: New treatments and novel insights into an old problem. Br J Cancer 99: 387-391, 2008.
118. Brown FC, Still E, Koche RP, Yim CY, Takao S, Cifani P, Reed C, Gunasekera S, Ficarro SB, Romanienko P, *et al*: MEF2C phosphorylation is required for chemotherapy resistance in acute myeloid leukemia. Cancer Discov 8: 478-497, 2018.
119. Saqub H, Proetsch-Gugerbauer H, Bezrookove V, Nosrati M, Vaquero EM, de Semir D, Ice RJ, McAllister S, Soroceanu L, Kashani-Sabet M, *et al*: Dinaciclib, a cyclin-dependent kinase inhibitor, suppresses cholangiocarcinoma growth by targeting CDK2/5/9. Sci Rep 10: 18489, 2020.
120. Savage G and Antman KH: Imatinib mesylate-a new oral targeted therapy. N Engl J Med 346: 683-693, 2002.
121. Zhong L, Li Y, Xiong L, Wang W, Wu M, Yuan T, Yang W, Tian C, Miao Z, Wang T and Yang S: Small molecules in targeted cancer therapy: Advances, challenges, and future perspectives. Signal Transduct Target Ther 6: 201, 2021.
122. Wang Z, Jia R, Wang L, Yang Q, Hu X, Fu Q, Zhang X, Li W and Ren Y: The emerging roles of Rad51 in cancer and its potential as a therapeutic target. Front Oncol 12: 935593, 2022.
123. Huang F and Mazin AV: A small molecule inhibitor of human RAD51 potentiates breast cancer cell killing by therapeutic agents in mouse xenografts. PLoS One 9: e100993, 2014.
124. Zhang L, Xu L, Zhang F and Vlashi E: Doxycycline inhibits the cancer stem cell phenotype and Epithelial-to-mesenchymal transition in breast cancer. Cell Cycle 16: 737-745, 2017.
125. Hirai H, Sootome H, Nakatsuru Y, Miyama K, Taguchi S, Tsujioka K, Ueno Y, Hatch H, Majumder PK, Pan BS and Kotani H: MK-2206, an allosteric Akt inhibitor, enhances antitumor efficacy by standard chemotherapeutic agents or molecular targeted drugs in vitro and in vivo. Mol Cancer Ther 9: 1956-1967, 2010.
126. Marzagalli M, Fontana F, Raimondi M and Limonta P: Cancer stem Cells-key players in tumor relapse. Cancers (Basel) 13: 376, 2021.
127. Naro C, Barbagallo F, Caggiano C, De Musso M, Panzeri V, Di Agostino S, Paronetto MP and Sette C: Functional interaction between the oncogenic kinase NEK2 and Sam68 promotes a splicing program involved in migration and invasion in Triple-negative breast cancer. Front Oncol 12: 880654, 2022.
128. Quintana-Portillo R, Canfrán-Duque A, Issad T, Sánchez-Margalet V and González-Yanes C: Sam68 interacts with IRS1. Biochem Pharmacol 83: 78-87, 2012.
129. Vilariño-García T, Guadix P, Dorado-Silva M, Sánchez-Martín P, Pérez-Pérez A and Sánchez-Margalet V: Decreased expression of Sam68 is associated with insulin resistance in granulosa cells from PCOS patients. Cells 11: 2821, 2022.
130. Najib S, Rodríguez-Baño J, Ríos MJ, Muniain MA, Goberna R and Sánchez-Margalet V: Sam68 is tyrosine phosphorylated and recruited to signalling in peripheral blood mononuclear cells from HIV infected patients. Clin Exp Immunol 141: 518-525, 2005.
131. Awe O, Sinkway JM, Chow RP, Wagener Q, Schulz EV, Yu JY, Nietert PJ, Wagner CL and Lee KH: Differential regulation of a placental SAM68 and sFLT1 gene pathway and the relevance to maternal vitamin D sufficiency. Pregnancy Hypertens 22: 196-203, 2020.
132. Shibuya M: Involvement of Flt-1 (VEGF receptor-1) in cancer and preeclampsia. Proc Jpn Acad Ser B Phys Biol Sci 87: 167-178, 2011.