

Sorcin a Potential Molecular Target for Cancer Therapy



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Abstract

Sorcin (Soluble resistance related calcium binding protein) is a small soluble penta EF family (PEF) of calcium (Ca²⁺) binding protein (22,000 Da). It has been reported to play crucial roles in the regulation of calcium homeostasis, apoptosis, vesicle trafficking, cancer development, and multidrug resistance (MDR). Overexpression of sorcin has been reported to be associated with different cancers such as breast cancer, colorectal cancer, gastric cancer, leukemia, lung cancer, nasopharyngeal cancer, ovarian cancer, etc. Essentially, expression of sorcin has been found to be elevated in cancer cells as compared to normal cells, indicating that it has prominent role in cancer. Moreover, sorcin was found to be the regulator of various proteins that has an association with carcinogenesis including NF-κB, STAT3, Akt, ERK1/2, VEGF, MMPs, caspases, etc. Sorcin was also found to regulate apoptosis, as silencing of the same resulted in increased levels of proapoptotic genes and induced mitochondrial apoptotic pathway in cancer. Interestingly, mutations in the *sorcin* gene have been closely linked with poor overall survival in bladder cancer, brain lower-grade glioma, glioblastoma, glioblastoma multiforme, kidney renal clear cell carcinoma, and stomach adenocarcinoma. Additionally, overexpression of sorcin was also found to induce MDR against different chemotherapeutic drugs. All these findings mark the importance of sorcin in cancer development and MDR. Therefore, there is urgent need to explore the functional mechanism of sorcin and to analyze whether silencing of sorcin would be able to chemosensitize MDR cells. The current review summarizes the structure, expression, and functions of sorcin and its importance in the regulation of various malignancies and MDR.

Translational Oncology (2018) 11, 1379–1389

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Received 23 August 2018; Revised 28 August 2018; Accepted 28 August 2018

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1936-5233/18

<https://doi.org/10.1016/j.tranon.2018.08.015>

Introduction

Targeting sorcin for cancer treatment

Cancer is one of the exponentially growing health disorders posing a huge threat to humankind. More than any risk factors, improper lifestyle has been found to be the major reason for the development of various cancers [1]. More than half a century of research identified multiple signaling molecules to be associated with cancer, deregulation of which plays crucial role in the onset and progression of disease. These signaling molecules include Akt, ACLY, Erk, I κ B kinase (IKK), NF- κ B, lipocalins, STAT3, Wnt, TNF α , and TNF α -induced proteins etc. [2–10]. Several such molecules have also been found to have diagnostic and therapeutic values as numerous drugs targeting these key molecules have been found to exert high therapeutic potential against different cancers [11–16]. Sorcin (soluble resistance related calcium binding protein) is one such signaling molecule recently gaining more attention in cancer research as it has been found to induce multidrug resistance (MDR) in cancers [17]. It is a 22-kDa, soluble, small, penta EF family (PEF) of calcium (Ca²⁺) binding protein which has an association with calcium (Ca²⁺) homeostasis, MDR, and cancer development [18–21]. *SRC1*, the sorcin encoding gene, was found to be located on human chromosome seven (7q21.12) with 9 exons, and the sorcin protein is composed of 198 amino acid residues [22]. It was reported to be a cytosolic protein, which shows an association with free ribosomes, rough endoplasmic reticulum, mitochondria, microfilament, and perinuclear membranes [23]. Sorcin was first identified in vincristine-resistant Chinese hamster lung cell line DC-3F/VCRd-5 L by Meyers and Biedler and has been shown to increase the drug efflux in MDR cells in a calcium (Ca²⁺)-dependent manner [17,24,25].

Interestingly, analysis of expression pattern of sorcin revealed it to be expressed in most human tissues such as the tissues of bone, heart, brain, kidney, breast, skin, B-lymphocytes, T-lymphocytes, and monocytes. Further, shouting its importance in cancer, sorcin was found to be overexpressed in different cancers including breast cancer, colorectal cancer, gastric cancer, leukemia, lung cancer, nasopharyngeal cancer, and ovarian cancer [26]. It was also shown that sorcin was generally unexpressed in terminally differentiated mature tissues but was highly expressed in majority of tumor tissues, marking it as a potent target for cancer diagnosis and therapy. Many reports show that sorcin may have important role in the progression of cancer by enhancing the various hallmark of cancer such as cell motility, invasion, migration, metastasis, epithelial to mesenchymal transition (EMT), and MDR. Further, sorcin was found to modulate the levels of important cellular proteins, which are involved in the process of tumorigenesis such as NF- κ B, CTSZ, STAT3, Akt, ERK1/2, VEGF, MMPs, caspases, etc. [20,26–29]. In addition, silencing of this protein resulted in apoptosis and reverted MDR of cancer cells, and additionally, sorcin depletion reduced the levels of various proteins involved in angiogenesis, invasion, and metastasis [27,29]. Remarkably, overexpression of sorcin was also shown to induce chemoresistance against a variety of chemotherapeutics including 5-fluorouracil, cisplatin, doxorubicin, etoposide, homoharringtonine, paclitaxel, vincristine, etc. [18]. Thus, it is apparent that sorcin indeed has a key role in cancer. However, the exact mechanism(s) of action of sorcin in the initiation and progression of many cancers remains obscure. Presently, a number of studies are being carried out with the aim of exploring the actual cellular functions of sorcin and its involvement in tumorigenesis and

development of MDR. Therefore, the current review discusses the collective role and the associated molecular mechanisms of this calcium (Ca²⁺) binding protein in cancer and MDR summing up the literature available.

Structure of Sorcin

Aforementioned, sorcin, also known as CP-22 and V19, is an acidic, soluble, calcium (Ca²⁺)-binding protein encoded by *SRC1* gene located at 7q21.12 with nine exons [23,30]. The *SRC1* gene spans about 21.9 kb in the human genomic DNA and transcribes into five variants, namely, isoform A, B, C, D, and XI [31]. Among these, isoform A is the most commonly studied variant, which is a 22-kDa protein made of 198 amino acids. Sorcin has been classified into the penta-EF-hand (PEF) protein family as it has five EF-hand motifs. Proteins of the PEF family were known to interact with the membranes through these EF-hand motifs in a Ca²⁺-dependent manner. Other proteins of this small PEF family are calpain, grancalcin, peflin, and PDCD6 (earlier known as ALG-2) [32–35]. Sorcin was found to share a high homology with the light chain of calpain protein [36]. X-ray diffraction analysis of sorcin protein crystals revealed sorcin to have a globular shape with an extended N-terminal. It has been shown to form homodimers, and the monomers of these homodimer consist of two domains viz., C-terminal Ca²⁺-binding domain known as sorcin calcium binding domain and N-terminal glycine-rich domain [35,37,38]. The C-terminal of sorcin protein is composed of mainly eight alpha helices connected by loops to form the five EF-hands. These five EF-hands were found to pair with each other (EF1 with EF2 and EF3 with EF4). The free unpaired EF5 hand helps in homodimer formation by pairing with the EF5 of other sorcin. In addition, EF4-EF5 was also shown to participate in the protein dimerization (Figure 1) [35,38].

Structural comparison with the other members of PEF family revealed the folds of the sorcin EF motifs, especially the EF1 hand, to be highly conserved. It also suggested that the EF1-EF2 pair has two important Ca²⁺-binding sites and changes its conformation to a larger extent upon calcium binding, signifying this first EF hand pair to have crucial role in sorcin-calcium signaling (Figure 1) [35]. In line with this, comparison of the crystal structure of apo-Sor and calcium bound sorcin (CaSor) also showed that calcium binding moves the D-helix that joins the EF1-EF2 pair with EF3 and opens the EF1 hand promoting the exposure of hydrophobic surfaces [38]. Sorcin is broadly distributed in vertebrates with highly conserved amino acid sequence. For instance, the protein sequences of mouse and human sorcin differ by only eight amino acids. However, notably, the phosphorylation sites of sorcin were found to differ between different species [39].

Expression Pattern

Aforementioned, sorcin was found to be expressed in most tissues including the tissues of normal bone, breast, brain, heart, kidney, and skin. Apart from normal tissues, overexpression of sorcin was reported in various cancers such as breast cancer, colorectal cancer, gastric cancer, lung cancer, ovarian cancer, leukemia, and myeloma [20,26,27,40,41]. In addition, the expression level of sorcin was found to be higher in hepatocellular carcinoma tissues than the neighboring nontumorous and normal liver tissues [28]. Interestingly, the terminally differentiated mature tissues were found to have no sorcin, whereas its expression was very high in majority of tumor tissues, signifying it to be a potent target for cancer [27].

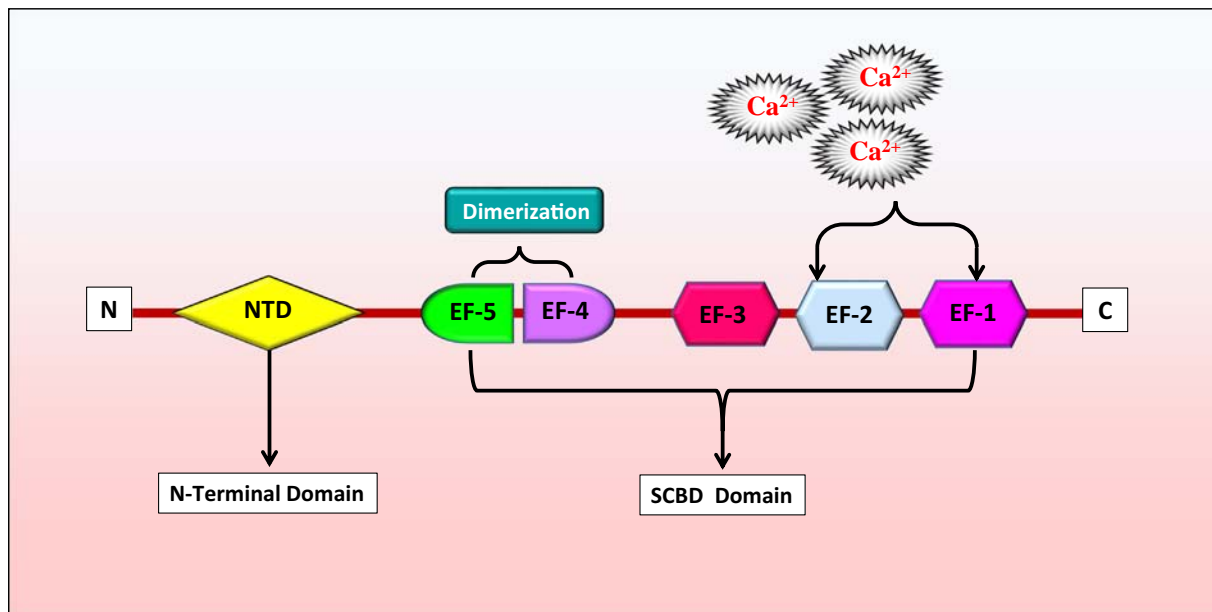


Figure 1. Structure of sorcin protein.

Molecular Targets

Sorcin is a regulatory protein, controlling the expression of various molecules in biological system. Sorcin was found to exert its oncogenic activity by inducing different signaling pathways such as ERK, MAPK/ERK, STAT3, PI3K/Akt, Akt/NF- κ B, etc. [26,28,42]. It was also shown to induce tumor invasion, migration, and metastasis through modulation of the levels of Cathepsin Z (CTS_Z), p-STAT3, and matrix metalloproteinases (MMP-2 and -9) [20]. Further, activation of STAT3 by sorcin was proved to develop chemoresistance and radioresistance in malignant cells through the interaction with transcription factors, including NF- κ B (nuclear factor kappa B) [43]. It was also suggested that sorcin might have an important role in EMT and cancer stem cells (CSCs) progression as it modulated the levels of E-cadherin, N-cadherin, fibronectin, α -SMA, vimentin, VEGF, and ERK signaling pathways [28,29]. Further supporting this, upregulation of sorcin was shown to induce the activity of vimentin (mesenchymal marker) protein, to increase the level of p-ERK1/2, and to downregulate the activity of E-cadherin (epithelial marker) [28]. In addition, overexpression of sorcin was also found to activate PI3K/Akt signaling pathway, which further plays a major role in migration, invasion, and epithelial to mesenchymal phenotype [26]. Adding to its tumorigenic potential, sorcin was also shown to be involved in the regulation of MDR, survival, and cell death associated proteins such as MDR1, MRP1, GST- π , Livin, Src, survivin, c-fos, c-jun, Bax, Bcl-2, caspase-3, caspase-12 and GRP78/BiP (binding immunoglobulin protein), cyclin-D1, c-Myc, p21, and p53 etc. [27,40,44,45]. Besides, sorcin was shown to exert its cytoprotective activity against chemotherapeutic agents by interacting and stabilizing TRAP1 (TNF receptor associated protein 1) against apoptosis in the mitochondria [46]. Similarly, sorcin overexpression was also found to increase the levels of MDR1/P-gp and contribute to the multidrug resistant phenotype by promoting the binding of CREB1 to cAMP response elements (CRE) present in the MDR1/P-gp promoter through increased phosphorylation of CREB1 [21].

Functions of Sorcin

The actual role of sorcin is not fully understood. However, it was observed that sorcin helps in the regulation of homeostasis, apoptosis, vesicles trafficking, and MDR in cells (Figure 2). Sorcin has a significant role in the regulation of calcium (Ca^{2+}) homeostasis in human body. Calcium (Ca^{2+}) plays significant roles in neurons, including synaptic plasticity and apoptosis, and deregulation of this neuronal calcium signaling was known to be one of the central mechanisms of different neurodegenerative diseases such as Alzheimer's disease (AD). Sorcin regulates the calcium homeostasis by two ways such as calcium-dependent binding to calcium channels and calcium binding itself. Sorcin expression enhances the concentration of calcium in endoplasmic reticulum (ER), inhibits ER stress, and induces the resistance to apoptosis. Moreover, the expression level of sorcin was found to be highly upregulated during ER stress [19,47]. Apart from calcium homeostasis, sorcin was also found to have a key role in the activation of mitosis and cytokinesis as loss of sorcin highly compromised the normal process of mitosis and cytokinesis [47].

It was also shown that sorcin can regulate apoptosis in cancer cells and induce cell cycle progression by calcium-dependent interaction with different kinases such as Polo-like kinase 1 (PLK1, a serine/threonine-protein kinase associated with mitotic spindle poles), Aurora A, and Aurora B. For instance, sorcin was found to interact with PLK1, get phosphorylated, and induce PLK1 autophosphorylation, ultimately regulating its kinase activity [38,47]. Further, in the heart, sorcin was found to regulate various proteins including cardiac R_yR2 (ryanodine receptor), L-type calcium channel, and sodium-calcium exchanger that has an association with excitation and contraction coupling [48]. It was found to inhibit the L-type calcium current ($I_{\text{Ca,L}}$) of the ventricular myocytes (isolated from rabbit) of rabbit [49]. Apart from this, sorcin also targets the sarcolemmal NCX1 (sodium/calcium exchanger) and induces its expression in the cardiac muscles, and silencing of sorcin by miR-1 helps to regulate the myocardial contraction through calcium

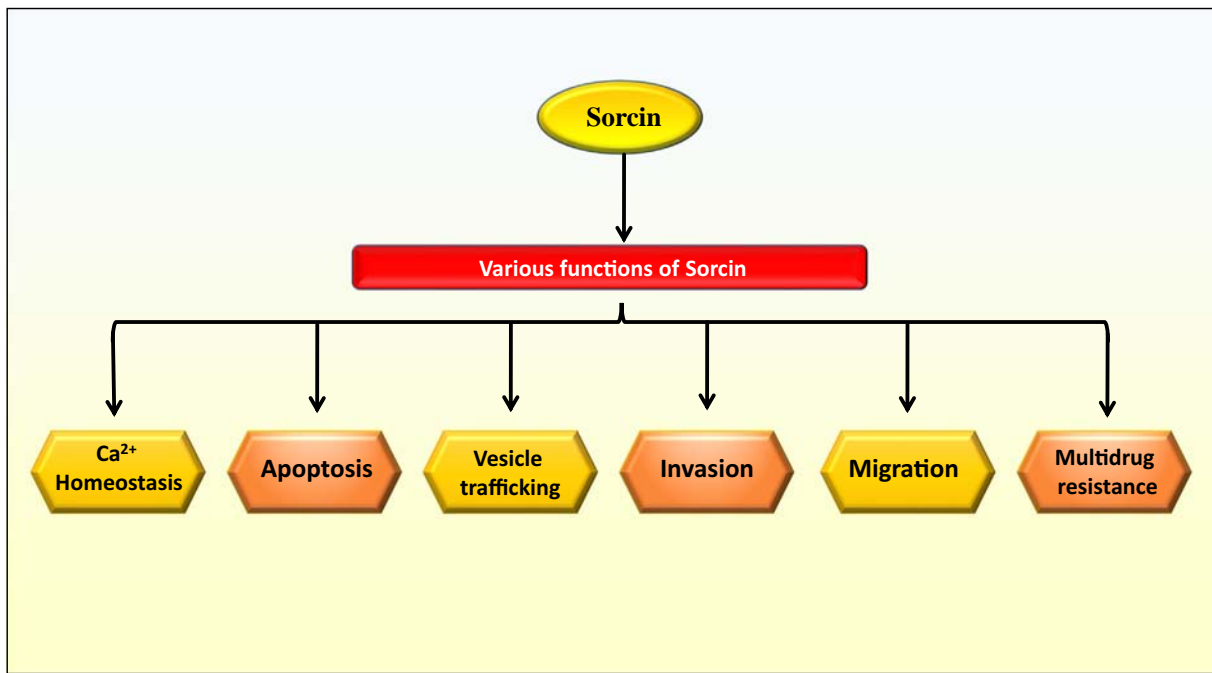


Figure 2. Functions of sorcin in various cellular processes.

signaling [50,51]. Furthermore, sorcin was also shown to regulate the dimensions and calcium concentration of the ER vesicles through activation of SERCA (sarcoplasmic/endoplasmic reticulum Ca²⁺--ATPase) and inhibition of RyR (ryanodine receptor) [47]. Altered expression of sorcin was found in the endometrium of women with mysterious infertility during the early-to-mid-secretory phase, suggesting a possible role of sorcin in endometrial receptivity and embryo implantation. Further, it was identified that sorcin regulates

the Ca²⁺-dependent angiogenesis in endometrial cells via activating VEGF/PI3K/Akt pathway and prepares the endometrium for implantation [52].

Roles in Malignancies

Invasion and migration are the two major manifestations of tumor progression. Numerous studies have shown two patterns of invasion in cancer: individual cell migration and collective cell migration by which

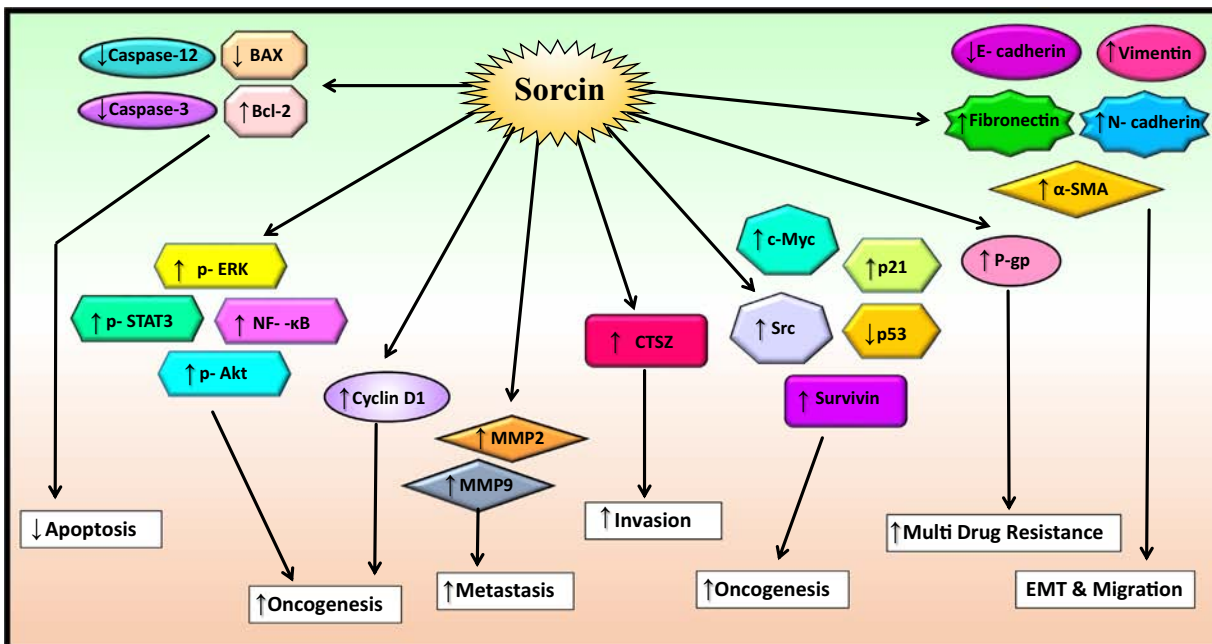


Figure 3. Sorcin upregulates the gene involved in cell migration, invasion, oncogenesis, and metastasis and downregulates the gene involved in apoptosis. ↑ = upregulation; ↓ = downregulation.

Table 1. Overall Survival by Kaplan-Meier Estimate

Cancer	Total No. of Samples	Cases with Alteration (No.)				Cases without Alteration (No.)			References
		Mutation	Total	Deceased	MMS	Total	Deceased	MMS	
Adrenocortical carcinoma	88	-	1	0	NA	87	32	79.01	[64]
Bladder cancer	408	X84_splice	6	3	28.38	399	174	34.95	[65]
Breast invasive cancer	816	-	5	0	NA	809	118	129.6	[66]
	482	-	1	0	NA	481	60	113.74	[67]
	963	-	7	0	NA	954	135	129.6	[68]
Brain lower-grade glioma	283	-	4	1	25.89	278	71	75.1	[69]
Breast cancer	2051	-	35	16	163.1	1831	1075	152.9333333	[70]
BUC	127	-	1	0	NA	126	46	20.47	[71]
	127	-	1	0	NA	125	61	23.19	[72]
Colorectal adenocarcinoma	212	D157N	2	0	NA	208	17	NA	[73]
	220	D157N	3	1	NA	216	38	NA	[74]
Cholangiocarcinoma	35	-	1	0	NA	32	15	24.34	[75]
CSCCEA	191	X18_splice	3	1	NA	188	40	101.74	[76]
Esophageal carcinoma	184	-	15	7	44.71	169	69	25.76	[77]
Glioblastoma	281	-	8	6	10.8	238	157	13.1	[78]
Glioblastoma multiforme	273	-	9	7	10.81	259	204	13.63	[79]
HNSCC	279	-	7	5	71.16	152	64	21.75	[80]
	504	-	18	10	30.91	484	205	56.44	[81]
RPCC	280	-	1	0	NA	278	41	NA	[82]
RCCC	418	-	2	1	1.94	413	138	75.5	[83]
	448	-	3	1	NA	445	151	90.41	[84]
LNDLBL	48	-	1	0	NA	47	9	211.07	[85]
OSC	311	-	10	8	50.33	299	197	44.51	[86]
Pancreatic adenocarcinoma	149	-	4	1	NA	145	81	19.65	[87]
Prostate adenocarcinoma	492	A161T, Q48	5	0	NA	487	9	NA	[88]
Papillary thyroid carcinoma	399	-	1	0	NA	321	13	NA	[89]
Stomach adenocarcinoma	287	-	8	1	18.33	217	53	30.88	[90]
	393	-	17	6	37.88	369	133	35.97	[91]
Skin cutaneous melanoma	287	P28L, C162F	5	1	297.67	276	159	80.62	[92]
Sarcoma	243	Y13Tfs 30	3	1	NA	240	91	65.41	[93]
Testicular germ cell cancer	149	-	2	0	NA	131	4	NA	[94]
Thyroid carcinoma	399	-	1	0	NA	398	14	NA	[95]
UCEC	240	A161T, R106I	2	0	NA	237	23	NA	[96]
	242	A161T, R106I	3	0	NA	239	32	NA	[97]

tumor cells are able to overcome the hurdle of the extracellular matrix (ECM) and spread into neighboring tissues [53]. Apart from this, cancer also associated with other important processes including inhibition of apoptosis, MDR, epithelial mesenchymal transition, etc., and sorcin has the ability to regulate different oncogenic genes involved in the regulation of these processes such as p-ERK, p-STAT3, NF-κB, p-Akt, survivin, Src, c-myc, etc. It also helps to inhibit apoptosis by inactivating caspase-3 and caspase-12 (Figure 3). Further, sorcin was suggested to promote the invasion and migration of different cancer cells as overexpression of sorcin resulted in an increased level of p-STAT3, MMP2, and MMP9. For instance, overexpression of sorcin was found to enhance the levels of CTSZ, p-STAT3, MMP2, and MMP9 in gastric cancer [20]. Also, the expression of sorcin was found to be 5.4-fold upregulated in gastric cancer cells (SGC7901 cells) than the normal cells [54]. Further, it was reported that upregulation of sorcin in HepG2, hepatocellular carcinoma cells, extensively increased the levels of mesenchymal marker vimentin and phosphorylated ERK1/2 (p-ERK1/2) and considerably reduced the levels of epithelial marker E-cadherin [28]. All these reports describe that sorcin may have an essential role in EMT. Further supporting this, sorcin was shown to stimulate EMT in colorectal cancer cells (HCT116 cells) through the activation of PI3K/Akt signaling pathway; upregulation of N-cadherin, fibronectin, vimentin, and α-SMA; and downregulation of E-cadherin [26].

As observed from the cBioPortal for Cancer Genomics data, several mutations of sorcin protein are associated with different kind of

cancers including bladder cancer, colorectal adenocarcinoma, prostate adenocarcinoma, skin cutaneous melanoma, sarcoma, and uterine corpus endometrial carcinoma, etc. (Table 1). In line with this, RNA sequencing analysis of patient samples revealed amplification of *SRI* gene to be associated with various cancers, which was evident from the TCGA cBioPortal database. Further, TCGA data showed that various cancers possess variable *SRI* gene amplification frequency. For example, esophagus cancer has the amplification frequency of 8.06% (15 cases), lung squamous cancer 4.11%, ovarian cancer 3.635%, stomach cancer 3.77%, pancreas cancer 2.15%, cholangiocarcinoma 1.96%, cervical cancer 1.29%, melanoma 0.84%, sarcoma 0.75%, breast cancer 0.81%, uterine cancer 0.18%, and testicular germ cell cancer 1.28%. In addition to gene amplification, different mutations of *SRI* gene were also reported in the TCGA database, and frequency of *SRI* gene mutation observed in different cancers is as follows: colorectal cancer 0.16%, uterine cancer 0.36%, prostate cancer 0.4%, and sarcoma 0.38%. To further reveal the association of sorcin with survival and prognosis of different cancer patients, the overall survival Kaplan-Meier estimate and disease/progression-free Kaplan-Meier estimate graphs from cBioportal for Cancer Genomics data were analyzed (Tables 1 and 2). As mentioned earlier, according to the TCGA database, sorcin shows different mutations in different cancers such as X84_splice (splice mutation) in bladder cancer, D157N (missense mutation) in colorectal adenocarcinoma, A161T (missense mutation) & Q48 (nonsense mutation) in prostate adenocarcinoma, P28L (missense mutation) & C162F (missense mutation) in skin cutaneous melanoma, Y13Tfs 30(FS del mutation) in sarcoma, and

Table 2. Disease/Progression-Free Survival by Kaplan-Meier Estimate.

Cancer	Total no. of Samples	Cases with Alteration (No.)			Cases without Alteration (No.)			References
		Total	Deceased	MMS	Total	Deceased	MMS	
Adrenocortical carcinoma	88	1	1	12.84	78	41	37.75	[64]
Bladder cancer	408	5	3	25.23	314	139	32.59	[65]
Breast invasive cancer	816	5	1	NA	753	84	214.72	[66]
	963	7	1	NA	872	101	214.72	[68]
Brain lower-grade glioma	283	4	3	10.84	256	87	47.7	[69]
BUC	127	1	1	25.23	98	50	18.23	[72]
Colorectal adenocarcinoma	220	3	1	NA	186	29	NA	[74]
Cholangiocarcinoma	35	1	0	NA	30	16	9.23	[75]
CSCCEA	191	2	0	NA	171	31	NA	[76]
Esophageal carcinoma	184	9	5	17.58	133	65	21.42	[77]
Glioblastoma	281	8	5	5.2	239	125	8.5	[78]
Glioblastoma multiforme	273	7	6	4.6	170	140	7.36	[79]
HNSCC	504	11	4	21.91	368	137	61.07	[81]
RPCC	280	1	0	NA	259	49	106.04	[82]
RCCC	448	2	0	NA	364	114	106.77	[84]
LNDLBL	48	1	0	NA	43	12	120.53	[85]
OSC	311	7	6	21.06	256	204	16.1	[86]
Pancreatic adenocarcinoma	149	3	3	18.23	112	68	14.75	[87]
Prostate adenocarcinoma	492	5	2	39.98	481	87	NA	[88]
Papillary thyroid carcinoma	399	1	0	NA	331	23	NA	[89]
Stomach adenocarcinoma	287	7	1	17.87	151	29	55.06	[90]
	393	16	6	18.86	289	87	55.06	[91]
Skin cutaneous melanoma	287	4	1	NA	246	192	49.21	[92]
Sarcoma	243	2	1	7.62	214	119	34	[93]
Testicular germ cell cancer	149	2	0	NA	129	33	191.43	[94]
Thyroid carcinoma	399	1	0	NA	385	35	NA	[95]
UCEC	240	2	0	NA	221	38	NA	[96]
	242	3	0	NA	225	46	NA	[97]

Abbreviations: *BUC*, bladder urothelial carcinoma; *CSCCEA*, cervical squamous cell carcinoma and endocervical adenocarcinoma; *HNSCC*, head & neck squamous cell carcinoma; *LNDLBL*, lymphoid neoplasm diffuse large B cell lymphoma; *MMS*, median month survival; *OSC*, ovarian serous cystadenocarcinoma; *RCCC*, renal clear cell carcinoma; *RPCC*, renal papillary cell carcinoma; *UCEC*, uterine corpus endometrial carcinoma.

A161T (missense mutation) & R106I (missense mutation) in uterine corpus endometrial carcinoma.

Similarly, analysis of the overall survival Kaplan-Meier estimate of different cancers revealed that the median month survival of patients with unaltered sorcin is higher than that of the patients with altered sorcin. The median month survival data for different cancer cases without sorcin gene alteration is as follows: bladder cancer 34.9 months, brain lower-grade glioma 75.1 months, glioblastoma 13.1 months, glioblastoma multiforme 13.63 months, kidney renal clear cell carcinoma 75.5 months, and stomach adenocarcinoma 30.88 months. However, in some of the cancers, patients with altered sorcin showed more median month survival such as breast cancer (163.1 months), esophageal carcinoma (44.71 months), head and neck squamous cell carcinoma (71.16 months), ovarian serous cystadenocarcinoma (50.33 months), and skin cutaneous melanoma (297.67 months) (Table 1). Likewise, the disease/progression-free survival of patients without sorcin alteration was as follows: adrenocortical carcinoma 37.75 months, bladder cancer 32.59 months, breast invasive cancer 214.72 months, brain lower grade glioma 47.7 months, bladder urothelial carcinoma 18.23 months, cholangiocarcinoma 9.23 months, esophageal carcinoma 21.42 months, glioblastoma 8.5 months, glioblastoma multiforme 7.36 months, head and neck squamous cell carcinoma 61.07 months, kidney renal papillary cell carcinoma 106.04 months, kidney renal clear cell carcinoma 106.77 months, lymphoid neoplasm diffuse large B-cell lymphoma 120.53 months, ovarian serous cystadenocarcinoma 16.1 months, pancreatic adenocarcinoma 14.75 months, stomach adenocarcinoma 55.06 months, skin cutaneous melanoma 49.21 months, sarcoma 34 months, and testicular germ cell cancer 191.43 months. And patients

with altered sorcin had the disease/progression-free survival as follows: adrenocortical carcinoma 12.84 months, bladder cancer 25.23 months, brain lower-grade glioma 10.84 months, bladder urothelial carcinoma 25.23 months, esophageal carcinoma 17.58 months, glioblastoma 5.2 months, glioblastoma multiforme 4.6 months, head and neck squamous cell carcinoma 21.91 months, ovarian serous cystadenocarcinoma 21.06 months, pancreatic adenocarcinoma 18.23 months, prostate adenocarcinoma 39.98 months, stomach adenocarcinoma 17.87 months, and sarcoma 7.62 months (Table 2).

Functions in MDR

MDR has turned out to be a major hurdle for effective cancer chemotherapies. MDR has been defined as the resistance of cancer cells to different chemotherapeutic drugs that may have diverse structures and mechanisms of action. It is the most prominent reason for the failure of most of the chemotherapeutic drugs in cancer treatment as the effect of these drugs decreases when the cancer cells acquired MDR. Cancer cells acquire MDR through ABC transporter family, resistance to apoptosis induction, autophagy, cancer stem cells, miRNA, hypoxia, DNA damage and repair, and epigenetic regulation. Therefore, there is an urgent need to discover MDR associated biomarkers to enhance the success of chemotherapeutic drugs for the treatment of cancer patients [55]. Sorcin is one such protein, which was recently found to be associated with MDR in various cancers. MDR is known to be mediated by different drug resistance genes such as MDR1, MRP1, etc. MDR1, MRP1, and GST- π together form the classical MDR pathway. Thus, these two proteins, MDR1 and MRP1, are well established to have an important role in chemotherapeutic drug efflux and lead to MDR.

Interestingly, sorcin was found to regulate the levels of MDR1 and MRP1 along with the expression of various other MDR related genes including GST- π , Livin, Src, survivin, Bcl-2, cyclin-D1, c-myc, p21, and p53. Silencing of sorcin resulted in the downregulation of these genes in addition to p-Akt and NF- κ B levels inducing chemoresistance in myeloma cells (Figure 3) [27]. Further, upregulation of sorcin was shown to modulate the activity of different chemotherapeutic drugs such as doxorubicin, paclitaxel, cisplatin, homoharringtonine, vincristine, etc. [25,56].

Doxorubicin is a well-known chemotherapeutic drug used for treating different cancers including breast cancer, bladder cancer, and blood cancer (leukemia). It was shown that sorcin has the ability to bind with doxorubicin, leading to the decreased levels of drug inside the cells, and also increases its efflux via MDR1 [18]. Likewise, chemoresistance to cisplatin in MDR cells is also associated with the co-amplification of sorcin [57]. Further, it was also reported that sorcin has prognostic value in childhood acute lymphoid leukemia (ALL), which may be related to the upregulation of MDR1/P-gp gene expression which plays an important role in the regulation of drug distribution in different tissues [58]. Similarly, co-amplification of sorcin and MDR1 gene observed in leukemia can be taken as a good indicator of clinical drug resistance and prognosis of the disease [59]. Further proving the importance of sorcin in MDR, overexpression of sorcin in K562 cells by gene transfection led to the increase in drug resistance, from 4.1- to 22.5-fold, to various chemotherapeutic drugs such as doxorubicin, etoposide, homoharringtonine, and vincristine [25]. Moreover, increased expression of this protein in multidrug-resistant cells of various cancers indicates that sorcin may have a pivotal role in the development of resistant phenotype [30,32,60]. In contrast to these reports, Parekh et al. (2002) showed the overexpression of sorcin to be associated with reduced paclitaxel resistance in various cancers [56]. Furthermore, it was shown that tetrandrine (Tet) treatment helps in the chemosensitization of K562/A02 cells by downregulating sorcin [61]. Likewise, haishengsu (HSS), a conventional drug from *Tegillarca granosa* that suppresses the expression of sorcin and P-gp protein was shown to increase the chemosensitivity in leukemic patients and to induce apoptosis in the drug resistant K562/ADM tumors of mice [62,63].

Conclusion

Taken together, sorcin (22 kDa) is a small penta EF family of soluble calcium (Ca²⁺) binding protein that shows an association with calcium homeostasis, endometrial receptivity, cancer development, and MDR. It also shows differential expression pattern in malignant cells and MDR cancer cells. It is known to be tightly associated with ribosomes, rough endoplasmic reticulum, mitochondria, and nuclear membranes. In the last few years, sorcin has appeared as one of the most fascinating executive for calcium homeostasis in the cells. However, the expression level of sorcin is much lower than the calmodulin (calcium binding protein) protein. Several reports have implicated that apart from calcium-ion regulation, sorcin may also be involved in maintaining the dimensions of ER vesicles, regulation of cell cycle progression through activation of mitosis and cytokinesis and in regulating the activity of Ca²⁺-dependent kinases. In addition to this, sorcin also was found to regulate angiogenesis, invasion, and migration of different tumor cells by regulating various key molecules involved in the processes such as NF- κ B, CTSZ, STAT3, Akt, ERK1/2, VEGF, MMPs, caspases, and signaling pathways including ERK, MAPK/ERK, and PI3K/Akt. Sorcin was also found to induce

metastasis and chemoresistance in malignant cells. Further, the calcium homeostasis, basic function of sorcin, is the important cellular response to stress conditions favoring the drug resistance in tumor progression. Analysis of the hepatocellular carcinoma patient samples revealed sorcin overexpression to be associated with worse prognosis. Upregulation of sorcin in malignant cells significantly induces the cell proliferation, migration, and invasion, and knockdown of the same diminished the proliferation, migration, and invasion of cancer cells, revealing the importance of sorcin in the development and progression of cancer. Adding to its cancer-promoting effects, sorcin was proved to induce MDR against various chemotherapeutic agents through modulation of MDR1, MRP1, NF- κ B, apoptotic, antiapoptotic, survival proteins. Downregulation of sorcin may lead to membrane hyperpolarization and reduce calcium content in mitochondria which may further promote the drug-induced apoptosis in malignant cells. TCGA data analysis also showed alteration status of sorcin gene to be significantly associated with survival of cancer patients, suggesting the prognostic value of this protein. Further, the increased levels of sorcin observed in different multidrug-resistant cells implicate the possibility of using it as a potential biomarker for predicting MDR in various cancers. Until now, maximum research on sorcin has focused on the connection between sorcin and diseases but rarely discussed about the regulation of sorcin by different chemotherapeutic drugs. Also, there is an indispensable need for novel therapeutic strategies targeting sorcin for better management of different multidrug resistant cancers. However, further studies are obligatory to unveil the actual role of sorcin in the development of cancers and the multidrug resistant (MDR) phenotype and to define sorcin as a novel diagnostic and therapeutic marker for different cancers.

Acknowledgement

This work was supported by BT/529/NE/TBP/2013 awarded to Ajaikumar B Kunnumakkara by Department of Biotechnology (DBT), Government of India. The author Kishore Banik acknowledges the UGC New Delhi for providing him the fellowship.

Conflict of Interest

The authors declare no conflict of interest.

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