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Clinical Significance of Stanniocalcin2 mRNA Expression in Patients With Colorectal Cancer

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Abstract. *Background/Aim: Stanniocalcin2 (STC2) is associated with proliferation, invasion, and metastasis in various cancers. We examined the clinical significance of STC2 mRNA expression in patients with colorectal cancer (CRC). Patients and Methods: Relative expression levels of STC2 mRNA in CRC tissues and corresponding normal mucosa obtained from 202 patients were measured using quantitative real-time reverse transcriptase-polymerase chain reaction. Results: Expression of STC2 mRNA was higher in the cancer tissue than in the adjacent normal mucosa. STC2 mRNA expression in cancer tissues was associated with tumour size, liver metastasis, venous invasion, and lymph node metastasis. High expression of STC2 mRNA was significantly associated with poorer postoperative survival (p=0.0003). Multivariate analysis showed that high expression of STC2 mRNA was an independent predictor of postoperative survival. Conclusion: High expression of STC2 mRNA in CRC tissue may be a useful prognostic marker in patients with CRC.*

The number of new cases of colorectal cancer (CRC) worldwide in 2020 was 1,931,590, accounting for 10.0% of all cancers, the third highest, and the number of deaths from CRC in 2020 was 915,880, accounting for 9.2% of all cancers, the second-highest (1).

Most CRC cases are not hereditary but sporadic. This is due to genetic instability and multiple somatic mutations. About 80% of CRC cases are diagnosed at stage I and are curable. Surgery is the primary treatment for localised advanced (stage II/III) CRC. In patients with stage III CRC, the standard treatment is curative resection and postoperative chemotherapy (2). Multimodality therapy in combination with surgery, cytotoxic chemotherapy, and molecular targeted agents prolong the survival of advanced CRC. However, only a small number of patients with highly advanced CRC can be cured using these treatments. Thus, it is very important to identify new targets and personalise therapy based on biomarkers (3-5).

The STC family consists of two members, STC1 and STC2, which are secreted glycoproteins that regulate homeostasis of phosphate and calcium (6). We previously reported the clinical significance of expression of *STC1* mRNA in patients with CRC (7).

STC2 is expressed in various normal tissues, including the pancreas, spleen, kidney, and skeletal muscle, and is involved in cellular calcium/phosphate regulation and cell metabolism (8, 9). In addition, STC2 is involved in human carcinogenesis (10, 11). STC2 is also reportedly associated with tumour invasion and metastasis in various cancers (12-15).

In the present study, we measured expression of *STC2* mRNA in CRC tissues and corresponding normal mucosa and examined the association between expression of mRNA and clinicopathological characteristics and postoperative survival to clarify the clinical significance of expression of *STC2* mRNA in cancer tissues in patients with CRC.

Patients and Methods

Patients and samples. This study was approved by the Ethics Committees of Yokohama City Medical Centre (approval number: 18-7A-4) and Kanagawa Cancer Centre (approval number: epidemiological study-29). We used cancer tissues and corresponding normal

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Key Words: Stanniocalcin2, colorectal cancer, prognostic factor.

Table I. *PCR primers and conditions*.

Gene	Primer	Annealing temperature (˚C)	Product length(bp)
STC2	5'-TCTCACCACTTCCATCGG-3' 5'-CGTCTCCAAACACACTCC-3'	56.0	97
β-actin	5'-AGTTGCGTTACACCCTTTCTTGAC-3' 5'-GCTCGCTCCAACCGACTGC-3'	60.0	171

mucosa from surgery samples of 202 patients with CRC who underwent surgery at the Kanagawa Cancer Centre and Yokohama City University Medical Centre between 2003 and 2006. Each tissue sample was immediately embedded in Optimum Cutting Temperature compound (Sakura Finetechnical Co., Ltd., Tokyo, Japan) after resection and was immediately frozen in liquid nitrogen and stored in an ultra-low temperature freezer at –80˚C. Each specimen was stained with hematoxylin and eosin for histopathological evaluation. Samples containing more than 80% of cancer cells were used as GC tissue for the preparation of total RNA extracts.

RNA extraction and complementary DNA (cDNA) synthesis. Total RNA was extracted from the CRC tissue and adjacent normal mucosa using TRIzol Reagent (GIbco, Life Technologies, Gaitherburg, MD, USA). cDNA was synthesised from 400 ng of total RNA using an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA, USA). After synthesis of cDNA, the cDNA was diluted to 20% with pure water and stored in an ultra-low temperature freezer at –80˚C.

Real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR). qRT-PCR was carried out using iQSYBR-Green Supermix (Bio-Rad Laboratories). PCR reactions were performed in a total volume of 30 μl, containing cDNA derived from 150 μg of RNA, 54 nM of each primer, 15 μl of iQSYBR-Green Supermix containing 100 U/ml of iTag DNA polymerase and 800 μM of dNTPs. Expression of *β-actin* mRNA was used as an internal control. PCR protocol was performed as follows: first 3 min at 95˚C; 40 cycles of cDNA denaturation for 15 s at 95˚C, annealing for 15 s at 56˚C for *STC2* mRNA and 60˚C for *β-actin* mRNA, and a primer extension for 30 s at 72˚C; last, 10 min at 72˚C. PCR primer sequences of *STC2* and *β-actin* are shown in Table I.

Statistical analysis. Expression levels of *STC2* mRNA in cancer tissues and corresponding normal mucosa were compared using the Wilcoxon test. Expression levels of *STC2* mRNA were categorised as low or high (low expression group: n=101, high expression group: n=101) according to the median expression level of *STC2* mRNA in tumour tissues. Associations between relative expression of *STC2* mRNA and explanatory variables, including age, sex, tumour size, depth of invasion, tumour location, lymph node metastasis, liver metastasis, TMN stage, venous invasion, lymphatic invasion, and histological type, were analysed using the χ^2 test. The association between expression of *STC2* mRNA and postoperative survival was esteemed using the Kaplan–Meier method, and differences in survival rates were analysed using the log-rank test. Univariate and multivariate analyses using A Cox proportional-hazards regression model were performed to determine the predictive postoperative survivals. All statistical analyses were performed using IBM SPSS Statistics 20 (SPSS, Inc., Chicago, IL, USA). Two-tailed *p*-values were calculated, and a difference was considered significant when *p*-value was less than 0.05.

Results

STC2 mRNA expression in CRC tissue and corresponding normal mucosa. Expression of *STC2* mRNA in CRC tissues was significantly higher than that in corresponding normal mucosa (p=0.0012 *via* Wilcoxon test; Figure 1).

Relationship between STC2 mRNA expression level and clinicopathological features. Expression levels of *STC2* mRNA were categorised as low expression group (n=101) and high expression group (n=101) according to the median expression level of *STC2* mRNA in cancer tissues. High expression of STC2 was significantly associated with tumour size >65 mm in diameter, presence of lymph node metastases, presence of venous invasion, and presence of liver metastases (Table II).

Relationship between STC2 mRNA expression level in CRC tissues and outcomes in patients with CRC. Postoperative survival in patients with high expression levels of *STC2* mRNA in CRC tissues was significantly poorer than that in those with low expression levels of *STC2* mRNA expression levels (p=0.0003; Figure 2).

Univariate and multivariate analyses of clinicopathological characteristics and expression of STC2 mRNA. Univariate analysis using Cox proportional-hazards model revealed that tumour size, histological type, depth of invasion, lymph node metastasis, lymphatic invasion, liver metastasis, and expression of *STC2* mRNA levels were significantly associated with the outcomes of patients with CRC. Multivariate Cox proportional-hazards regression analysis showed that *STC2* mRNA expression, as well as depth of tumour, lymph node metastasis, and liver metastasis, were independently related to postoperative survival (p=0.016, 0.018, 0.011, >0.001, respectively; Table III).

Discussion

In this study, to evaluate the clinical significance of *STC2* mRNA expression in patients with CRC, we measured

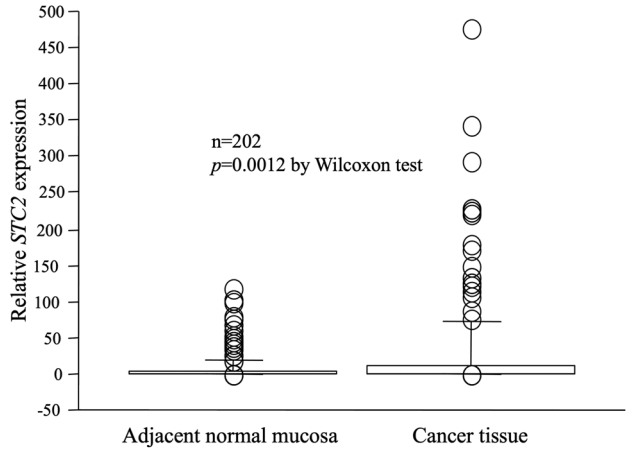

Figure 1. *Expression of STC2 mRNA in CRC tissues and adjacent normal mucosa. Expression of STC2 mRNA in CRC tissues was significantly higher than those in adjacent normal mucosa (p=0.0012 via Wilcoxon test).*

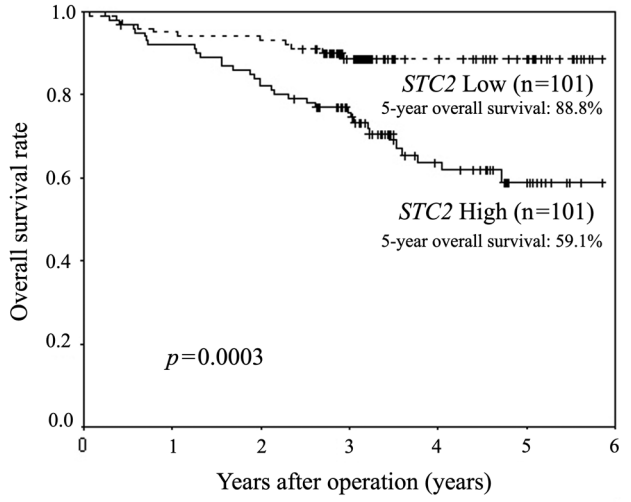

Figure 2. *Relationships between the expression of STC2 and outcomes in patients with CRC. Postoperative survival in patients with high expression of STC2 expression in cancer tissue was significantly poorer than that in patients with low expression of STC2 mRNA (59.1% vs. 88.8%; p=0.0003 via the log-rank test).*

Table II. *Association between the expression of STC2 mRNA and clinicopathological characteristics.*

Variables/Categories	*STC2* expression		*p*-Value
	low (n=101)	high (n=101)	
Age	65.9±10.9	65.5±10.8	0.820
Gender			
Male	55	55	0.556
Female	46	46	
Tumour size			
<5 cm	63	50	**0.044**
≥5 cm	38	51	
Histological type			
Well-differentiated ad-ca	34	24	0.274
Moderately differentiated ad-ca	51	64	
Poorly differentiated ad-ca	8	5	
Mucinous carcinoma	8	8	
Depth of invasion			
T1	9	8	0.499
T2	19	14	
T3	41	37	
T4	32	42	
Tumour location			
Colon	60	50	0.102
Rectum	41	51	
Lymph node metastasis			
Absent	57	44	**0.046**
Present	44	57	
Lymphatic invasion			
Absent	72	60	0.052
Present	29	41	
Venous invasion			
Absent	45	31	**0.029**
Present	56	70	
Liver metastasis			
Absent	92	69	**<0.001**
Present	9	32	

ad-ca: Adenocarcinoma. Bold values indicate statistical significance.

expression of mRNA in cancer tissues and corresponding normal mucosa specimens from patients and analysed the association of the expression of *STC2* mRNA with clinicopathological characteristics and postoperative survivals.

First, we compared expression of *STC2* mRNA in CRC tissues and corresponding normal mucosa from 202 cases. A previous study reported that expression of *STC2* mRNA expression in cancer tissue in 63 patients with oesophageal cancer was higher than that in the corresponding normal mucosa ($p<0.001$) (12). Wang *et al*. compared expression of *STC2* mRNA in cancer tissue and corresponding normal mucosal from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). They reported that expression levels of *STC2* mRNA in cancer tissues were higher compared with those in corresponding normal tissues in patients with CRC in the TCGA database (n=383), and the same results were obtained from all eight gene expression profiles downloaded from the GEO database gene expression analyses identifying a relationship between STC 2 and the malignant behaviour of CRC (16). In the present study, expression of *STC2* mRNA in CRC tissues was significantly higher than that in the corresponding normal mucosa ($p<0.001$).

Table III. *Univariate and multivariate analysis of clinicopathological characteristics and STC2 mRNA expression for OS.*

Variables/Categories	n	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Age(years)							
<65	84	1					
≥65	118	1.356	0.804-2.287	0.253			
Gender							
Male	110	1					
Female	92	0.851	0.512-1.414	0.534			
Tumour size							
<5 cm	113	1					
≥5 cm	89	2.549	1.518-4.281	**<0.001**	1.463	0.850-2.516	0.17
Histological type							
Well, Mod	173	1					
Por, Muc	29	2.064	1.117-3.812	**0.021**	1.855	0.944-3.648	0.073
Depth of invasion							
T1, T2	50	1					
T3, T4	152	11.978	2.926-49.042	**0.001**	6.028	1.406-25.850	**0.018**
Location							
Colon	110	1					
Rectum	92	1.309	0.792-2.163	0.294			
Lymph node metastasis							
Absent	101	1					
Present	101	4.302	2.365-7.825	**<0.001**	2.518	1.234-5.138	**0.011**
Lymphatic invasion							
Absent	132	1					
Present	70	2.848	1.720-4.717	**<0.001**	1.213	0.652-2.255	0.542
Venous invasion							
Absent	76	1	0.833-2.469	0.193			
Present	126	1.434					
Liver metastasis							
Absent	161	1					
Present	41	5.461	3.285-9.078	**<0.001**	2.874	1.657-4.984	**<0.001**
STC2 mRNA expression							
Low	101	1					
High	101	2.388	1.398-4.079	**0.001**	1.72	0.977-3.027	**0.016**

n: Number of patients; well: well-differentiated adenocarcinoma; mod: moderately differentiated adenocarcinoma; por: poorly differentiated adenocarcinoma; muc: mucinous carcinoma. Bold values indicate statistical significance.

Next, we studied the relationship between expression of *STC2* mRNA and clinicopathological characteristics. A previous study reported that expression of *STC2* mRNA in CRC tissue was associated with lymph node metastasis, distant metastasis including liver metastasis, and clinical stage (17). Wang *et al*. reported the association between *STC2* mRNA expression and the clinicopathological features in patients with CRC from the TCGA dataset (n=383). They reported that expression of *STC2* mRNA in cancer tissues was associated with the position (colon *vs*. rectum), side (left *vs*. right), depth (T1+T2 *vs*. T3+T4), lymph node metastasis, and AJCC stage (I+II *vs*. III+IV) (16). In our study, expression of *STC2* mRNA in CRC tissues was significantly associated with tumour size, lymph node metastasis, venous invasion, and liver metastasis.

Next, we examined the relationship between expression of *STC2* mRNA in cancer tissues and postoperative survival. It was reported that STC2 over-expression is correlated with poor prognosis in patients with nasopharyngeal carcinomas (18). Zhang *et al*. reported that the positive expression of STC2 correlates with poor overall survival (OS) and disease-free survival in patients with hepatocellular carcinoma (19). It was reported that patients with pancreatic cancer with high *STC2* expression have a lower 5-year OS rate than patients with low *STC2* expression (20). In the present study, the 5-year OS was significantly poorer in the high expression of *STC2* mRNA group than that in the low expression of *STC2* group.

Furthermore, we performed univariate and multivariate analyses of clinicopathological characteristics *and STC2* mRNA expression to identify independent predictive factors for postoperative survival in patients with CRC. In a previous TCGA database analysis (n=383), it was reported that *STC2* expression levels in CRC tissues and distant metastasis were independent predictive factors for

postoperative survival [Hazard ratio (HR)=2.338, 95% confidence interval (CI)=1.189-4.599, p=0.014] (14). It was also reported, using multivariate Cox regression analysis, that OS of 115 CRC patients, distant metastasis, and STC2 expression (HR=1.976, 95%CI=1.092–3.576, p=0.024) were independent prognostic factors for CRC. Here, similar to the above, univariate Cox regression analysis showed that tumour size, histological type, depth of invasion, lymph node metastasis, lymphatic invasion, liver metastasis, *and STC2* mRNA expression in cancer tissues were significant predictive factors for OS. Multivariate Cox regression analyses also showed that lymph node metastasis, depth of invasion, liver metastasis, and expression of *STC2* mRNA (HR=1.72, 95%CI=1.011-3.027, p=0.016) were independent predictive factors of postoperative survival.

Elucidation of the mechanism of relationship between high STC2 expression and poor outcomes in patients with CRC remains insufficient. Three mechanisms were considered from previous reports. The first is the increase in cell proliferation, migration, and invasion by STC2. In a study using head and neck squamous cell carcinoma cells, Yang *et al*. reported that STC2 may induce the invasion of cancer cells and exert a strong growth permissive effect on cancer cells (21). The second is the anti-apoptotic effect of STC2. Cells expressing STC2 are reportedly resistant to apoptosis (22) through the inhibition of plasma membrane store-operated Ca^{2+} entry (23). The anti-apoptosis effect of STC2 was shown in cells under hypoxic stress, processes that have profound consequences for tumour growth. Moreover, the *STC2* was shown to be a downstream target of HIF-1 and PERK-ATF4 (24-26). The third is the promotion of the epithelial-mesenchymal transition (EMT) by STC2. Chen *et al*. reported that STC2 promotes CRC tumorigenesis and EMT progression by activating ERK/MEK and PI3K/AKT signalling pathways (27).

Our study has several limitations. First, we only examined the expression of *STC2* mRNA in cancer tissues and corresponding normal mucosa obtained from patients with CRC. Although we think that there is a strong association between the expression of *STC2* mRNA and that of protein, we should have performed immunohistochemical studies using the same specimens. Second, we must be conscious of the existence of heterogeneity in the CRC specimens, which might pose a challenge. mRNA extraction was performed using 5-mm square CRC tissue specimens. Although these specimens were collected from the vicinity of the most advanced part of the cancer tissue, they might not faithfully represent the entire tumour.

In conclusion, our study is representative of CRC pathogenesis and high expression of *STC2* mRNA in the cancer tissue may be a useful prognostic marker in patients with CRC.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

TW and TO designed the study, participated in the analyses, and drafted the manuscript. All other Authors made substantial contributions to data collection, analysis, and interpretation, as well as to the editing and approval of the final manuscript.

References

1 International Agency for Research on Cancer: Global Cancer observatory. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf [Last accessed on February 21, 2021]

2 Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol *27(8)*: 1386-1422, 2016. PMID: 27380959. DOI: 10.1093/annonc/mdw235

3 Scheipner L, Smolle MA, Barth D, Posch F, Stotz M, Pichler M, StÖger H, Gerger A and Riedl JM: The AST/ALT ratio is an independent prognostic marker for disease-free survival in stage II and III colorectal carcinoma. Anticancer Res *41(1)*: 429-436, 2021. PMID: 33419840. DOI: 10.21873/anticanres.14792

4 Huang RH, Yang WK, Wu CM, Yeh CM and Sung WW: Over-expression of CEP55 predicts favorable prognosis in colorectal cancer patients with lymph node involvement. Anticancer Res *41(1)*: 543-547, 2021. PMID: 33419854. DOI: 10.21873/anticanres.14806

5 Vycital O, Pitule P, Hosek P, Kriz T, Treska V and Liska V: Expression of Serpin B9 as a prognostic factor of colorectal cancer. Anticancer Res *39(11)*: 6063-6066, 2019. PMID: 31704833. DOI: 10.21873/anticanres.13813

6 Chang AC and Reddel RR: Identification of a second stanniocalcin cDNA in mouse and human: Stanniocalcin 2. Mol Cell Endocrinol *141(1-2)*: 95-99, 1998. PMID: 9723890. DOI: 10.1016/s0303-7207(98)00097-5

7 Tamura S, Oshima T, Yoshihara K, Kanazawa A, Yamada T, Inagaki D, Sato T, Yamamoto N, Shiozawa M, Morinaga S, Akaike M, Kunisaki C, Tanaka K, Masuda M and Imada T: Clinical significance of STC1 gene expression in patients with colorectal cancer. Anticancer Res *31(1)*: 325-329, 2011. PMID: 21273618

8 Ishibashi K and Imai M: Prospect of a stanniocalcin endocrine/paracrine system in mammals. Am J Physiol Renal Physiol *282(3)*: F367-F375, 2002. PMID: 11832417. DOI: 10.1152/ajprenal.00364.2000

9 Olsen HS, Cepeda MA, Zhang QQ, Rosen CA, Vozzolo BL and Wagner GF: Human stanniocalcin: A possible hormonal regulator

of mineral metabolism. Proc Natl Acad Sci USA *93(5)*: 1792-1796, 1996. PMID: 8700837. DOI: 10.1073/pnas.93.5.1792

10 Law AY and Wong CK: Stanniocalcin-2 is a HIF-1 target gene that promotes cell proliferation in hypoxia. Exp Cell Res *316(3)*: 466-476, 2010. PMID: 19786016. DOI: 10.1016/j.yexcr.2009.09.018

11 Gagliardi AD, Kuo EY, Raulic S, Wagner GF and DiMattia GE: Human stanniocalcin-2 exhibits potent growth-suppressive properties in transgenic mice independently of growth hormone and IGFs. Am J Physiol Endocrinol Metab *288(1)*: E92-105, 2005. PMID: 15367391. DOI: 10.1152/ajpendo.00268.2004

12 Kita Y, Mimori K, Iwatsuki M, Yokobori T, Ieta K, Tanaka F, Ishii H, Okumura H, Natsugoe S and Mori M: STC2: A predictive marker for lymph node metastasis in esophageal squamous-cell carcinoma. Ann Surg Oncol *18(1)*: 261-272, 2011. PMID: 20734150. DOI: 10.1245/s10434-010-1271-1

13 Yokobori T, Mimori K, Ishii H, Iwatsuki M, Tanaka F, Kamohara Y, Ieta K, Kita Y, Doki Y, Kuwano H and Mori M: Clinical significance of stanniocalcin 2 as a prognostic marker in gastric cancer. Ann Surg Oncol *17(10)*: 2601-2607, 2010. PMID: 20422456. DOI: 10.1245/s10434-010-1086-0

14 Buckanovich RJ, Sasaroli D, O'Brien-Jenkins A, Botbyl J, Hammond R, Katsaros D, Sandaltzopoulos R, Liotta LA, Gimotty PA and Coukos G: Tumor vascular proteins as biomarkers in ovarian cancer. J Clin Oncol *25(7)*: 852-861, 2007. PMID: 17327606. DOI: 10.1200/JCO.2006.08.8583

15 Meyer HA, Tölle A, Jung M, Fritzsche FR, Haendler B, Kristiansen I, Gaspert A, Johannsen M, Jung K and Kristiansen G: Identification of stanniocalcin 2 as prognostic marker in renal cell carcinoma. Eur Urol *55(3)*: 669-678, 2009. PMID: 18450365. DOI: 10.1016/j.eururo.2008.04.001

16 Wang J, Sahengbieke S, Xu X, Zhang L, Xu X, Sun L, Deng Q, Wang D, Chen D, Pan Y, Liu Z and Yu S: Gene expression analyses identify a relationship between stanniocalcin 2 and the malignant behavior of colorectal cancer. Onco Targets Ther *11*: 7155-7168, 2018. PMID: 30425508. DOI: 10.2147/OTT.S167780

17 Zhang C, Chen S, Ma X, Yang Q, Su F, Shu X, Xie W, Feng M and Xiong B: Upregulation of STC2 in colorectal cancer and its clinicopathological significance. Onco Targets Ther *12*: 1249-1258, 2019. PMID: 30863092. DOI: 10.2147/OTT.S191609

18 Lin S, Guo Q, Wen J, Li C, Lin J, Cui X, Sang N and Pan J: Survival analyses correlate stanniocalcin 2 overexpression to poor prognosis of nasopharyngeal carcinomas. J Exp Clin Cancer Res *33*: 26, 2014. PMID: 24606961. DOI: 10.1186/1756-9966-33-26

19 Zhang ZH, Wu YG, Qin CK, Rong ZH, Su ZX and Xian GZ: Stanniocalcin 2 expression predicts poor prognosis of hepatocellular carcinoma. Oncol Lett *8(5)*: 2160-2164, 2014. PMID: 25289096. DOI: 10.3892/ol.2014.2520

20 Lin C, Sun L, Huang S, Weng X and Wu Z: stc2 is a potential prognostic biomarker for pancreatic cancer and promotes migration and invasion by inducing epithelial-mesenchymal transition. Biomed Res Int *2019*: 8042489, 2019. PMID: 32258098. DOI: 10.1155/2019/8042489

21 Yang S, Ji Q, Chang B, Wang Y, Zhu Y, Li D, Huang C, Wang Y, Sun G, Zhang L, Guan Q, Xiang J, Wei W, Lu Z, Liao T, Meng J, Wang Z, Ma B, Zhou L, Wang Y and Yang G: STC2 promotes head and neck squamous cell carcinoma metastasis through modulating the PI3K/AKT/Snail signaling. Oncotarget *8(4)*: 5976-5991, 2017. PMID: 27863406. DOI: 10.18632/oncotarget.13355

22 Chang AC, Jellinek DA and Reddel RR: Mammalian stanniocalcins and cancer. Endocr Relat Cancer *10(3)*: 359-373, 2003. PMID: 14503913. DOI: 10.1677/erc.0.0100359

23 Zeiger W, Ito D, Swetlik C, Oh-hora M, Villereal ML and Thinakaran G: Stanniocalcin 2 is a negative modulator of store-operated calcium entry. Mol Cell Biol *31(18)*: 3710-3722, 2011. PMID: 21746875. DOI: 10.1128/MCB.05140-11

24 Law AY and Wong CK: Stanniocalcin-2 is a HIF-1 target gene that promotes cell proliferation in hypoxia. Exp Cell Res *316(3)*: 466-476, 2010. PMID: 19786016. DOI: 10.1016/j.yexcr.2009.09.018

25 Ito D, Walker JR, Thompson CS, Moroz I, Lin W, Veselits ML, Hakim AM, Fienberg AA and Thinakaran G: Characterization of stanniocalcin 2, a novel target of the mammalian unfolded protein response with cytoprotective properties. Mol Cell Biol *24(21)*: 9456-9469, 2004. PMID: 15485913. DOI: 10.1128/MCB.24.21.9456-9469.2004

26 Law AY, Lai KP, Ip CK, Wong AS, Wagner GF and Wong CK: Epigenetic and HIF-1 regulation of stanniocalcin-2 expression in human cancer cells. Exp Cell Res *314(8)*: 1823-1830, 2008. PMID: 18394600. DOI: 10.1016/j.yexcr.2008.03.001

27 Chen B, Zeng X, He Y, Wang X, Liang Z, Liu J, Zhang P, Zhu H, Xu N and Liang S: STC2 promotes the epithelial-mesenchymal transition of colorectal cancer cells through AKT-ERK signaling pathways. Oncotarget *7(44)*: 71400-71416, 2016. PMID: 27662663. DOI: 10.18632/oncotarget.12147

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