Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 November 7; 13(41): 5476-5480
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Neural cell adhesion molecule-180 expression as a prognostic criterion in colorectal carcinoma: Feasible or not?

Oge Tascilar, Güldeniz Karadeniz Cakmak, Ishak Ozel Tekin, Ali Ugur Emre, Bulent Hamdi Ucan, Oktay Irkorucu, Kemal Karakaya, Mesut Gül, Hüseyin Bülent Engin, Mustafa Comert

Oge Tascilar, Güldeniz Karadeniz Cakmak, Ali Ugur Emre, Bulent Hamdi Ucan, Oktay Irkorucu, Kemal Karakaya, Mesut Gül, Mustafa Comert, Department of Surgery, Zonguldak Karaelmas University, The School of Medicine, Kozlu-Zonguldak 67600, Turkey
Ishak Ozel Tekin, Department of Immunology, Zonguldak Karaelmas University, The School of Medicine, Kozlu-Zonguldak 67600, Turkey
Hüseyin Bülent Engin, Department of Medical Oncology, Zonguldak Karaelmas University, The School of Medicine, Kozlu-Zonguldak 67600, Turkey
Correspondence to: Dr. Güldeniz Karadeniz Cakmak, Zonguldak Karaelmas Universitesi, Arastirma ve Uygulama Hastanesi Bashekimligi, Kozlu-Zonguldak 67600, Turkey. gkkaradeniz@yahoo.com
Telephone: +90-372-2610169 Fax: +90-372-2610155
Received: June 29, 2007 Revised: August 4, 2007

Tascilar O, Cakmak GK, Tekin IO, Emre AU, Ucan BH, Irkorucu O, Karakaya K, Gül M, Engin HB, Comert M. Neural cell adhesion molecule-180 expression as a prognostic criterion in colorectal carcinoma: Feasible or not?. *World J Gastroenterol* 2007; 13(41): 5476-5480

http://www.wjgnet.com/1007-9327/13/5476.asp

Abstract

AIM: To evaluate the frequency of neural cell adhesion molecule (NCAM)-180 expression in fresh tumor tissue samples and to discuss the prognostic value of NCAM-180 in routine clinical practice.

METHODS: Twenty-six patients (16 men, 10 women) with colorectal cancer were included in the study. Fresh tumor tissue samples and macroscopically healthy proximal margins of each specimen were subjected to flow-cytometric analysis for NCAM-180 expression.

RESULTS: Flow-cytometric analysis determined NCAM-180 expression in whole tissue samples of macroscopically healthy colorectal tissues. However, NCAM-180 expression was positive in only one case (3.84%) with well-differentiated Stage Ⅱ disease who experienced no active disease at 30 mon follow-up.

CONCLUSION: As a consequence of the limited number of cases in our series, it might not be possible to make a generalisation, nevertheless the routine use of NCAM-180 expression as a prognostic marker for colorectal carcinoma seems to be unfeasible and not cost-effective in clinical practice due to its very low incidence.

Key words: Neural cell adhesion molecule-180; Colorectal cancer; Prognosis; Flow-cytometry

INTRODUCTION

Cancer is currently one of the major causes of morbidity and mortality in humans. Tumor progression to local invasion and metastasis are clinically the most relevant processes for prognosis. However the molecular pathways involved in tumor progression are the least well defined at the cellular level, which represents one of prime challenges in cancer research. Tumor suppressor genes are the major target for treatment modalities in most malignant diseases, including gastrointestinal neoplasies. For colon carcinoma, Deleted in Colon Carcinoma (DCC) accounts for one of the best described tumor suppressors involved in adhesive interactions. DCC is a member of the immunglobulin (Ig) superfamily. The neural cell adhesion molecule (NCAM, CD56) is another member of this family possessing structural and sequence homology to DCC[1,2]. Members of the Ig family of cell adhesion molecules (CAMs) play an important role in progression to tumour malignancy and metastasis. NCAM is an embryologic adhesion molecule and a cell membrane protein that modulates neuroendocrine cell growth, migration, and differentiation[3]. NCAM mediates cell-cell and cell-matrix adhesion, contact inhibition and tissue morphogenesis and also is proposed to be critical in signal transduction[3,4]. The major variants of NCAM are classified based on the sialic acid content as either NCAM-H (high-sialic-acid content) or NCAM-L (low-sialic-acid content). The properties of NCAM-H molecules are the following: relative molecular weight between 200-250 kDa, more prevelant in embrionic tissue, blocks adhesion-binding sites and fascilitates cell migration during embriogenesis[5-7]. Therefore, cell-cell or cell-matrix adhesions can be altered by downregulation of NCAM molecules or by upregulation of sialic acid content within the NCAM protein. NCAM-L with a molecular weight of 120-180 kDa predominates in adult tissue and is expressed in three major isoforms, resulting from alternative mRNA splicing and depending on cell type and stage of differentiation[5,8,9]. The major

isoforms have the 5-distal immunoglobulin and 2-membrane proximal fibronectin (FN)-Ⅲ domains. NCAM-120 is glycophosphatidylinositol-linked to the plasma membrane by a sequence encoded by exon 15[9]. NCAM-140 has the basic NCAM-120 structure with a transmembrane sequence and a short (40-kDa) intracellular tail. NCAM-180 has a longer intracellular tail (90 kDa) encoded by exons 17, 19, and unique to this isoform, exon 18. The intracellular component of NCAM-180 anchors the molecule to the cytoskeleton. NCAM-180 is believed to be an important structural molecule that mediates cell-cell adhesion by providing a mechanical linkage between the cytoskeleton and the extracellular adhesive end of the molecule resulting in tissue stabilisation[10]. NCAM-180 was found to be expressed in normal colonic epithelium villous tips and the expression was demonstrated to be lost in highly aggressive colon cancers[7,11]. This study was undertaken to further evaluate the frequency of NCAM-180 expression in fresh tumor tissue samples by flow-cytometric analysis and to discuss the prognostic value of NCAM-180 in colorectal carcinoma in routine clinical practice.

MATERIALS AND METHODS

Patients and tumor samples

Fresh tumor tissue samples were obtained at operation from 26 patients with colorectal cancer who underwent surgery between January 2002 and January 2006. Two samples from each case, one of which was chosen directly from the center of a main tumor lesion and the other from the macroscopically healthy proximal margins, were transferred to flow-cytometric analysis immediately. The remaining specimen was fixed in 10% phosphate buffered formaldehyde, and embedded in paraffin for histopathological analysis. Patient characteristics are shown in Table 1. Oncologic follow-up was performed in each case within 6-12 mo periods. Clinical data were obtained by direct interviews with patients as a part of oncologic follow-up. Patients were defined as having an aggressive clinical course if they presented with an obstructing or perforating lesion or had metastatic disease. Death within 18 mo of presentation was also classified as having an aggressive clinical course. Participation in the study was voluntary and all patients gave their informed consent to participate. The study was approved by the Local Ethics Committee of Zonguldak Karaelmas University Hospital, Zonguldak, Turkey.

Flow-cytometric analysis

All biopsy materials were dissociated mechanically with Medimachine (Becton Dickinson, CA, USA). The dissociated cells were prepared as single cell suspension in PBS (phosphate buffered salt solution) .The cell number was calibrated as 10×10^6/mL. Each 100 μL sample incubated with 10 μL anti-CD56-PE (phycoerythrin conjugated NCAM monoclonal antibody) for 15 min at room temperature. Samples were processed by a Coulter Q Prep Workstation and run with a Beckman-Coulter Epics XL MCL flow cytometer (Beckman coulter, Florida, USA). At least 20000 events were acquired for each sample. Data analysis was performed using EXPO32 (Beckman-Coulter) software. Only CD45 negative population gated were used for NCAM analysis. The upper limit of background fluorescence was set such that no more than 1% of the events with the matched isotype was in the positive region.

Table 1 Background of 26 cases of resected colorectal carcinoma

Case	Gender	Age (yr)	Location	Tumour
1	F	49	Colon	Adenocarcinoma
2	F	70	Rectum	Adenocarcinoma
3	M	86	Colon	Adenocarcinoma
4	M	76	Colon	Adenocarcinoma
5	M	73	Colon	Adenocarcinoma
6	F	76	Colon	Adenocarcinoma
7	M	72	Colon	Adenocarcinoma
8	F	68	Colon	Adenocarcinoma
9	M	72	Colon	Adenocarcinoma
10	M	50	Rectum	Adenocarcinoma
11	M	88	Colon	Adenocarcinoma
12	F	68	Rectum	Adenocarcinoma
13	F	48	Colon	Adenocarcinoma
14	F	75	Rectum	Adenocarcinoma
15	M	37	Rectum	Adenocarcinoma
16	M	57	Rectum	Adenocarcinoma
17	F	71	Colon	Adenocarcinoma
18	M	70	Colon	Adenocarcinoma
19	M	47	Colon	Adenocarcinoma
20	M	47	Colon	Adenocarcinoma
21	F	71	Colon	Adenocarcinoma
22	M	53	Colon	Adenocarcinoma
23	M	80	Rectum	Adenocarcinoma
24	F	49	Rectum	Adenocarcinoma
25	M	76	Colon	Adenocarcinoma
26	M	62	Rectum	Adenocarcinoma

Histological classification

Pathologic stagings were performed based on the TNM staging system developed by the American Joint Committee on Cancer[12]. Histologic tumor typing was applied according to the classification system indicating poor, moderate or well differentiation. Macroscopically healthy proximal margins were verified to be tumor free by histopathologic examination.

RESULTS

Of the 26 patients, 16 (61.5%) were male and 10 (38.5%) were female. The mean age was 65.04 ± 13.60 (range, 37-88) years. Tumors were found to be localized in colonic segments in 19 (73.07%) and in rectum in the rest 7 (26.93%) cases. Four patients died because of cardiovascular or pulmonary complications following surgery. No patients died during follow-up. The mean follow-up period was 19.05 ± 12.33 (range, 4-56) mo. Histopathologic stage, differentiation status, NCAM-180 expression and postoperative survival periods are shown in Table 2. The number of patients in Stage Ⅰ, Ⅱ, Ⅲ and Ⅳ disease were 3 (11.53%), 7 (26.92%), 9 (34.61%), and 7 (26.92%), respectively. Tumors were detected to be well-differentiated in 4 (15.38%), moderately-differentiated in 15 (57.69%) and poorly-differentiated in 7 (26.92%) cases. Flow-cytometric analysis determined NCAM-180 expression in whole tissue samples of macroscopically

Table 2 Results of histopathologic evaluation and flow cytometric analysis of NCAM-180 status

Case	pTNM	Stage	Histology	NCAM-180	Outcome
1	T3N0M0	Ⅱ	Moderate	-	No active disease at 21 mo follow-up
2	T4N1M1	Ⅳ	Poor	-	Died of metastatic diesease 8 mo postresection
3	T4N2M1	Ⅳ	Moderate	-	No active disease at 9 mo follow-up
4	T3N0M0	Ⅱ	Well	-	No active disease at 20 mo follow-up
5	T4NIM1	Ⅳ	Poor	-	Died of cardiopulmonary complication postoperatively
6	T3N1M0	Ⅲ	Moderate	-	No active disease at 6 mo follow-up
7	T2N0M0	Ⅰ	Moderate	-	Metachrone colonic disease at 15 mo
8	T2N0M0	Ⅰ	Moderate	-	No active disease at 15 mo follow-up
9	T4N2M0	Ⅲ	Moderate	-	Died of metastatic diesease 18 mo postresection
10	T3N2M0	Ⅲ	Moderate	-	No active disease at 18 mo follow-up
11	T2N0M0	Ⅰ	Moderate	-	Died of cardiopulmonary complication postoperatively
12	T3N0M1	Ⅳ	Poor	-	Died of cardiopulmonary complication postoperatively
13	T3N1M0	Ⅲ	Moderate	-	No active disease at 32 mo follow-up
14	T3N1M0	Ⅲ	Moderate	-	No active disease at 20 mo follow-up
15	T3N0M0	Ⅱ	Poor	-	No active disease at 16 mo follow-up
16	T3N1M0	Ⅲ	Well	-	No active disease at 19 mo follow-up
17	T3N0M0	Ⅱ	Well	+	No active disease at 30 mofollow-up
18	T3N1M0	Ⅲ	Well	-	No active disease at 44 mo follow-up
19	T4N2M1	Ⅳ	Poor	-	Died of metastatic diesease 5 mo postresection
20	T4N2M1	Ⅳ	Poor	-	Died of metastatic diesease 4 mo postresection
21	T3N0M0	Ⅱ	Moderate	-	Died of metastatic diesease 56 mo postresection
22	T4N1M1	Ⅳ	Moderate	-	Died of metastatic diesease 15 mo postresection
23	T4N1M0	Ⅲ	Moderate	-	Died of cardiopulmonary complication postoperatively
24	T3N0M0	Ⅱ	Poor	-	No active disease at 18 mo follow-up
25	T3N0M0	Ⅱ	Moderate	-	No active disease at 16 mo follow-up
26	T4N1M0	Ⅲ	Moderate	-	No active disease at 14 mo follow-up

healthy colorectal tissues. However, NCAM-180 expression was positive in only one case (3.84%) with well-differentiated Stage Ⅱ disease, and this patient experienced no active disease at 30 mo follow-up.

Correlation between NCAM-180 expression in colorectal cancer and other parameters

It is not possible to compare overall survival outcomes in this series with only one (3.84%) positive NCAM-180 expression. However, NCAM-180 expression was positive in a well-differentiated Stage Ⅱ tumor with an uneventfull clinical course for 30 mo following surgery. Considering well-differentiated tumors, one of three patients without NCAM-180 expression experienced a longer disease free survival period (44 *vs* 30 mo). Moreover, NCAM-180 expression was not detected in both moderate or poor differentiated tumors. Evaluation of the patients with stage Ⅱ disease demonstrated that one of six patients without NCAM-180 expression survived 56 mo after diagnosis and no active disease was detected in the other 5 patients within a mean follow-up period of 18.2 (range, 16-21) mo.

DISCUSSION

Tumoral invasion and metastasis are the most critical and complex processes in aggressive human cancers and are one of the major causes of cancer deaths. Cell adhesion molecules, including the immunoglobulin superfamily, play a crucial role in determining tumor development and the metastatic cascade[13,14]. Variations in cell-cell and cell-matrix adhesion accompany the progression from benign tumours to invasive, malignant cancer and the subsequent metastatic dissemination of tumour cells. The hallmark of neoplastic and metastatic growth is thought to be reduced adhesiveness between cells and also between cells and the extracellular matri[3]. Several groups of adhesion molecules are importantly involved in regulation of tumor invasion and metastasis.

NCAM (CD56) is a calcium independent cell adhesion molecule, which mediates homotypic and heterotypic cell-cell and cell-matrix adhesion[15-17]. NCAM has been found to be a significant factor for survival in various solid tumors. A correlation between reduced NCAM expression and poor prognosis has been reported for some cancer types[11,18,19]. The existence of NCAM-180 has been proposed to be a good prognostic criterion in colorectal carcinoma[11]. Previous studies have demonstrated that NCAM-180 is present in normal colonic epithelium and in benign colonic tumors and loss of NCAM-180 expression might result in defective intracellular adhesion between colonocytes in aggressive colon carcinoma[7,11]. In this study we investigated the NCAM-180 expression rate in fresh tumor tissue samples of colorectal carcinoma and the association of an aggresive clinical course with loss of this expression.

NCAM expression has been investigated in various solid and neuroendocrine tumours. There is a consensus that presence of its polisialiated (embryonic) form, which is less adhesive than the adult form [that contains a relatively low polisialic acid (PSA) content], is associated with a poor prognosis. Correlation between N-CAM expression and perineural spread has been confirmed in a variety of human carcinomas. The existence of the polisialiated form of NCAM in Wilms' tumor, neuroblastoma, pituitary tumor, small cell lung cancer, gallbladder and bile duct cancer,

squamous cell cancer of head and neck, and prostat cancer results in perineural invasion and agrressive metastatic behaviour with a poor clinical outcome[20-28]. As the expression of the polisialiated form of NCAM correlates with tumor growth and invasiveness because of its role in cell disassociation, it was considered to be a poor prognostic criterion in pituitary tumors and rhabdomyosarcoma[22,29]. Polysialation has been proposed to involve steric inhibition of membrane-membrane apposition and cell adhesiveness, based on the biophysical properties of the polysialic acid[30]. In renal cell carcinoma, NCAM expression was suggested to be a risk factor for tumor metastasis[31]. Moreover, NCAM is not polysialylated in renal cell carcinoma suggesting that it plays another role in these tumors involving homophilic adhesion[31]. Conversely, for other tumors like pancreatic adenocarcinomas, reduced levels of NCAM expression were found to correlate with increased tumor malignancy[19]. This result was also observed in a transgenic mouse model of β-cell pancreatic carcinoma by crossing these mice with NCAM knockout mice[32]. The hypothesis was reduced levels of NCAM could increase cell dissociation from primary tumors. Moreover, an overall decrease in the NCAM level has been observed in another subset of tumors including colon carcinoma and astrocytoma. In these tumors NCAM expression is markedly down-regulated, and the loss of NCAM correlates with poor prognosis[7,11,18,33]. In gastrointestinal neoplasia, when pancreatic, colorectal and gastric cancer were considered, poorly differentiated tumors had lower levels of NCAM than well or moderately differentiated tumors[18].

Previous studies have demonstrated that NCAM-180 is present in normal colonic epithelium and NCAM-180 expression was found to be absent in clinically aggressive colon carcinomas[11]. Consistent with this thesis, colorectal carcinomas expressing NCAM-180 should experience a good clinical course with longer disease free survival. In other words, overexpression of the polysialylated form of NCAM or reduced expression of NCAM-180 has been suggested to decline intracellular adhesion, facilitating metastatic behavior in cancer. This study was designed to determine the rate of NCAM-180 expression in fresh colorectal tumour tissue and correlation of NCAM-180 expression with clinical course. In our series of 26 colorectal carcinoma, we determined NCAM-180 expression in only one patient (3.84%) (pathologic stage Ⅱ-well differentiated tumour) with a good clinical course during a follow-up period of 30 mo. This was an expected finding according to the previous literature[7,11]. However, we detected that 6 of the other patients with the same clinical and pathological stage at diagnosis and surgery, experienced either similar or a better clinical course during follow-up as well. Moreover, 2 patients without NCAM-180 expression and in an advanced pathological stage at diagnosis survived more than the patient with NCAM-180 expression. These are controversial results predicting that attribution of NCAM-180 expression as a good prognostic criterion in colorectal carcinoma is something to be interrogated before acceptance.

NCAM-180 has been proposed as a candidate tumor supressor in colorectal carcinoma previously and might play a crucial role in tumor behaviour by mediating colonic epithelial integrity and preventing tumour invasiveness and metastasis due to cellular adhesive properties. When colorectal cancer is considered, loss of NCAM-180 expression might lead to reduced homotypic binding between cancerous cells, resulting in detachment from the primary cancerous mass and invading other organs, acting systematically. However, in our series the NCAM-180 expression rate was only 3.84% and statistical correlation analysis of survival with NCAM-180 expression was not possible according to this low frequency. Moreover, the comparision according to tumor differentiation and stage revealed that loss of NCAM-180 expression in either well-differentiated or stage Ⅱ disease did not result in a worst clinical course. As a consequence of the limited number of cases in our series, it might not be possible to make a generalisation, nevertheless the routine use of NCAM-180 expression as a prognostic marker for colorectal carcinoma seems not to be feasible and cost-effective in clinical practice due to being present at a very low frequency. Further studies with a greater number of cases are thus called for to study the underlying mechanisms of tumor metastasis and prognosis in colorectal carcinoma.

ACKNOWLEDGMENTS

Presented in "Turkish National Surgery Congress" 24-28 May, 2006.

COMMENTS

Background

Cancer being one of the most mortal disease worldwide, tumor markers and prognostic criterions attract a great enthusiasm above researchers. Tumor suppressor genes and cell adhesion molecules are considered to play a crucial role in tumor pathophysiology.

Research frontiers

Neural cell adhesion molecule (NCAM-CD56) mediates cell-cell and cell-matrix adhesion, contact inhibition and tissue morphogenesis and also proposed to be critical in signal transduction. The major variants of NCAM are classified based on the sialic acid content as either NCAM-H (high-sialic-acid content) or NCAM-L (low-sialic-acid content). NCAM-L with a molecular weight of 120-180 kDa, predominates in adult tissue and is expressed in three major isoforms. NCAM-180 is believed to be an important structural molecule that mediates cell-cell adhesion by providing a mechanical linkage between the cytoskeleton and the extracellular adhesive end of the molecule resulting in tissue stabilisation.

Innovations and breakthroughs

A correlation between reduced NCAM expression and poor prognosis has been reported for some cancer types. NCAM-180 expression has been demonstrated to be lost in highly aggressive colon cancer and proposed to function as a tumor supressor. From this point of view we aim to evaluate the frequency of NCAM-180 expression in fresh tumor tissue samples by flow-cytometric analysis and to discuss the prognostic value of NCAM-180 in colorectal carcinoma in routine clinical practice.

Applications

The most critical deficit in the ability to treat cancer effectively is the lack of knowledge about cellular basis and markers for early diagnosis. The verification of an association between various types of malignancies and adhesion molecules might provide novel targets to cancer therapy by indicating the accurate goals.

Terminology

Neural cell adhesion molecule (NCAM-CD56) is a well identified cell membrane protein and a member of immunoglobulin superfamily, possessing structural and sequence resemblance to Deleted in Colon Carcinoma (DCC), which is another member of the same superfamily.

Peer review

The authors evaluated the frequency of NCAM-180 expression in fresh tumor tissue samples by flow-cytometric analysis and found that NCAM-180 expression in whole tissue samples of macroscopically healthy colorectal tissues, but only in one case (3.84%) with well-differentiated Stage Ⅱ disease. As discussed by the authors that the limited number of cases in the series, it is impossible to make a generalization. Further study with a large series of cases should be carried out to evaluated the clinicopathological significance of NCAM-180 expression in colorectal cancers.

REFERENCES

1 **Fearon ER**, Cho KR, Nigro JM, Kern SE, Simons JW, Ruppert JM, Hamilton SR, Preisinger AC, Thomas G, Kinzler KW. Identification of a chromosome 18q gene that is altered in colorectal cancers. *Science* 1990; **247**: 49-56

2 **Fearon ER**, Pierceall WE. The deleted in colorectal cancer (DCC) gene: a candidate tumour suppressor gene encoding a cell surface protein with similarity to neural cell adhesion molecules. *Cancer Surv* 1995; **24**: 3-17

3 **Christofori G**. Changing neighbours, changing behaviour: cell adhesion molecule-mediated signalling during tumour progression. *EMBO J* 2003; **22**: 2318-2323

4 **Cavallaro U**, Christofori G. Cell adhesion in tumor invasion and metastasis: loss of the glue is not enough. *Biochim Biophys Acta* 2001; **1552**: 39-45

5 **Rothbard JB**, Brackenbury R, Cunningham BA, Edelman GM. Differences in the carbohydrate structures of neural cell-adhesion molecules from adult and embryonic chicken brains. *J Biol Chem* 1982; **257**: 11064-11069

6 **Rutishauser U**, Acheson A, Hall AK, Mann DM, Sunshine J. The neural cell adhesion molecule (NCAM) as a regulator of cell-cell interactions. *Science* 1988; **240**: 53-57

7 **Huerta S**, Srivatsan ES, Venkatesan N, Peters J, Moatamed F, Renner S, Livingston EH. Alternative mRNA splicing in colon cancer causes loss of expression of neural cell adhesion molecule. *Surgery* 2001; **130**: 834-843

8 **Goridis C**, Brunet JF. NCAM: structural diversity, function and regulation of expression. *Semin Cell Biol* 1992; **3**: 189-197

9 **Hemperly JJ**, DeGuglielmo JK, Reid RA. Characterization of cDNA clones defining variant forms of human neural cell adhesion molecule N-CAM. *J Mol Neurosci* 1990; **2**: 71-78

10 **Pollerberg GE**, Burridge K, Krebs KE, Goodman SR, Schachner M. The 180-kD component of the neural cell adhesion molecule N-CAM is involved in cell-cell contacts and cytoskeleton-membrane interactions. *Cell Tissue Res* 1987; **250**: 227-236

11 **Roesler J**, Srivatsan E, Moatamed F, Peters J, Livingston EH. Tumor suppressor activity of neural cell adhesion molecule in colon carcinoma. *Am J Surg* 1997; **174**: 251-257

12 **Greene FL**, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002: 113-125

13 **Koukoulis GK**, Patriarca C, Gould VE. Adhesion molecules and tumor metastasis. *Hum Pathol* 1998; **29**: 889-892

14 **Meyer T**, Hart IR. Mechanisms of tumour metastasis. *Eur J Cancer* 1998; **34**: 214-221

15 **Walsh FS**, Doherty P. Neural cell adhesion molecules of the immunoglobulin superfamily: role in axon growth and guidance. *Annu Rev Cell Dev Biol* 1997; **13**: 425-456

16 **Crossin KL**, Krushel LA. Cellular signaling by neural cell adhesion molecules of the immunoglobulin superfamily. *Dev Dyn* 2000; **218**: 260-279

17 **Panicker AK**, Buhusi M, Thelen K, Maness PF. Cellular signalling mechanisms of neural cell adhesion molecules. *Front Biosci* 2003; **8**: d900-d911

18 **Fogar P**, Basso D, Pasquali C, De Paoli M, Sperti C, Roveroni G, Pedrazzoli S, Plebani M. Neural cell adhesion molecule (N-CAM) in gastrointestinal neoplasias. *Anticancer Res* 1997; **17**: 1227-1230

19 **Tezel E**, Kawase Y, Takeda S, Oshima K, Nakao A. Expression of neural cell adhesion molecule in pancreatic cancer. *Pancreas* 2001; **22**: 122-125

20 **Roth J**, Zuber C, Wagner P, Blaha I, Bitter-Suermann D, Heitz PU. Presence of the long chain form of polysialic acid of the neural cell adhesion molecule in Wilms' tumor. Identification of a cell adhesion molecule as an oncodevelopmental antigen and implications for tumor histogenesis. *Am J Pathol* 1988; **133**: 227-240

21 **Hildebrandt H**, Becker C, Glüer S, Rösner H, Gerardy-Schahn R, Rahmann H. Polysialic acid on the neural cell adhesion molecule correlates with expression of polysialyltransferases and promotes neuroblastoma cell growth. *Cancer Res* 1998; **58**: 779-784

22 **Daniel L**, Trouillas J, Renaud W, Chevallier P, Gouvernet J, Rougon G, Figarella-Branger D. Polysialylated-neural cell adhesion molecule expression in rat pituitary transplantable tumors (spontaneous mammotropic transplantable tumor in Wistar-Furth rats) is related to growth rate and malignancy. *Cancer Res* 2000; **60**: 80-85

23 **Miyahara R**, Tanaka F, Nakagawa T, Matsuoka K, Isii K, Wada H. Expression of neural cell adhesion molecules (polysialylated form of neural cell adhesion molecule and L1-cell adhesion molecule) on resected small cell lung cancer specimens: in relation to proliferation state. *J Surg Oncol* 2001; **77**: 49-54

24 **Seki H**, Koyama K, Tanaka J, Sato Y, Umezawa A. Neural cell adhesion molecule and perineural invasion in gallbladder cancer. *J Surg Oncol* 1995; **58**: 97-100

25 **Seki H**, Tanaka J, Sato Y, Kato Y, Umezawa A, Koyama K. Neural cell adhesion molecule (NCAM) and perineural invasion in bile duct cancer. *J Surg Oncol* 1993; **53**: 78-83

26 **McLaughlin RB**, Montone KT, Wall SJ, Chalian AA, Weinstein GS, Roberts SA, Wolf PF, Weber RS. Nerve cell adhesion molecule expression in squamous cell carcinoma of the head and neck: a predictor of propensity toward perineural spread. *Laryngoscope* 1999; **109**: 821-826

27 **Vural E**, Hutcheson J, Korourian S, Kechelava S, Hanna E. Correlation of neural cell adhesion molecules with perineural spread of squamous cell carcinoma of the head and neck. *Otolaryngol Head Neck Surg* 2000; **122**: 717-720

28 **Li R**, Wheeler T, Dai H, Ayala G. Neural cell adhesion molecule is upregulated in nerves with prostate cancer invasion. *Hum Pathol* 2003; **34**: 457-461

29 **Daniel L**, Durbec P, Gautherot E, Rouvier E, Rougon G, Figarella-Branger D. A nude mice model of human rhabdomyosarcoma lung metastases for evaluating the role of polysialic acids in the metastatic process. *Oncogene* 2001; **20**: 997-1004

30 **Fujimoto I**, Bruses JL, Rutishauser U. Regulation of cell adhesion by polysialic acid. Effects on cadherin, immunoglobulin cell adhesion molecule, and integrin function and independence from neural cell adhesion molecule binding or signaling activity. *J Biol Chem* 2001; **276**: 31745-31751

31 **Daniel L**, Bouvier C, Chetaille B, Gouvernet J, Luccioni A, Rossi D, Lechevallier E, Muracciole X, Coulange C, Figarella-Branger D. Neural cell adhesion molecule expression in renal cell carcinomas: relation to metastatic behavior. *Hum Pathol* 2003; **34**: 528-532

32 **Perl AK**, Dahl U, Wilgenbus P, Cremer H, Semb H, Christofori G. Reduced expression of neural cell adhesion molecule induces metastatic dissemination of pancreatic beta tumor cells. *Nat Med* 1999; **5**: 286-291

33 **Sasaki H**, Yoshida K, Ikeda E, Asou H, Inaba M, Otani M, Kawase T. Expression of the neural cell adhesion molecule in astrocytic tumors: an inverse correlation with malignancy. *Cancer* 1998; **82**: 1921-1931

S- Editor Zhu LH **L- Editor** Lutze M **E- Editor** Li HY