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RESEARCH ARTICLE

Overexpression of ANXA1 confers independent negative prognostic impact in rectal cancers receiving concurrent chemoradiotherapy

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Abstract Neoadjuvant concurrent chemoradiation therapy (CCRT) is an increasingly common therapeutic strategy for rectal cancer. Clinically, it remains a major challenge to predict therapeutic response and patient outcomes after CCRT. Annexin I (ANXA1), encoded by *ANXA1*, is a Ca^{2+}/phospholipid-binding protein that mediates actin dynamics and cellular proliferation, as well as suggesting tumor aggressiveness and predicting therapeutic response in certain malignancies. However, expression of ANXA1 has never been reported in rectal cancer receiving CCRT. This study examined the predictive and prognostic impact of ANXA1 expression in patients with rectal cancer following neoadjuvant CCRT. We identified *ANXA1* as associated with resistance to CCRT through data mining from a published transcriptomic dataset. Its immunoexpression was retrospectively assessed using *H* scores on pre-treatment biopsies from 172 rectal cancer patients treated with neoadjuvant CCRT followed by curative surgery. Results were correlated with clinicopathological features, therapeutic response, tumor regression grade (TRG), and metastasis-free survival (MeFS), as well as local recurrent-free survival (LRFS) and disease-specific survival (DSS). High expression of ANXA1 was associated with advanced pre-treatment tumor status (T3, T4, $p=0.022$), advanced pre-treatment nodal status (N1, N2, $p=0.004$), advanced post-treatment tumor status (T3, T4, $p<0.001$), advanced post-treatment nodal status (N1, N2, $p=0.001$) and inferior TRG ($p=0.009$). In addition, high expression of ANXA1 emerged as an adverse prognosticator for DSS ($p<0.0001$), LRFS ($p=0.0001$) and MeFS ($p=0.0004$). Moreover, high expression of ANXA1 also remained independently prognostic of worse DSS (hazard ratio [HR]=3.998; $p=0.007$), LRFS (HR=3.206; $p=0.028$) and MeFS (HR=3.075; $p=0.017$). This study concludes that high expression of ANXA1 is associated with poor therapeutic response and adverse outcomes in rectal cancer patients treated with neoadjuvant CCRT.

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Introduction

Colorectal cancer (CRC) is one of the leading causes of death globally. In Taiwan, the incidence of CRC has increased gradually; estimated new cases of rectal cancer numbers up to 4,900 per year [1]. The surgical approach is the main choice for potentially curative treatment and recurrence remains a major issue. To enhance local control and cure rates, neoadjuvant concurrent chemoradiotherapy (CCRT) is recommended for locally advanced rectal cancers [2–4]. Although the outcomes with this approach are inspiring, 5-year local and distant recurrences are still noted and the rates range from 6 to 9.6 and 33 to 36 %, respectively [1]. These figures leave room for improvement in patient outcomes. Thus, determining effective biomarkers for predicting the response to neoadjuvant CCRT in rectal cancer patients is vital to aid in further risk stratification.

Annexin I (ANXA1), the first characterized member of the annexin superfamily, is an extensively studied protein, which has a core domain responsible for calcium- or phospholipid binding and an amino-terminal domain responsible for its biological activity and specific function [5]. ANXA1 takes part in various physiological processes, including cellular differentiation [6, 7], cell proliferation [6–9], and signal transduction [10–12]. In addition, it has been reported that dysregulation of ANXA1 is correlated with tumor progression in many cancers, including glial tumors [13], head and neck cancer [14], nasopharyngeal carcinoma [15], larynx cancer [16], esophageal cancer [17], gastric cancer [18], breast cancer [19], hepatocellular carcinoma [20], pancreatic cancer [21], urinary bladder urothelial carcinoma [22], and prostate cancer [23].

Based on data mining and bioinformatic validation, ANXA1 expression is significant in rectal cancers treated with neoadjuvant concurrent chemoradiotherapy (CCRT). To the best of our knowledge, the clinical implications of ANXA1 have not been studied in rectal cancer patients and it has not previously been linked with response to CCRT. In this study, we evaluate its role as a predictive biomarker in a well-characterized cohort of rectal cancer patients treated with neoadjuvant CCRT.

Materials and methods

Analysis of published transcriptomic dataset

In order to identify genes critical in the response to neoadjuvant CCRT, we reappraised one public transcriptome of tissues from 46 rectal cancer patients receiving neoadjuvant CCRT (GSE35452). To this end, we imported the raw CEL files of Affymetrix Human Genome U133 Plus 2.0 microarray platform into Nexus Expression 3 software (BioDiscovery) in order to analyze all probe sets without pre-selection. Comparative analysis and functional profiling were performed to identify significant differentially expressed genes, with special attention to pathways involving anti-apoptosis (GO: 0006916). We chose those with $p<0.01$ and log 2-transformed expression fold change$>\pm 0.1$ for further analysis.

Patient eligibility and follow-up

The institutional review board approved procurement of formalin-fixed tissue of rectal cancer patients for this study (IRB 10302–014). We retrieved a total of 172 records of rectal cancer patients with paraffin-embedded tissue blocks and regular follow-up from the archive of Chi Mei Medical Center between 1998 and 2004 [1, 24]. At initial presentation, these patients were confirmed as having an adenocarcinoma of the rectum using a colonoscopic biopsy, and no distant metastasis by chest x-radiography and/or abdominopelvic CT. All 172 patients received radiation therapy at a total dose of 45 Gy in 25 fractions over a period of 5 weeks with 24-h continuous infusion of 5-fluorouracil concurrently before surgery. Adjuvant systemic chemotherapy was administered if the pre-treatment (Pre-Tx) or post-treatment (Post-Tx) tumor or nodal status was beyond T3 or N1, respectively. All patients were regularly monitored after diagnosis until death or their last appointment.

Histopathologic evaluation

Two pathologists (CF Li and TJ Chen), blinded to the patients' clinical information, performed pathologic analyses of the tumor specimens. Post-Tx T and N stages of all patients were documented according to the 7th American Joint Committee on Cancer (AJCC) TNM staging system. Tumor regression grade (TRG), used as the end point for evaluation of tumor response after neoadjuvant CCRT, was assessed as previously described.

ANXA1 immunohistochemistry and scoring

Tissue sections from Pre-Tx rectal tumor biopsies were cut from paraffin-embedded tissue blocks at 3-mm thickness onto precoated slides. For ANXA1 immunostaining, slides were deparaffinized with xylene, rehydrated with ethanol, and then heated for 7 min by microwave for retrieval of antigen epitopes in a 10-mM citrate buffer (pH 6). Endogenous peroxidase was quenched by 3 % H_2O_2. Slides were washed with Tris-buffered saline for 15 min and then incubated with a primary monoclonal antibody against ANXA1 (Clone 29, 1:100; BD Biosciences, USA). The ANXA1 staining was

interpreted using the *H* score, defined by the following equation: *H* score=$\Sigma Pi(i+1)$, where *i* is the intensity of the stained tumor cells (0 to 3+), and *Pi* is the percentage of stained tumor cells with various intensities. We classified tumors with *H* scores higher than the median of all scored cases as having high ANXA1 expression.

Statistical analysis

The SPSS 14 software package was used for statistical analysis. The correlations between ANXA1 expression and various clinicopathological parameters were evaluated by Chi-square test. The endpoints analyzed were local recurrence-free survival (LRFS), metastasis-free survival (MeFS), and disease-specific survival (DSS), calculated from the date of operation to the date of event. We plotted survival curves using the Kaplan-Meier method and performed log-rank tests to evaluate prognostic differences between groups, then used the Cox proportional hazards model for multivariate comparisons. For all analyses, two-sided tests with $p<0.05$ were considered significant.

Results

Upregulation of ANXA1 gene predicts poor response to CCRT

From the dataset of 46 rectal cancer cases in the public transcriptome GSE35452, we focused on 371 probes covering 48 named genes regulating apoptosis. In non-responders to CCRT, only *ANXA1* showed significant upregulation (log2 ration=0.4402, $p=0.0035$, Fig. 1). *MYBL2*, *BNIP3*, *PAK7*, *TGM2*, *LDHB*, *CTCFL*, and *BAG4* displayed significantly downregulated mRNA expression ($p<0.01$, Fig. 1, and Table 1). This finding prompted us to further characterize the expression status and clinical relevance of *ANXA1* in rectal cancers.

Immunohistochemical expression of ANXA1 and its association with clinicopathological features

To further investigate the correlation between ANXA1 expression and its clinical relevance in rectal cancers treated with neoadjuvant CCRT, we first used immunohistochemistry to examine the expression of ANXA1 in clinical specimens. When detected in cell cytoplasm, ANXA1 immunoexpression was successfully scored in all 172 cases with a wide range of *H* scores, varying from 105 to 375 (Fig. 2). As shown in Table 2, ANXA1 upregulation was correlated with an advanced Pre-Tx tumor and nodal status ($p=0.022$ and 0.004, respectively), Post-Tx tumor status and nodal status ($p<0.001$ and 0.015, respectively), and a lesser degree of tumor regression following neoadjuvant CCRT ($p=0.009$). These findings suggest a biological role for ANXA1 in modulating tumor progression and the sensitivity of rectal cancers to CCRT.

Prognostic impact of ANXA1 expression in rectal cancer

Next, we analyzed the correlation between ANXA1 expression and the prognosis of the rectal cancer patients. The mean follow-up time of these patients was 48.2 months (range, 6.2 to 131.2). A number of clinicopathological parameters, including the Pre-Tx nodal status, Post-Tx tumor status, Post-Tx nodal status, vascular invasion, and TRG were predictive of at least one of the three endpoints of this study at the univariate level (Table 3). Notably, cancers with high expression of ANXA1 were also characterized by a more aggressive clinical course, with significantly shorter DSS

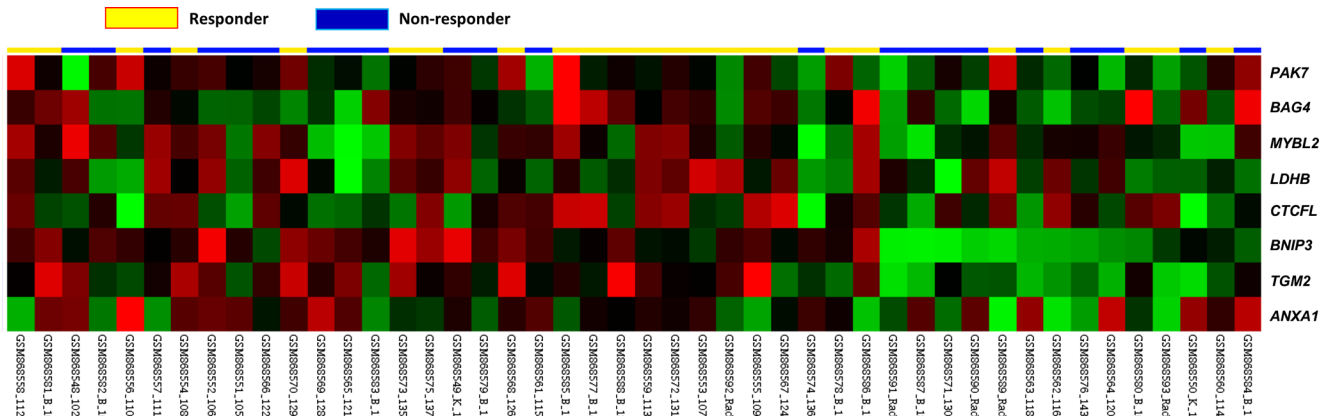

Fig. 1 Analysis of *ANXA1* expression in CCRT responders versus non-responders from a published transcriptomic dataset of rectal cancers. In the clustering analysis of gene-regulating apoptosis, *ANXA1* was significantly upregulated in patients responsive to CCRT. Tissue specimens from non-responders (*blue lines*) and responders (*yellow lines*) are indicated on *top* of the *heatmap*, and expression levels of upregulated and downregulated genes are expressed as a spectrum of brightness of *red* and *green*, respectively, with those unaltered in mRNA expression coded as *black*

Table 1 Summary of differentially expressed genes associated with anti-apoptosis (GO: 0006916) in relation to response to CRT in rectal carcinoma

Probe	Comparison log ratio	Comparison *p* value	Gene symbol	Gene name	Biological process	Molecular function
201012_at	0.4402	0.0035	*ANXA1*	Annexin A1	Anti-apoptosis, arachidonic acid secretion, cell cycle, cell motility, cell surface receptor linked signal transduction, inflammatory response, keratinocyte differentiation, lipid metabolic process, peptide cross-linking, regulation of cell proliferation, and signal transduction	Calcium ion binding, calcium-dependent phospholipid binding, phospholipase A2 inhibitor activity, phospholipase inhibitor activity, phospholipid binding, protein binding, protein binding; bridging, receptor binding, and structural molecule activity
201710_at	−0.5661	0.0069	*MYBL2*	v-myb Myeloblastosis viral oncogene homolog (avian)-like 2	Anti-apoptosis, multicellular organismal development, regulation of progression through cell cycle, regulation of transcription, regulation of transcription; DNA-dependent, transcription and transcription from RNA polymerase II promoter	DNA binding and transcription factor activity
201849_at	−0.6901	0.0048	*BNIP3*	BCL2/adenovirus E1B 19 kDa interacting protein 3	DNA fragmentation during apoptosis, anti-apoptosis, apoptosis, cell death, chromatin remodeling, defense response to virus, induction of apoptosis, negative regulation of membrane potential, negative regulation of survival gene product activity, neuron apoptosis, oxygen and reactive oxygen species metabolic process, positive regulation of apoptosis, regulation of mitochondrial membrane permeability, and response to hypoxia	Identical protein binding, protein binding, protein heterodimerization activity, and protein homodimerization activity
210721_s_at	−0.1276	0.0021	*PAK7*	p21(CDKN1A)-activated kinase 7	Anti-apoptosis and protein amino acid phosphorylation	ATP binding, kinase activity, nucleotide binding, protein binding, protein kinase activity, protein serine/threonine kinase activity, and transferase activity
211003_x_at	−0.5527	0.0004	*TGM2*	Transglutaminase 2 (C polypeptide; protein-glutamine-gamma-glutamyltransferase)	G-protein coupled receptor protein signaling pathway, anti-apoptosis, cAMP-mediated signaling, cytokine, and chemokine-mediated signaling pathway, isopeptide cross-linking via N6-(L-isoglutamyl)-L-lysine, peptide cross-linking, positive regulation of cell adhesion, and programmed cell death	ATP binding, GTP binding, GTPase activity, acyltransferase activity, calcium ion binding, metal ion binding, protein-glutamine gamma-glutamyltransferase activity, and transferase activity
213564_x_at	-0.3606	0.0045	*LDHB*	Lactate dehydrogenase B	Anaerobic glycolysis, anti-apoptosis, apoptosis, cellular carbohydrate metabolic process, glycolysis, protein folding, and tricarboxylic acid cycle intermediate metabolic process	Hsp70/Hsc70 protein regulator activity, L-lactate dehydrogenase activity, oxidoreductase activity, oxidoreductase activity; acting on the CH–OH group of donors, and NAD or NADP as acceptor, protein binding
216508_x_at	−0.3052	0.0083	*CTCFL*	CCCTC-binding factor (zinc finger protein)-like, high-mobility group (nonhistone chromosomal) protein 1-like 1, high-mobility	DNA recombination, DNA repair, DNA unwinding during replication, anti-apoptosis, base-excision repair; DNA ligation, cell cycle, establishment and/or maintenance of	DNA bending activity, DNA binding, metal ion binding, nucleic acid binding, protein binding, transcription factor binding, and zinc ion binding

Table 1 (continued)

Probe	Comparison log ratio	Comparison *p* value	Gene symbol	Gene name	Biological process	Molecular function
				group (nonhistone chromosomal) protein 1-like 6, and high-mobility group box 1	chromatin architecture, negative regulation of progression through cell cycle, negative regulation of transcriptional preinitiation complex assembly, regulation of transcription from RNA polymerase II promoter, regulation of transcription; DNA-dependent, and signal transduction, transcription	
219624_at	−0.2947	0.0087	*BAG4*	BCL2-associated athanogene 4	Anti-apoptosis, apoptosis, and protein folding	Protein binding and receptor signaling protein activity

($p<0.0001$; Fig. 3), LRFS ($p=0.0001$; Fig. 3), and MeFS ($p=0.0004$; Fig. 3). After multivariate comparisons, only high ANXA1 expression remained as an independent prognosticator for all endpoints, including DSS ($p=0.007$, hazard ratio [HR]=3.998), LRFS ($p=0.028$, hazard ratio [HR]=3.206), and MeFS ($p=0.017$, [HR]=3.075) (Table 4).

Discussion

Major challenges in managing rectal cancer include controlling the local tumor and preserving the anal sphincter. Because reports show better local control and survival in patients receiving neoadjuvant CCRT, it is an increasingly common treatment strategy for patients with rectal cancer [25–27]. In addition, to preserving the sphincter, especially in patients with distal rectal cancers, converting the surgical procedure from an abdominoperineal resection to a sphincter-preserving operation such as low anterior resection with coloanal anastomosis may be possible after neoadjuvant CCRT [28–30]. However, the response rate to neoadjuvant CCRT differs among rectal cancers and there is a higher risk of serious toxicity with this multimodal treatment strategy [24]. Hence, new predictive biomarkers are urgently needed for individualized treatment in rectal cancers.

A recent study started from metabolic pathways and identified that deficiency of asparagine synthetase had negative prognostic impact in rectal cancers receiving CCRT [31]. In this study, we observed that high expression of ANXA1 in patients with rectal cancers was correlated with advanced Post-Tx tumor status ($p<0.001$) but also associated with lower-degree TRG ($p=0.009$), findings suggesting that ANXA1 might be related to tumor progression. Moreover, at the univariate level, ANXA1 overexpression significantly predicted inferior DSS, LRFS, and MeFS. In addition, ANXA1 overexpression served as an independent prognosticator for poor DSS, LRFS, and MeFS at the multivariate level. The abovementioned results reinforced the hypothesis that ANXA1 may have a role in tumor progression and may be used as a negative predictive biomarker.

There are studies showing that dysregulation of ANXA1 is involved in the oncogenic process. For example, ANXA1 plays a role in the regulation of actin dynamics. Although the mechanism is not fully understood, it has been suggested that ANXA1 interaction with actin is Ca^{2+}-dependent and that actin polymerization is affected by ANXA1 through binding to the phospholipids and profiling [32]. The importance of microfilament actin includes maintaining cellular morphology, cell adhesion and motility, and controlling the cell cycle [33]. Malignant cells often exhibit dramatic changes in these biological features and altered cellular morphology, loss of cell adhesion, increased motility, and altered cell cycle control.

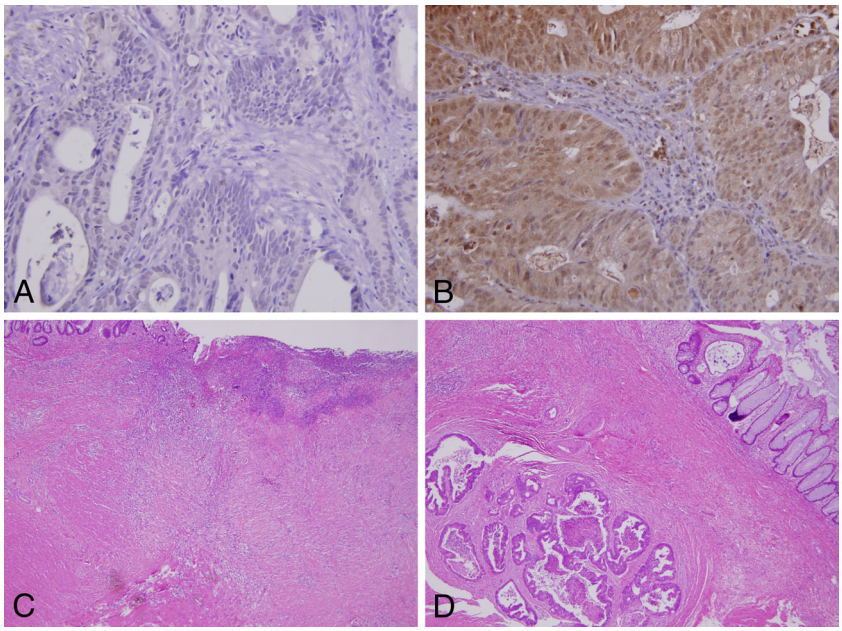

Fig. 2 Representative immunostainings of ANXA1 expression in rectal cancers. Low expression (**a**) and high expression (**a**) of ANXA1 in pre-treatment specimens were linked to remarkable tumor regression (**c**) and low tumor regression grade (**d**), respectively, after CCRT

It has been postulated that alterations in actin polymerization or remodeling play a vital role in regulating the morphological and phenotypical events of a malignant cell. In addition, the epithelial–mesenchymal transition (EMT) is crucial in the progression of epithelial tumors to a malignant phenotype [34]. Actin remodeling presumably plays a key role in the process of EMT [35]. However, there is no consistent pattern of ANXA1 expression levels in different malignancies; both decreased and increased levels are observed in various human cancers. The down-regulation of ANXA1 has been reported in head and neck squamous cell carcinoma (SCC) [14], in nasopharyngeal carcinoma [15], in esophageal SCC [17], and in prostate cancer [23]. Decreased ANXA1 expression level in head and neck SCC is associated with lack of differentiation, higher stage, and positive of lymph node metastasis [14]. Downregulated ANXA1 in nasopharyngeal carcinoma seems related to the presence of squamous differentiation [15]. In contrast, ANXA1 overexpression is reported in breast cancer

Table 2 Associations and comparisons between ANXA1 expression and clinicopathological factors in 172 rectal cancer patients receiving neoadjuvant CRT

Parameter		Number	ANXA1 Expression		*p* value
			Low exp (<median)	High exp. (≥median)	
Gender	Male	108	57	51	0.344
	Female	64	29	35	
Age	<70	106	48	58	0.117
	≧70	66	38	28	
Pre-Tx tumor status (Pre-T)	T1–T2	81	48	33	**0.022***
	T3–T4	91	38	53	
Pre-Tx nodal status (Pre-N)	N0	125	71	54	**0.004***
	N1–N2	47	15	32	
Post-Tx tumor status (Post-T)	T1–T2	86	55	31	**<0.001***
	T3–T4	86	31	55	
Post-Tx nodal status (Post-N)	N0	123	71	52	**0.001***
	N1-N2	49	15	34	
Vascular invasion	Absent	157	83	74	**0.015***
	Present	15	3	12	
Perineurial invasion	Absent	167	85	82	0.173
	Present	5	1	4	
Tumor regression grade	Grade 0–1	37	12	25	**0.009***
	Grade 2~3	118	61	57	
	Grade 4	17	13	4	

*Statistically significant

Table 3 Univariate log-rank analysis for important clinicopathological variables and ANXA1 expression

Parameter		No. of case	DSS		LRFS		MeFS	
			No. of event	*p* value	No. of event	*p* value	No. of event	*p* value
Gender	Male	108	20	0.9026	7	0.2250	17	0.3520
	Female	64	11		20		14	
Age	<70	106	19	0.8540	18	0.6615	20	0.7427
	≧70	66	12		9		11	
Pre-Tx tumor status (Pre-T)	T1–T2	81	10	0.0776	10	0.2261	11	0.1745
	T3–T4	91	21		17		20	
Pre-Tx nodal status (Pre-N)	N0	125	19	0.0711	15	**0.0070***	19	0.0973
	N1–N2	47	21		12		12	
Post-Tx tumor status (Post-T)	T1–T2	86	7	**0.0006***	7	**0.0040***	8	**0.0033***
	T3–T4	86	24		20		23	
Post-Tx nodal status (Post-N)	N0	123	21	0.5998	16	0.1320	20	0.4634
	N1–N2	49	10		11		11	
Vascular invasion	Absent	157	25	**0.0184***	21	**0.0028***	27	0.4470
	Present	15	6		6		4	
Perineurial invasion	Absent	167	29	0.2559	25	0.0940	30	0.9083
	Present	5	2		2		1	
Tumor regression grade	Grade 0–1	37	13	**0.0038***	10	**0.0090***	14	**0.0006***
	Grade 2~3	118	17		17		16	
	Grade 4	17	1		0		1	
Down stage after CCRT	Non-Sig.	150	29	0.1651	24	0.5961	30	0.0853
	Sig. (≥2)	22	2		3		1	
ANXA1 expression	Low exp. (<median)	86	5	<**0.0001***	5	**0.0001***	6	**0.0004***
	High exp. (≥median)	86	26		22		25	

DSS disease-specific survival, *LRFS* local recurrence-free survival, *MeFS* metastasis-free survival,
*Statistically significant

compared to normal mammary tissues [19]; in pancreatic cancer, it is correlated with poor differentiation [21] and in urinary bladder urothelial carcinoma, it is associated with inferior outcomes [22]. Nevertheless, the studies just

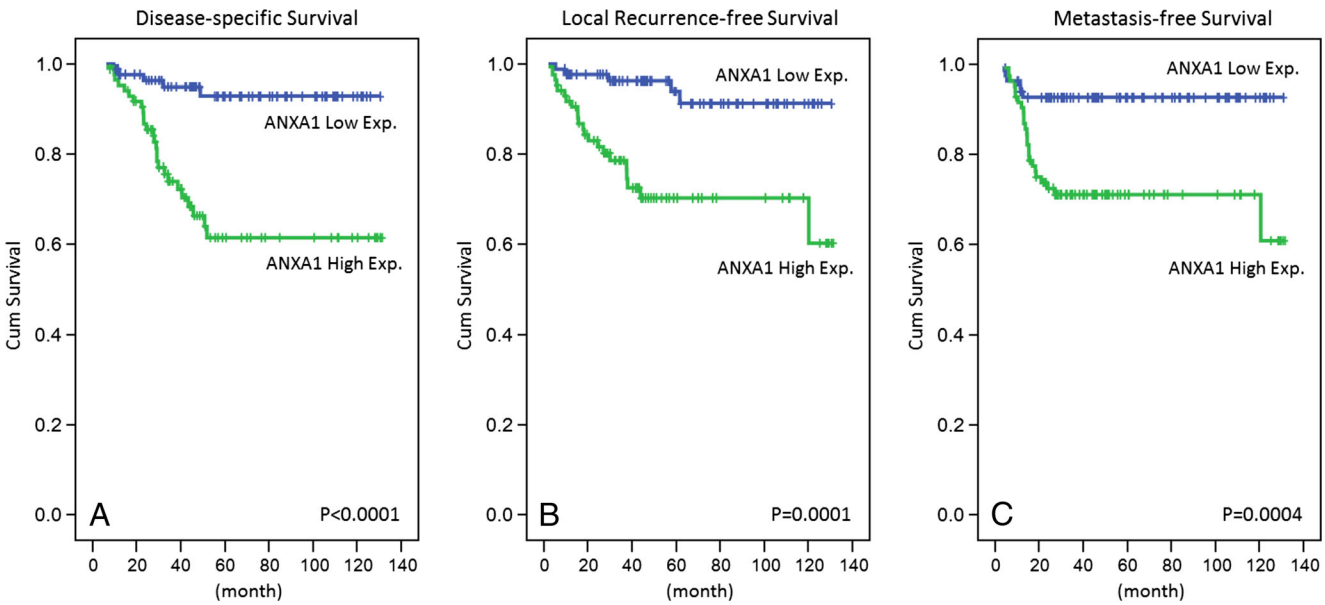

Fig. 3 Kaplan-Meier survival curves plotted to predict survival. Using the log-rank test, high expression of ANXA1 predicted inferior disease-specific survival (**a**), local recurrence-free survival (**b**), and metastasis-free survival (**c**)

Table 4 Multivariate analysis

Parametet	DSS			LRFS			MeFS		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Tumor regression grade	1.927	0.262–1.027	0.060	2.179	0.215–0.979	0.044*	2.299	0.218–0.869	0.018*
ANXA1 expression	3.998	**1.471–18.868**	**0.007***	**3.206**	**1.135–9.053**	**0.028***	**3.075**	**1.222–7.737**	**0.017***
Vascular invasion	1.960	0.777–4.944	0.154	2.026	0.726–5.657	0.178		–	
Post-Tx tumor status (Post-T)	2.014	0.830–4.888	0.122	1.687	0.682–4.174	0.258	1.703	0.724–4.005	0.223
Pre-Tx nodal status (Pre-N)	–	–	–	1.734	0.723–4.158	0.217		–	

DSS disease-specific survival, *LRFS* local recurrence-free survival, *MeFS* metastasis-free survival

*Statistically significant

referenced suggest that ANXA1 has a complicated and context-dependent role in the oncogenic progress. This observation is also supported by the diverse biological activity of ANXA1, including anti-inflammatory activity, inhibition of cell adhesion, enhancement, or inhibition of cellular proliferation and apoptosis.

In addition to actin remodeling, ANXA1 takes part in the signal pathway that increases cellular proliferation [7, 12], suggesting that ANXA1 could have a role in the oncogenic process of CRC by activating cellular proliferation signals. Apoptosis induced by tumor necrosis factor-alpha (TNF-a) is overcome by upregulated ANXA1 triggered by dexamethasone in human leukemic cells and there is a clear correlation with higher ANXA1 levels in TNF-a-resistant cells compared to TNF-a-sensitive cells [36]. Carollo et al. has reported a similar mechanism in the resistance of prostate cancer to doxorubicin and etoposide [37]. All the above findings imply that there may be a link between increased ANXA1 levels and resistance to immune surveillance of the tumor cell. Likewise, the augmentation of ANXA1 levels in CRC is a possible escape mechanism for colorectal cancer cells to avoid immune system attack.

Another interesting finding revealed by data mining is that the mRNA expression of *MYBL2*, *BNIP3*, *PAK7*, *TGM2*, *LDHB*, *CTCFL*, and *BAG4* are downregulated. MYBL2 belongs to the v-myb family of transcription factors. It has been shown that MYBL2 has effects on both proliferation and differentiation pathways in colon epithelial cells [38] but there is no study focusing on its role in colorectal cancer yet. BNIP3, a member of the Bcl-2 family, is a mediator of cell survival and regulates programmed cell death and autophagy in colorectal cancer cells [39]. Another altered gene, *PAK7*, has been reported to play a role in inhibition of camptothecin-induced apoptosis [40]. The roles of *TGM2* [41], *LDHB* [42], *CTCFL* [43], and BAG [44] in the pathogenesis of colorectal cancer had also been disclosed. However, their role and the correlations to CCRT remain to be elucidated.

In conclusion, this is the first time that ANXA1 has been shown to correlate with advanced tumor status and lower grade TRG following neoadjuvant CCRT. More importantly, high expression of ANXA1 is a significant prognosticator for worse prognosis, especially DSS, in rectal cancer patients after neoadjuvant CCRT. Our data suggest that high expression of ANXA1 contributes to disease progression and resistance to CCRT in rectal cancers. Large-scale studies to investigate molecular mechanisms underlying the expression of this protein and to further evaluate its potential prognostic value are warranted.

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Conflict Of Interest None.

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