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Steroid receptor-associated and regulated protein is a biomarker in predicting the clinical outcome and treatment response in malignancies

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Abstract

Background: Steroid receptor-associated and regulated protein (SRARP) has recently been identified as a novel tumor suppressor in malignancies of multiple tissue origins. *SRARP* is located on chromosome 1p36.13 and is widely inactivated by deletions and epigenetic silencing in malignancies. Therefore, additional studies are required to explore *SRARP* as a potential cancer biomarker.

Aim: This study explores the application of *SRARP* as a novel biomarker in malignancies of multiple tissue origins using the analysis of large genomic datasets.

Methods and results: A comprehensive genomic analysis of large cancer datasets was carried out to examine the association of *SRARP* expression and copy-number with molecular and clinical features in malignancies of multiple tissue origins. This study demonstrated that *SRARP* under-expression and copy-number loss are strongly associated with the loss of other tumor suppressors such as *TP53* and *NF1* mutations and oncogenic gains, including *N-MYC* amplification and *ERG* rearrangement, suggesting that *SRARP* inactivation is associated with wider genomic instability in malignancies. Importantly, *SRARP* under-expression and copy-number loss are strong predictors of poor clinical and/or pathological features in breast, colorectal, lung, prostate, gastric, endometrial, cervical, brain, ovarian, bladder, thyroid, and hepatocellular cancers as well as neuroblastoma, uveal melanoma, and acute myeloid leukemia with highly significant odds ratios. Finally, higher *SRARP* expression and copy-number predict a better response to several cancer drugs.

Conclusion: This study suggests that the *SRARP* inactivation presents a robust biomarker in predicting molecular and clinicopathological features, and treatment response in malignancies.

KEYWORDS

biomarker, cancer outcome, SRARP, treatment response

1 | INTRODUCTION

Steroid receptor-associated and regulated protein (SRARP) has been recently identified as a novel tumor suppressor and a corepressor of the androgen receptor (AR).[1,2] *SRARP* and its gene pair, *HSPB7*, are located 5.2 kb apart on chromosome 1p36.13 and are widely inactivated by deletions and epigenetic silencing in malignancies.[1] Tumor suppressor functions of *SRARP* and *HSPB7* are supported by the fact that the overexpression of these genes markedly suppresses colony formation and cell viability in cancer cell lines of different

tissue origins.[1] In addition, these effects are associated with the down-regulation of Akt and extracellular signal-regulated kinases (ERK) signaling, and SRARP expression inversely correlates with genes that promote cell proliferation and signal transduction, further supporting its functions as a tumor suppressor.[1] It is also notable that 1p36 is frequently deleted in malignancies and 1p36.1 losses occur in 34% of tumors.[3] However, despite extensive studies, there has been limited success for identifying candidate tumor suppressors on chromosome 1p36.[3,4] Therefore, further studies are required to elucidate the biological and prognostic implications of genes located on 1p36 in malignancies.

Furthermore, SRARP expression highly correlates with AR in breast cancer and there is a transcriptional interplay between these two genes.[2] In this process, AR exerts dual regulatory effects on SRARP and although an increased AR activity suppresses SRARP transcription, a minimum level of AR activity is required to maintain baseline SRARP expression in AR+ cancer cells.[1,2] SRARP, in turn, interacts with AR as a corepressor and negatively regulates the AR-mediated induction of prolactin-induced protein and AR reporter activity.[2] SRARP also has a relatively higher expression in breast tumors that are estrogen receptor positive (ER+), lower grade, and lobular histology.[2,5] Other studies have suggested that SRARP is involved in the transcriptional activities of ER in ER+ breast cancer cells.[6] Therefore, while *SRARP* is broadly inactivated in malignancies and function as a tumor suppressor, when expressed in AR+ cells, this gene carries a transcriptional regulatory function as a corepressor of AR.[1,2]

Importantly, genome and epigenome-wide associations of *SRARP* with survival strongly support its function as a tumor suppressor.[1] In this respect, DNA hypermethylation, lower expression, somatic mutations, and lower copy-number of *SRARP* are strongly associated with worse cancer outcome.[1] Moreover, DNA hypermethylation and lower expression of *SRARP* in normal adjacent tissues predict poor survival, suggesting that *SRARP* inactivation is an early event in carcinogenesis.[1] Therefore, genomic and epigenomic inactivation of *SRARP* may provide valuable prognostic markers in malignancies and normal adjacent tissues with translational applications, and additional studies are required to explore the potential applications of *SRARP* as a biomarker.

Of note, HSPB7 also has tumor suppressor function in several cancer cell lines.[1,7] Although *HSPB7* copy-number loss predicts poor survival, *HSPB7* expression and DNA methylation levels do not have the same prognostic impact as those of *SRARP* in malignancies and normal adjacent tissues.[1] These findings have led to a focus on the prognostic implications of *SRARP* in the current study. Here, a comprehensive analysis of large datasets was conducted to explore *SRARP* as a biomarker in malignancies of multiple tissue origins.

2 | MATERIALS AND METHODS

2.1 | Differential analysis for *SRARP* expression and copy-number

Differential analysis for *SRARP* expression and copy-number was carried out using the datasets available in *ONCOMINE* database, Research Premium Edition (Life Technologies, Grand Island, New York), (www.oncomine.org).[8] First, differential analysis was conducted to examine the association of *SRARP* expression and copy-number with response to cancer therapies. To achieve this, a total of 20 treatment response datasets from brain, breast, colorectal, leukemia, lung, lymphoma, melanoma, multicancer, myeloma, and sarcoma malignancies, including both targeted therapy and chemotherapy studies were analyzed.[9-13] Fold change of *SRARP* expression or copy-number for each treatment sensitive/resistant group and *P* value for each fold-change at a significance level of $P < .05$ were calculated. A Student's *t* test was performed to calculate the *P* value, and fold-change for the magnitude of differential expression between the two groups was calculated and presented in log2 scale. Biostatistics was carried out using the IBM SPSS Statistics 25 (Armonk, New York).

In addition, to examine whether SRARP expression is induced following treatments, differential expression of SRARP between treatment and control groups was analyzed using datasets for hypoxia in human mammary breast epithelial cells, bortezomib treatment in breast cancer cells, chemotherapy with epirubicin plus cyclophosphamide followed by docetaxel (EC-D) in breast cancer, and ErbB2 inhibition with pertuzumab and trastuzumab in ovarian cancer.[14-17] Fold change of SRARP expression for each treatment/control group and *P* value for each fold change were calculated.

Furthermore, the association of *SRARP* under-expression and copy-number loss with tumor suppressor and oncogenic features, molecular and pathological subtypes, and clinical outcome were assessed in malignancies of multiple tissue origins. In this process, using datasets available in *ONCOMINE* database, a total of 14 tumor suppressor and oncogenic features,[9,18-26] and 40 molecular, pathological, and clinical features were analyzed.[9,20,22,25,27-54]A Student's *t* test was performed in each dataset to calculate the *P* value for the significance of differential analysis for each gene between the two groups. Next, genes were ranked based on their *P* values and the percentile of *SRARP* under-expression or copy-number loss, and the *P* value and odds ratio (OR) of *SRARP* differential analysis were measured in each dataset. Moreover, the association of each cancer drug, for which *SRARP* was found to be a predictor of response, was investigated with the *SRARP*-associated tumor suppressor genes or oncogenes using the differential analysis. Fold-change for each treatment sensitive/resistant group was calculated at a significance level of $P < .05$.

2.2 | Cell culture and treatments

MCF-7 and T-47D breast cancer cell lines were obtained from the European Collection of Authenticated Cell Cultures (ECACC) through Sigma-Aldrich (St. Louis, Missouri). Cell lines were authenticated using STR DNA Profiles and were tested free from mycoplasma contamination. Cell lines were cultured in DMEM/F12 medium (Life Technologies, Grand Island, New York) supplemented with 10% fetal bovine serum (FBS), (Fisher Scientific, Waltham, Massachusetts). Cell line treatments with proteasome inhibitor bortezomib (Selleck Chemicals, Houston, Texas) were performed at 0.8 nM concentration for

48 hours. Treatments with epirubicin (Sigma-Aldrich, St Louis, Missouri) was carried out at 50 nM concentration for 48 hours. Cell lines treated with vehicle only were applied as control groups.

2.3 | RNA extraction and quantitative real time-polymerase chain reaction

RNA extraction was performed using the RNeasy Mini Kit (Qiagen, Valencia, California). SRARP gene expression was measured by quantitative real time-polymerase chain reaction (qRT-PCR). Taqman Gene Expression Assay (Life Technologies) for SRARP (assay ID: Hs00698851_m1) was employed for qRT-PCR as instructed by the manufacturer. Housekeeping gene RPLP0 (Life Technologies) was used as control. Fold-change in gene expression is gene expression in treated group/average gene expression in the control group. Experiments were carried out in four replicates. Statistical analysis was carried out using the paired sample *t* test.

3 | RESULTS

3.1 | *SRARP* is a biomarker for better response to cancer therapies

SRARP functions as a tumor suppressor and its inactivation predicts poor clinical outcome in malignancies.[1] Therefore, it was hypothesized that *SRARP* may be a biomarker for response to cancer therapies. To examine this hypothesis, differential analysis was conducted to examine the association of *SRARP* expression and copy-number with the response to cancer therapies in a total of 20 treatment response datasets, including both targeted therapy and chemotherapy studies. Fold-change of *SRARP* expression or copy-number for each treatment sensitive/resistant group and *P* value for each fold-change were calculated.

Importantly, higher levels of *SRARP* expression or copy-number predicted a significantly better response to cancer therapies in all 20 datasets ($P < .05$, Table 1 and Figures 1A-D). Of note, *SRARP* predicted a better response to the cancer therapies against several targets in the ERK signaling pathway across multiple malignancies (Table 1). The most prominent fold ratio was observed with ErbB2 inhibitor lapatinib in breast cancer in which SRARP expression was 4.7-fold higher in sensitive compared to resistant samples ($P < .05$, Table 1). In addition, higher *SRARP* copy-number predicted a significantly better response to CHIR-265, an inhibitor of B-RAF and RAF1, in brain cancer, myeloma, and a multicancer dataset ($P < .05$, Table 1 and Figure 1C). Furthermore, higher *SRARP* copy-number and expression levels predicted a better response to mTOR inhibitors temsirolimus or sirolimus in brain tumors (DNA), lung cancer (DNA), and sarcoma (RNA), ($P < .05$, Table 1 and Figure 1B). Moreover, *SRARP* copy-number predicted an improved response to IGF1R inhibitor GSK1139710 in a multicancer dataset ($P < .05$, Table 1).

It is notable that higher *SRARP* copy-number predicted a significantly better response to other targeted therapies, including to a pan-

TABLE 1 Association of steroid receptor-associated and regulated protein (SRARP) expression and copy-number with response to cancer therapies. Cancer type, drug, reference number for the dataset, target of therapies, data type (DNA or RNA), fold change of sensitive/resistant, *P* value for fold change ($P < .05$), and sample numbers (No.) are shown

Cancer	Drug	Target	Data	Fold	*P* value	Sample No.
Brain	CHIR-265[9]	B-RAF, RAF1	DNA	1.21	7.37E-04	18
Brain	Temsirolimus[10]	mTOR	DNA	1.2	2.20E-02	11
Breast	Lapatinib[9]	ErbB2	RNA	4.7	0.044	22
Colorectal	Topotecan[9]	Topoisomerase I	DNA	1.11	0.035	12
Leukemia	Compound E[11]	γ-secretase-notch	RNA	1.64	0.004	14
Leukemia	Compound E[12]	γ-secretase-notch	RNA	1.3	0.029	20
Lung	Purvalanol[13]	CDK (1,2,4), Src	DNA	1.1	0.026	40
Lung	Sirolimus[13]	mTOR	DNA	1.1	0.044	55
Lymphoma	Paclitaxel[9]	Microtubules	RNA	1.17	0.01	22
Melanoma	GSK1070916[10]	Aurora kinase	DNA	1.13	8.00E-03	11
Melanoma	Topotecan[9]	Topoisomerase I	RNA	1.11	0.028	16
Multicancer	PHA-665752[9]	c-Met	DNA	1.1	0.022	460
Multicancer	GSK1139710[10]	IGF1R	DNA	1.15	0.038	138
Multicancer	Panobinostat[9]	HDAC (pan)	DNA	1.03	0.024	253
Multicancer	GSK661637[10]	Pan-PLK	DNA	1.1	0.017	163
Multicancer	Pazopanib[10]	VEGFR1-3	DNA	1.1	0.005	193
Multicancer	CHIR-265[9]	B-RAF, RAF1	DNA	1.05	3.67E-04	271
Myeloma	CHIR-265[9]	B-RAF, RAF1	DNA	1.13	0.019	11
Sarcoma	Panobinostat[9]	HDAC (pan)	DNA	1.13	0.021	10
Sarcoma	Temsirolimus[10]	mTOR	RNA	1.17	0.032	12

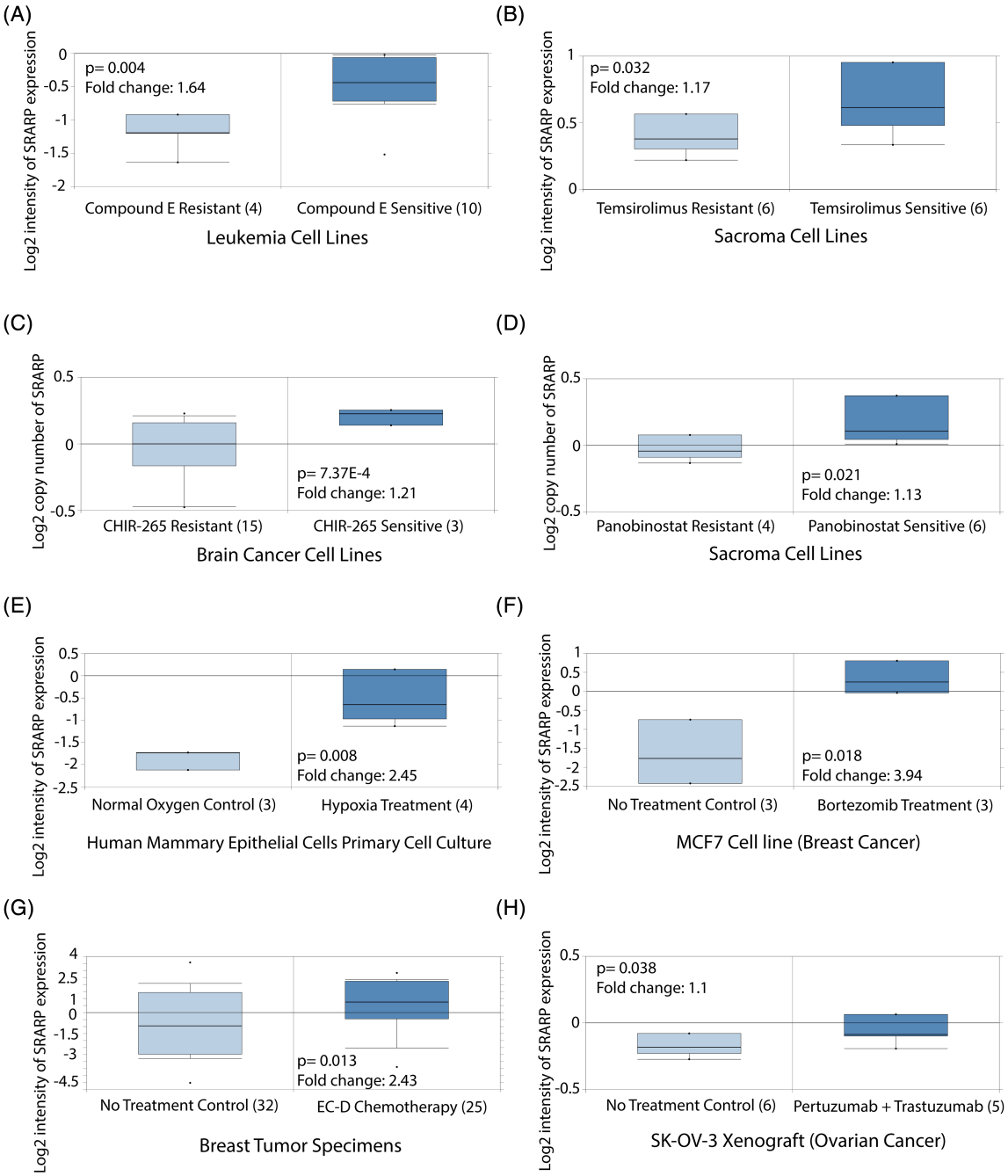

FIGURE 1 The association of steroid receptor-associated and regulated protein (SRARP) expression and copy-number with response to cancer treatments and induction of SRARP expression following therapies. A, Differential expression of SRARP in leukemia cell lines treated with compound E. Fold-change and *P* value for the magnitude of differential expression between the sensitive and resistant groups were calculated and presented in log2 scale using box plots. B, Differential expression of SRARP in sarcoma cell lines treated with temsirolimus. C, Differential copy-number of *SRARP* in brain cancer cell lines treated with CHIR-265. Fold-change and *P* value for the magnitude of differential copy-number between the sensitive and resistant groups were calculated and presented in log2 scale using box plots. D, Differential copy-number of *SRARP* in sarcoma cell lines treated with panobinostat. E, Differential expression of SRARP in human mammary epithelial cells following hypoxia. Fold-change and *P* value for the magnitude of differential expression between the treatment and control groups were calculated and presented in log2 scale using box plots. F, Differential expression of SRARP in MCF-7 breast cancer cell line treated with bortezomib. G, Differential expression of SRARP in breast tumor specimens following treatment with EC-D chemotherapy. H, Differential expression of SRARP in SK-OV-3 ovarian cancer xenograft treated with pertuzumab and trastuzumab

HDAC inhibitor panobinostat in sarcoma (Figure 1D), and a multicancer dataset; VEGFR1-3 inhibitor pazopanib in a multicancer dataset; multikinase inhibitor purvalanol in lung cancer; Aurora Kinase inhibitor GSK1070916 in melanoma; c-Met inhibitor PHA-665752 in a multicancer dataset; and pan-PLK inhibitor GSK661637 in a multicancer dataset ($P < .05$, Table 1). Furthermore, higher SRARP

expression levels predicted an improved response to compound E, an inhibitor of γ-secretase-Notch, in two leukemia datasets ($P < .05$, Figure 1A and Table 1). In addition, higher *SRARP* copy-number and expression levels predicted a better response to chemotherapy agent topotecan in colorectal cancer and melanoma, respectively ($P < .05$, Table 1). Finally, higher SRARP expression was a predictor of an improved response to antimicrotubular chemotherapy with paclitaxel in lymphoma ($P < .05$).

To examine whether SRARP expression is induced following treatments, differential expression of SRARP between treatment and control groups was analyzed using datasets for hypoxia, proteasome inhibitor bortezomib, chemotherapy with EC-D, and ErbB2 inhibition with pertuzumab and trastuzumab (Figures 1E-H). Notably, hypoxia-induced SRARP expression by 2.45-fold in human mammary epithelial cells ($P = .008$, Figure 1E), bortezomib increased SRARP expression by 3.94-fold in MCF-7 breast cancer cell line ($P = .018$, Figure 1F), and EC-D chemotherapy induced SRARP expression by 2.43-fold in breast tumor specimens ($P = .013$, Figure 1G). In addition, treatment with pertuzumab and trastuzumab increased SRARP expression by 1.1-fold in an ovarian cancer xenograft model ($P = .038$, Figure 1H).

The effects of bortezomib and epirubicin treatments on the expression of SRARP were further investigated using breast cancer cell lines MCF-7 and T-47D. SRARP expression was assessed using qRT-PCR after cell line treatments and fold changes in gene expression were calculated relative to the control group in each cell line. Bortezomib treatment induced SRARP expression by approximately 3- to 4-fold in MCF-7 and T-47D cell lines ($P < .01$, Figure 2A). In addition, epirubicin treatment increased SRARP expression by about 2-fold in MCF-7 and T-47D cells compared to the vehicle control ($P < .01$, Figure 2B). These *in vitro* findings are consistent with the data presents in Figure 1 and suggest that SRARP expression is induced by selective cancer therapies.

Collectively, these findings suggest that higher *SRARP* expression and copy-number are predictors of better response to several targeted therapies and chemotherapies in malignancies of multiple tissue origins and particularly, *SRARP* is a biomarker of better response to inhibitors of the ERK signaling pathway. In addition, SRARP is induced following hypoxia in normal mammary cells, and following cancer therapies in malignant breast tissues and cell lines, suggesting that it may be involved in the treatment-mediated effects on cancer cells.

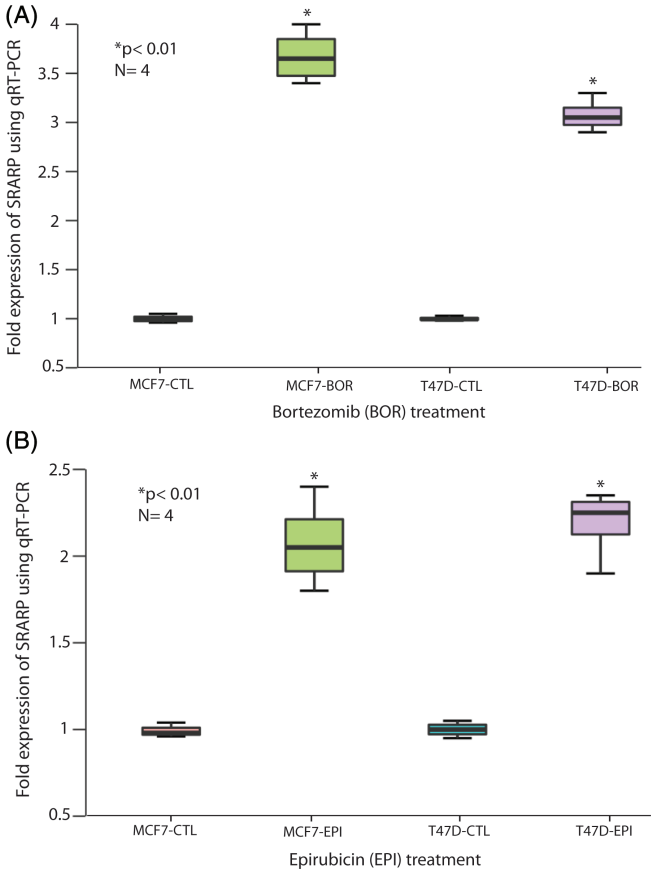

FIGURE 2 The effects of bortezomib and epirubicin treatments on steroid receptor-associated and regulated protein (SRARP) expression using quantitative real time-polymerase chain reaction (qRT-PCR). A, The effect of bortezomib (BOR) treatment on the expression of SRARP in breast cancer cell lines MCF-7 and T-47D. SRARP expression was assessed using qRT-PCR and fold changes in gene expression were calculated relative to the control group in each cell line. *$P < .01$ was calculated using the paired sample *t* test. B, The effect of epirubicin (EPI) treatment on the expression of SRARP in breast cancer cell lines MCF-7 and T-47D. SRARP expression was assessed using qRT-PCR. *$P < .01$ was calculated using the paired sample *t* test

3.2 | *SRARP* inactivation is associated with the loss of tumor suppressors and oncogenic gains

Carcinogenesis involves a process of inactivation of tumor suppressors and gain in oncogenes. It has recently been shown that *SRARP* is a tumor suppressor commonly inactivated in malignancies by epigenetic silencing, copy-number loss, and somatic mutations.[1] To further investigate the involvement of *SRARP* in carcinogenesis, the association of *SRARP* expression and copy-number with 14 tumor suppressor and oncogenic features were examined in cancer datasets. The percentile of *SRARP* under-expression or copy-number loss, *P* value, and OR were calculated using differential analysis.

Notably, *SRARP* under-expression and copy-number loss were significantly associated with mutations and deletions of tumor suppressors in malignancies (Table 2). Strikingly, *SRARP* was highly associated with *NF1* mutation in sarcoma featuring among the top 5% of copy-number losses with a highly significant OR of 4429.6, $P = 5.54E\text{-}249$ (Table 2). In breast cancer, *SRARP* was in the top 1% of under-expressed genes associated with *TP53* mutation ($P = 2.72E\text{-}14$, OR: 57.8) and the top 5% of under-expressed genes associated with *BRCA1* mutation ($P = 6.63E\text{-}12$, OR: 14), (Table 2). In prostate cancer, *SRARP* featured among the top 1% of under-expressed genes in *ETS2* deletion ($P = .0002$, OR: 5.3) and top 5% of copy-number losses in *ZFHX3* mutation ($P = 1.69E\text{-}76$, OR: 23.2), (Table 2). In addition, *SRARP* was in the top 5% of under-expressed genes associated with

TABLE 2 Association of steroid receptor-associated and regulated protein (SRARP) expression and copy-number with tumor suppressor and oncogenic features in malignancies. For each molecular feature, cancer type, change in *SRARP* expression or copy-number, *P* value, odds ratio, and name of dataset are shown

Cancer type	Molecular feature	Change in SRARP	*P* value	Odds ratio	Dataset
Breast	*TP53* mutation	Top 1% under-expressed	2.72E-14	57.8	Gluck et al[18]
Breast	*BRCA1* mutation	Top 5% under-expressed	6.63E-12	14	Waddell et al[19]
Cecum	*K-RAS* mutation	Top 10% copy loss	2.94E-05	1.4	TCGA [20]
Hepatocellular	*TP53* mutation	Top 5% under-expressed	1.33E-04	1.3	Chiang et al[21]
Lung	*K-RAS* mutation	Top 1% copy-number loss	1.97E-58	49.3	TCGA[22]
Lung adeno	*APC* deletion	Top 10% under-expressed	1.69E-05	1.4	Ding et al[23]
Myeloma	*IGH-CCD1* fusion	Top 10% under-expressed	8.48E-28	2.1	Chapman et al[24]
Neuroblastoma	*ALK* amp	Top 5% copy-number loss	7.54E-82	25.3	Chen et al[25]
Neuroblastoma	*N-MYC* amp	Top 1% copy-number loss	3.79E-254	946.1	Chen et al[25]
Prostate	*ETS2* deletion	Top 1% under-expressed	.0002	5.3	Grasso et al[26]
Prostate	*ETS* gene Fusion	Top 1% under-expressed	3.08E-09	9.1	Grasso et al[26]
Prostate	*ERG* rearrang	Top 5% under-expressed	1.76E-197	186.2	Grasso et al[26]
Prostate	*ZFHX3* mutation	Top 5% copy-number loss	1.69E-76	23.2	Grasso et al[26]
Sarcoma	*NF1* mutation	Top 5% copy-number loss	5.54E-249	4429.6	Barretina et al[9]

Note: "amp" is amplification, "rearrang" is rearrangement, and "adeno is adenocarcinoma.

TP53 mutation in hepatocellular carcinoma (*P* = 1.33E-04, OR: 1.3) and top 10% of under-expressed genes associated with *APC* deletion in lung adenocarcinoma (*P* = 1.69E-05, OR: 1.4), (Table 2).

Moreover, *SRARP* under-expression and copy-number loss were also associated with oncogenic gains (Table 2). In neuroblastoma, *SRARP* was among the top 1% of copy-number losses associated with *N-MYC* amplification at a highly significant OR of 946.1 (*P* = 3.79E-254) and top 5% of copy-number losses associated with *ALK* amplification (OR: 25.3, 7.54E-82), (Table 2). In addition, *K-RAS* mutation was significantly associated with *SRARP* copy-number losses in lung and cecum cancers with OR of 49.3 (*P* = 1.97E-58) and 1.4 (*P* = 2.94E-05), respectively (Table 2). In prostate cancer, *SRARP* was in the top 1% of under-expressed genes associated with *ETS* gene fusion (*P* = 3.08E-09, OR: 9.1) and top 5% of under-expressed genes associated with *ERG* rearrangement (*P* = 1.76E-197, OR: 186.2), (Table 2). Finally, *SRARP* was among the top 10% of under-expressed genes associated with *IGH-CCD1* fusion in myeloma (*P* = 8.48E-28, OR: 2.1).

The association of each cancer drug, for which *SRARP* was found to be a predictor of response (Table 1), was investigated with the *SRARP*-associated tumor suppressors or oncogenes using the differential analysis. These analyses indicated that the expression or copy-number variations of several *SRARP*-associated tumor suppressors and oncogenes are predictors of response to cancer therapies like those observed with *SRARP* (*P* < .05, Table 3). The significant associations were observed across various cancer types for targeted therapies such as PHA-665752, CHIR-265, temsirolimus and Panobinostat as well as for chemotherapy drugs topotecan and paclitaxel (Table 3). Of note, higher copy-number or expression of tumor suppressor genes (*TP53*, *BRCA1*, *APC*, *ETS2*, *ZFHX3*, and *NF1*) and lower copy-number or expression of oncogenes (*K-RAS*, *ALK*, and *N-MYC*) were associated with a better response to cancer drugs (Table 3). Among the *SRARP*-associated cancer genes, *TP53* and *NF1* showed the greatest number of associations with the response to cancer drugs (Table 3).

Therefore, *SRARP* under-expression and copy-number loss are highly associated with the loss of other tumor suppressor genes and oncogenic gains, suggesting that *SRARP* inactivation is associated with wider genomic instability in malignancies.

3.3 | *SRARP* inactivation predicts poor pathological and clinical features in malignancies

The value of *SRARP* under-expression and copy-number loss as a biomarker for molecular, pathological, and clinical features was investigated in malignancies of multiple tissue origins using differential analysis. Importantly, *SRARP* under-expression and copy-number loss were strong predictors of poor clinical outcome and advanced disease in multiple malignancies (Table 4). Notably, *SRARP* was in the top 5% of copy-number losses associated with dead at 3 years in neuroblastoma (*P* = 3.00E-244, OR: 2185), advanced stage in cervical cancer (*P* = 5.78E-244, OR: 2176), dead at 5 years in breast cancer (*P* = 1.51E-04, OR: 2.6), dead at 5 years and advanced stage in colon cancer (*P* = 5.42E-76, OR: 6.6 and *P* = 4.16E-121, OR: 46.4), dead at 1 year in endometrial cancer (*P* = 4.41E-52, OR: 14.9), advanced stage and high grade in gastric cancer (*P* = 1.86E-10, OR: 4.2 and *P* = 1.29E-08, OR: 3.7), recurrence at 3 years in hepatocellular carcinoma (*P* = 1.20E-207, OR: 244.2), and metastasis in thyroid cancer (*P* = 1.31E-34, OR: 10.1), (Table 4). In addition, *SRARP* was among the top 1% of copy-number loss, predicting dead at 1 year in

TABLE 3 List of cancer drugs for which steroid receptor-associated and regulated protein (SRARP) is a predictor of response and are also associated with the expression and copy-number variations of the *SRARP*-associated tumor suppressors or oncogenes. Gene names, cancer drugs, data type (DNA or RNA), fold change of sensitive/resistant, cancer type, and name of dataset are shown

Gene	Drug	Data	Fold	Cancer	Dataset
TP53	Topotecan	DNA	1.2	Colorectal	Barretina et al[9]
	PHA-665752	RNA	1.35	Multicancer	Barretina et al[9]
	Paclitaxel	RNA	1.54	Lymphoma	Barretina et al[9]
	CHIR-265	RNA	1.25	Multicancer	Barretina et al[9]
	Topotecan	RNA	2.13	Melanoma	Barretina et al[9]
	GSK1070916	RNA	1.47	Melanoma	Wooster et al[10]
	GSK661637	RNA	1.3	Multicancer	Wooster et al[10]
	Temsirolimus	DNA	1.15	Brain	Wooster et al[10]
BRCA1	Panobinostat	RNA	1.3	Multicancer	Barretina et al[9]
	CHIR-265	RNA	1.4	Myeloma	Barretina et al[9]
	GSK661637	RNA	1.18	Multicancer	Wooster et al[10]
K-RAS	Topotecan	DNA	0.80	Colorectal	Barretina et al[9]
	Panobinostat	DNA	0.75	Sarcoma	Barretina et al[9]
	Panobinostat	RNA	0.81	Sarcoma	Barretina et al[9]
APC	CHIR-265	RNA	2.5	Myeloma	Barretina et al[9]
ALK	Paclitaxel	DNA	0.88	Lymphoma	Barretina et al[9]
	CHIR-265	DNA	0.85	Brain	Barretina et al[9]
	Temsirolimus	RNA	0.71	Brain	Wooster et al[10]
N-MYC	PHA-665752	DNA	0.83	Multicancer	Barretina et al[9]
	CHIR-265	DNA	0.88	Brain	Barretina et al[9]
ETS2	Compound E	RNA	1.85	Leukemia	Palomero et al[11]
ZFHX3	Topotecan	RNA	1.2	Melanoma	Barretina et al[9]
NF1	PHA-665752	RNA	1.6	Multicancer	Barretina et al[9]
	CHIR-265	RNA	1.36	Myeloma	Barretina et al[9]
	Topotecan	RNA	1.37	Colorectal	Barretina et al[9]
	Topotecan	RNA	1.32	Melanoma	Barretina et al[9]
	Compound E	RNA	1.34	Leukemia	Palomero et al[11]

Note: For each fold change, *P* value is <.05.

oligodenroglioma (*P* = 9.05E-73, OR: 65.5) and advanced nodal stage in rectal cancer (*P* = 2.34E-127, OR: 50.6), (Table 4).

Moreover, SRARP was in the top 1% of under-expressed genes associated with recurrence at 1 year and high grade in breast cancer (*P* = 3.55E-94, OR: 90.3 and *P* = 9.96E-10, OR: 62.9), recurrence at 3 years in lobular breast carcinoma (*P* = 5.96E-14, OR: 12.1), high grade in breast ductal carcinoma *in situ* (*P* = 4.44E-15, OR: 13), dead at 1 year in lung cancer (*P* = 6.75E-04, OR: 4.5), and advanced stage in ovarian cancer (*P* = .009, OR: 3.6), (Table 4). SRARP was among the top 5% of under-expressed genes, predicting dead at 3 years in acute myeloid leukemia (*P* = .008, OR: 2.1), recurrence in astrocytoma (*P* = 4.56E-05, OR: 1.9), dead at 5 years in bladder cancer (*P* = .002, OR: 2.3), metastasis in uveal melanoma (*P* = 2.40E-04, OR: 2.7), high grade in ovarian cancer (*P* = 2.39E-04, OR: 2.5), metastasis in prostate cancer (*P* = 5.34E-06, OR: 1.8), and dead at 3 years in renal cancer (*P* = 3.16E-04, OR: 2.5), (Table 4). SRARP was also in the top 10% of under-expressed genes associated with advanced colon and rectal cancers (*P* = 3.14E-05, OR: 1.3 and *P* = .002, OR: 1.3), (Table 4). In addition, differential analysis revealed that *SRARP* is among the top 1% to 5% of genes with the highest copy-number loss in adrenocortical, brain, breast, colon, hepatocellular, liposarcoma, lung adenocarcinoma, rectal and renal cancers (Table 4).

Collectively, these findings strongly suggest that *SRARP* under-expression and copy-number loss are robust biomarkers for poor clinical and pathological features in malignancies of multiple tissue origins.

4 | DISCUSSION

SRARP has recently been identified as a tumor suppressor and corepressor of AR that is commonly inactivated by epigenetic silencing, copy-number loss, and somatic mutations in malignancies.[1,2] In

TABLE 4 Association of *SRARP* under-expression and copy-number loss with molecular, pathological, and clinical features in malignancies. For each feature, cancer type, change in *SRARP* expression or copy-number, *P* value, odds ratio, and name of dataset are shown

Cancer type	Feature	Change in SRARP	*P* value	Odds ratio	Dataset
Adrenocortical	Copy-number loss	Top 5% copy-number loss	8.61E-202	216.6	Stephan et al[35]
AML	Dead at 3 y	Top 5% under-expressed	.008	2.1	Heuser et al[36]
Astrocytoma	Recurrence	Top 5% under-expressed	4.56E-05	1.9	Phillips et al[38]
Bladder	Dead at 5 y	Top 5% under-expressed	.002	2.3	Lee et al[39]
Brain and CNS	Copy-number loss	Top 5% copy-number loss	0.00E+00	39	Neale et al[40]
Breast	High grade	Top 1% under-expressed	9.96E-10	62.9	Sotiriou et al[41]
Breast	Copy-number loss	Top 1% copy-number loss	5.89E-163	253.4	TCGA[45]
Breast	Recurrence (1 y)	Top 1% under-expressed	3.55E-94	90.3	Esserman et al[42]
Breast DCIS	High grade	Top 1% under-expressed	4.44E-15	13	Ma et al[43]
Breast lobular	Recurrence (3 y)	Top 1% under-expressed	5.96E-14	12.1	Esserman et al[42]
Breast	Dead at 5 y	Top 5% copy-number loss	1.51E-04	2.6	Curtis et al[44]
Cervical	Advanced stage	Top 5% copy-number loss	5.78E-244	2176	TCGA[45]
Colon	Dead at 5 y	Top 5% copy-number loss	5.42E-76	6.6	TCGA[20]
Colon	Copy-number loss	Top 5% copy-number loss	1.55E-114	41.9	TCGA[20]
Colon	Advanced stage	Top 5% copy-number loss	4.16E-121	46.4	TCGA[20]
Colon	Advanced N	Top 10% under-expressed	3.14E-05	1.3	TCGA[20]
Endometrial	Dead at 1 y	Top 5% copy-number loss	4.41E-52	14.9	TCGA[28]
Gastric	Advanced Stage	Top 5% copy-number loss	1.86E-10	4.2	TCGA[29]
Gastric	High grade	Top 5% copy-number loss	1.29E-08	3.7	Deng et al[30]
GIST	Sarcoma type	Top 1% under-expressed	5.12E-07	3.8	Linn et al[31]
Glioblastoma	vs normal	Top 1% under-expressed	8.85E-06	1.9	Bredel et al[32]
Head-neck	Hypopharyngeal	Top 1% under-expressed	.003	3.8	Slebos et al[33]
Hepatocellular	Copy-number loss	Top 5% copy-number loss	7.74E-148	11.8	Guichard et al[34]
Hepatocellular	Recurrence (3 y)	Top 5% copy-number loss	1.20E-207	244.2	Guichard et al[34]
Liposarcoma	Copy-number loss	Top 5% copy-number loss	6.89E-07	1.9	Barretina et al[9]
Lung[a]	Dead at 1 y	Top 1% under-expressed	6.75E-04	4.5	Okayama et al[27]
Lung[b]	Copy-number loss	Top 1% copy-number loss	4.05E-180	321.2	TCGA[22]
Melanoma (U)	Metastasis	Top 5% under-expressed	2.40E-04	2.7	Laurent et al[46]
Neuroblastoma	Dead at 3 y	Top 5% copy-number loss	3.00E-244	2185	Chen et al[25]
Oligo-DG	Copy-number loss	Top 5% copy-number loss	5.40E-116	9.4	TCGA[47]
Oligo-DG	Dead at 1 y	Top 1% copy-number loss	9.05E-73	65.5	Kotliarov et al[48]
Ovarian	Advanced stage	Top 1% under-expressed	.009	3.6	Tothill et al[49]
Ovarian	High grade	Top 5% under-expressed	2.39E-04	2.5	Tothill et al[49]
Prostate	Metastasis	Top 5% under-expressed	5.34E-06	1.8	Vanaja et al[50]
Rectal	Copy-number loss	Top 1% copy-number loss	1.52E-239	756.7	Firestein et al[51]
Rectal	Advanced N	Top 1% copy-number loss	2.34E-127	50.6	TCGA[20]
Rectal	Advanced stage	Top 10% under-expressed	.002	1.3	Bittner et al[52]
Renal	Copy-number loss	Top 1% copy-number loss	0.00E+00	3357.8	Beroukhim et al[53]
Renal	Dead at 3 y	Top 5% under-expressed	3.16E-04	2.5	TCGA[53]
Thyroid	Metastasis	Top 5% copy-number loss	1.31E-34	10.1	TCGA[37]

Note: "Melanoma (U)" is a uveal melanoma, "N" is a nodal stage, and "Ovarian" is a ovarian endometrioid adenocarcinoma.

Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system; DCIS, ductal carcinoma in situ; GIST, gastrointestinal stromal tumor; Oligo-DR, oligodenroglioma; SRARP, steroid receptor-associated and regulated protein.

[a]Lung adenocarcinoma.

[b]Lung adenocarcinoma, mixed subtype-smoker.

addition, *SRARP* inactivation predicts worse clinical outcome in cancer datasets.[1] Using a genomic approach, this study investigated the application of *SRARP* as a biomarker for therapeutic response and clinical and pathological features in malignancies.

Consistent with its tumor suppressor function, *SRARP* inactivation is an early event in carcinogenesis that occurs in normal adjacent tissues and predicts worse clinical outcome.[1] This study demonstrated that *SRARP* under-expression and copy-number loss are strongly associated with the loss of other tumor suppressors and pro-oncogenic gains (Table 2). In this process, *SRARP* inactivation is associated with the loss of tumor suppressors *TP53*, *BRCA1*, *APC*, *ETS2*, *ZFHX3*, and *NF1* in several malignancies. In addition, *SRARP* loss is associated with pro-oncogenic gains, including *K-RAS* mutation, *ALK* and *N-MYC* amplifications, *IGH-CCD1* fusion, *ETS* gene fusion, and *ERG* rearrangements. Furthermore, *SRARP* is among the genes with the highest copy-number loss or under-expression in multiple malignancies such as breast, lung, colorectal, renal, brain, hepatocellular, and hypopharyngeal cancers. Therefore, we can conclude that *SRARP* is a tumor suppressor that is broadly inactivated across cancer types and *SRARP* inactivation is associated with wider genomic instability in malignancies.

Importantly, this study suggests that *SRARP* is a robust biomarker in predicting treatment response, pathological, and clinical features in cancer. In this respect, *SRARP* under-expression and copy-number loss are strong predictors of cancer mortality, advanced stage, recurrence, and poor pathological features in malignancies of multiple tissue origins (Table 4). For instance, *SRARP* copy-number loss is a strong predictor of dead at 3 years in neuroblastoma (OR: 2185). This provides another robust association between *SRARP* loss and neuroblastoma in addition to its associations with *N-MYC* and *ALK* amplifications. It is notable that deletions of the distal short arm of chromosome 1 (1p) were first reported in neuroblastomas in 1977 and 1p36 deletions are present in a broad range of human cancers.[3,55] However, despite extensive studies, there has been limited success for identifying candidate tumor suppressors on chromosome 1p36.[3] The current study suggests that the *SRARP* represents one of the 1p36 genes that its copy-number loss has prognostic implications as a predictor of clinical outcome in neuroblastoma.

Furthermore, *SRARP* under-expression and copy-number loss are associated with several features of poor outcome in breast cancer, including recurrence at 1 and 3 years, dead at 5 years, and high grade (Tables 4). In addition, *SRARP* is one of the most deleted genes in breast cancer, which is accompanied by *TP53* and *BRCA1* mutations and is a predictor of response to lapatinib in this disease. Furthermore, author has previously demonstrated that SRARP overexpression in AR −/ER- breast cancer cells results in a strong tumor suppressor activity.[1] Therefore, *SRARP* is a tumor suppressor in a subset of breast cancers and its loss is accompanied by that of other tumor suppressors, predicting poor clinical features in this disease. In hepatocellular carcinoma, *SRARP* is one of the most deleted genes and its loss is associated with disease recurrence and *TP53* mutations. In addition, *SRARP* is highly deleted in colorectal cancers and its under-expression or copy-number loss predicts cancer mortality, advanced stage, and *K-RAS* mutation. Notably, SRARP expression also predicts a better response to DNA damaging agent topotecan in colorectal cancer. Collectively, the findings in this study indicate that *SRARP* under-expression and copy-number loss have a consistent pattern in predicting poor clinical-pathological features accompanied by pro-oncogenic changes in multiple malignancies.

Other examples of *SRARP* application as a biomarker in common malignancies include lung and prostate cancers. In this respect, *SRARP* is one of the most deleted genes in lung adenocarcinoma (OR: 321) that predicts cancer mortality at 1 year and is accompanied by *K-RAS* mutation and *APC* deletion in this disease. Furthermore, SRARP expression predicts an improved response to targeted therapies with mTOR inhibitor sirolimus and multikinase inhibitor purvalanol in lung cancer. In prostate cancer, *SRARP* under-expression predicts metastasis and its copy-number loss is accompanied by losses in tumor suppressors *ETS2* and *ZFHX3* in addition to pro-oncogenic gains of *ETS* gene fusion and *ERG* rearrangements (Tables 2 and 4). It is notable that *ETS2* is a tumor suppressor gene in prostate cancer and its loss along with other genes within the *TMPRSS2-ERG* interstitial region contributes to disease progression partly attributed to activation of MAPK signaling.[56] This presents a potential for cooperation between cancer gene changes associated with *SRARP* inactivation and regulation of MAPK signaling. Importantly, the associations of *SRARP* loss with poor clinical and molecular features are consistent with the fact that SRARP overexpression has a potent tumor suppressor function in prostate and lung cancer cells,[1] presenting a clinical application for *SRARP* as a biomarker in these malignancies.

Moreover, *SRARP* acts a robust biomarker in several less common malignancies such as predicting advanced stage in cervical cancer (OR: 2176); recurrence and mortality in brain tumors; mortality in acute myeloid leukemia, bladder, renal and endometrial cancers; advanced stage and high grade in gastric and ovarian cancers; and metastasis in uveal melanoma and thyroid cancer (Table 4). These findings are significant since these malignancies are understudied, and there is a need for the identification of novel biomarkers in these diseases.

Finally, SRARP expression predicts a better response to the inhibitors of ERK signaling and other cancer therapies in multiple malignancies, presenting an additional valuable application for *SRARP* as a cancer biomarker (Table 1). It is notable that the expression or copy-number variations of several *SRARP*-associated tumor suppressors and oncogenes are predictors of response to cancer therapies like those observed with *SRARP*. Therefore, *SRARP* prediction of treatment response may not be a direct cause and effect relationship. Instead, the association of *SRARP* inactivation with broader genomic instability and the tumor suppressor function of this gene are the likely underlying reasons for predicting the response to selective cancer therapies. Altogether, *SRARP* expression and copy-number are potential predictive biomarkers for patient stratification in malignancies with diverse applications in prognostication and cancer therapeutics. Future prospective clinical trials are required to further assess the applications of these findings in patient care.

5 | CONCLUSIONS

This study suggests that *SRARP* is a robust biomarker in predicting treatment response, pathological and clinical features in malignancies of multiple tissue origins. Therefore, assessment of *SRARP* expression and copy-number may have translational applications as a biomarker in cancer prognostication and management.

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CONFLICT OF INTEREST

The author has stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Ali Naderi conceived the study, carried out the bioinformatics and biostatistics analyses of datasets, performed the experiments, interpreted the analyzed data, and drafted the manuscript.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by the author.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in ONCOMINE database, Research Premium Edition (www.oncomine.org).

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