

Combined analysis of Rac1, IQGAP1, Tiam1 and E-cadherin expression in gastric cancer

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Rho GTPases are a family of major regulators of E-cadherin-mediated cell adhesion that are implicated in the carcinogenic process by deregulated expression of the family members itself or of upstream modulators or downstream effectors. Combined investigation of the Rho GTPase Rac1, the effector protein IQGAP1 and the activator Tiam1 in relation to expression or mutation of E-cadherin in gastric adenocarcinomas has not been reported. The aim of the study was to determine the expression and prognostic significance of Rac1, IQGAP1, Tiam1 and E-cadherin in gastric adenocarcinomas. Gastric carcinomas of 76 patients were investigated immunohistochemically in a tissue microarray study for expression of Rac1, IQGAP1, Tiam1 and E-cadherin. Correlations with clinical and follow-up data were examined. Moderate or strong reactivity for Rac1 was observed in 46% and for Tiam1 in 56% of tumors. Expression of IQGAP1 was present in 59% and of E-cadherin in 87% of tumors. While Rac1 and E-cadherin expression were not related to prognosis, a trend was observed between a lack of IQGAP1 expression (log-rank 0.088) as well as presence of Tiam1 (log-rank 0.097) and favorable prognosis in Kaplan–Meier survival analysis. Expression of Rac1 was positively linked to IQGAP1 expression ($P = 0.007$, $r = 0.343$) and tended to be inversely associated with expression of E-cadherin ($P = 0.055$, $r = -0.245$). In conclusion, we observed deregulated expression of Rac1, IQGAP1, Tiam1 and E-cadherin in gastric cancer. We present evidence that either upregulation (for Rac1 and IQGAP1) or downregulation (for Tiam1 and E-cadherin) occurs. Rac1 and E-cadherin expression were not related to prognosis, while trends pointing to favorable prognosis of patients with Tiam1 expression and a lack of IQGAP1 expression were observed. These results indicate that the investigated regulators of E-cadherin-mediated cell adhesion play a role in gastric carcinogenesis.

Modern Pathology (2008) 21, 544–552; doi:10.1038/modpathol.2008.3; published online 1 February 2008

Keywords: E-cadherin; gastric carcinoma; IQGAP1; Rac1; Rho GTPase; Tiam1

Rho GTPases regulate key signalling processes of cells including E-cadherin-mediated cell adhesion, cell polarity, apoptosis and proliferation.^{1,2} Recently, Rho GTPases have been implicated in different aspects of the tumor development: dedifferentiation, upregulation of uncontrolled proliferation, angiogenesis, invasion and metastasis.³

Rho GTPases are regulated by a mechanism that depends on their ability to cycle between an active GTP-bound state and an inactive GDP-bound state. This regulatory cycle is under the control of three distinct families of proteins, guanine exchange factors, GTPase-activating proteins and guanine nucleotide dissociation inhibitors. Upon GTP-loading, Rho GTPases interact with a large number of cellular proteins. These downstream effectors ultimately transmit the signal within the cell.

Rho GTPases are implicated in the carcinogenic process by deregulated expression of the family members itself or of upstream modulators or downstream effectors.³ Overexpression of the Rho GTPases is likely to result in an increase in the

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Received 18 June 2007; revised 11 December 2007; accepted 31 December 2007; published online 1 February 2008

turnover of GTP-loading, leading to overactivation of subsequent downstream signalling. So far, activating point mutations in the GTP-binding domain of Rho GTPases have not been detected, which is a major difference between Ras and Rho GTPases.

Rho GTPases are essential for the formation of adherens junctions. The key adhesion molecule in adherens junctions is E-cadherin. Rac1 regulates in concert with Rho and Cdc42 the establishment and maintenance of adherens junctions in epithelial cells.⁴ The GEF Tiam1 has been identified as a specific activator of Rac1.⁵ Tiam-1-mediated activation of Rac1 stimulates cadherin-mediated cell–cell adhesion.⁶ In contrast, IQGAP1 is an effector of Rac1 that accumulates at sites of cell–cell contact and plays the role of a negative regulator of cell adhesion.^{7–9}

Gastric carcinoma is one of the leading malignancies worldwide that is frequently associated with mutations or downregulation of the cell adhesion protein and tumor suppressor E-cadherin.¹⁰ Somatic E-cadherin mutations that impair the adhesive function of the protein have been described in diffuse type gastric carcinomas.^{11–16} The predominant type of mutations in gastric cancer were splice-site mutations and in-frame deletions and most of the mutations were located in exons 8 or 9.^{16,17}

Although a number of *in vitro* investigations have established the significance of Rac1, IQGAP1 and Tiam1 as regulators of E-cadherin-mediated cell adhesion, little is known about the relevance of these markers in gastric cancer. Therefore, the aim of the study was to determine the expression and prognostic significance of Rac1, IQGAP1 and Tiam1 in gastric cancer. Further, we investigated whether the expression of these markers was correlated with each other or with the expression level of E-cadherin.

Materials and methods

Patient Selection

Patients ($n=76$) with gastric adenocarcinoma according to the World Health Organization classification were included in the tissue microarray.¹⁸ All patients underwent primary surgical resection without chemo- or radiotherapy at the Department of Surgery, Klinikum rechts der Isar, Technische Universität München, between 1990 and 2000. TNM status was determined according to the current International Union Against Cancer classification.¹⁹ Data were acquired with approval from the ethics committee of the Technische Universität München. A minimum follow-up of at least 10 years was available for 60 patients. All 76 tumors were screened for the presence of the mutant E-cadherin variant with deletion of exon 9 with a mutation-specific E-cadherin antibody and one tumor with *del 9* mutation was identified. In addition, a second

gastric adenocarcinoma with *del 9* mutation was detected by routine examination and included into the study.

Construction of Tissue Microarrays

Paraffin wax blocks of 76 patients were obtained from the archives of the Institute of Pathology of the Technische Universität München. Representative, non-necrotic tumor areas were selected on hematoxylin–eosin-stained slides from these blocks. Three tissue cylinders per tumor with a diameter of 0.6 mm covering these areas were obtained from the paraffin blocks by core-needle biopsies using a manual arrayer (Beecher Instruments, Sun Prairie, WI, USA) and positioned in a recipient paraffin wax array block.

Antibodies

The following antibodies were used for immunohistochemistry: monoclonal anti-human Rac1 antibody (BD Transduction laboratories, clone 102), monoclonal anti-human IQGAP1 antibody (BD Transduction laboratories, clone 24), rabbit anti-human Tiam1 antibody (Calbiochem, Merck KGaA, Darmstadt, Germany No. ST1070) and monoclonal anti-E-cadherin antibody HECD-1 (Alexis Deutschland, Grünberg, Germany), mutation-specific antibody recognizing the mutant E-cadherin variant lacking exon 9.²⁰

Immunohistochemical Analysis

Manual staining protocols were used with the following dilutions: Rac1 1:7500, IQGAP1 1:2500, Tiam1 1:500 and E-cadherin 1:500. Antigen retrieval was performed using citrate buffer using a microwave (for Rac1 and IQGAP1 staining) or a pressure cooker (for Tiam1 and E-cadherin staining). A peroxidase block (3% H₂O₂ for 15 min at room temperature), an avidin biotin block (Vectastain, 2 × 15 min at room temperature) and blocking with 5% anti-goat serum in Dako dilution solution (2 h, room temperature) was performed. Staining was carried out with LSAB-DAB from Dako Diagnostika GmbH (Hamburg, Germany). As positive controls, we used breast carcinoma (for Rac1), gastric mucosa (for IQGAP1 and E-cadherin) and colon carcinoma as well as mouse skin (for Tiam1). In addition, formalin-fixed paraffin-embedded cell pellets from MDA-MB-435S cells transfected with wild-type E-cadherin were used as positive controls because these cells express all the investigated markers. Immunohistochemical analysis of mutant *del 9* E-cadherin was carried out as described previously.²¹ The immunohistochemical analyses were carried out with the 76 tumor samples on the tissue

microarray and for the two cases with *del 9* mutation the whole paraffin blocks were used.

Reactivity Score and Interpretation of the Immunohistochemical Staining

Rac1 staining was cytoplasmic, IQGAP1 staining membranous and cytoplasmic and Tiam1 staining membranous in tumor cells. For Rac1, IQGAP1 and Tiam1, tumors were considered as negative, when no staining or staining in <10% neoplastic cells was observed. Weak staining in >10% neoplastic cells was considered as 1+ positive, moderate staining in >10% neoplastic cells as 2+ positive and strong staining in >10% neoplastic cells as 3+ positive.

For the analysis of E-cadherin staining, tumors were considered as negative, when no staining was detectable. Membranous staining in <10% neoplastic cells was evaluated as 1+ positive, in >10 and <50% of neoplastic cells as 2+ positive and in >50% of neoplastic cells as 3+ positive. Tumors were considered as *del 9* positive when membranous staining was detected in tumor cells, without quantifying the percentage of positive tumor cells.

Staining of tissue microarrays for Rac1, IQGAP1, Tiam1 and E-cadherin was interpreted only when identical results were obtained for all three-tumor spots (Table 2). Rac1 staining was interpretable in 67 cases (88% of all cases), IQGAP1 staining in 63 cases (89% of all cases), Tiam1 staining in 71 cases (93% of all cases) and E-cadherin staining in 69 cases (91% of all cases).

Statistical Analysis

Evaluation was performed by two investigators (AW and BL) who were unaware of clinical features and survival. Statistical analyses were performed using Fisher's exact, Kruskal–Wallis or χ^2 tests when appropriate. Kaplan–Meier survival time analysis was used to correlate Rac1, IQGAP1, Tiam1 and E-cadherin reactivity, pT and pN with clinical evolution. Cox regression analysis was performed correlating the investigated markers with prognosis. Correlation analysis between the investigated markers was performed using the Spearman's rho test. A two-sided *P*-value less than 0.05 was considered to be statistically significant.

Results

Immunohistochemical Expression of Rac1, IQGAP1, Tiam1 and E-cadherin

In normal gastric mucosa, negative or weakly positive cytoplasmic Rac1 staining in surface epithelium was observed. Lymphocytes were positive for Rac1 and this staining served as internal control. Further, membrane staining of surface epithelium was

detected for IQGAP1. Moderate to strong membranous Tiam1 staining and strong membranous E-cadherin staining of epithelial cells was detected in non-cancerous gastric mucosa.

The clinical and pathological features of the gastric cancer patients are shown in Table 1. Rac1 reactivity was absent in two cases (3%, score 0), weak in 34 cases (51%, score 1+), moderate in 26 cases (39%, score 2+) and strong in five cases (7%, score 3+). Rac1 expression was detected in the cytoplasm of the tumor cells as well as in lymphocytes. Examples for adenocarcinomas displaying cytoplasmic staining of Rac1 are shown in Figure 1a–d.

IQGAP1 reactivity was absent in 26 cases (41%, score 0), weak in 29 cases (46%, score 1+), moderate in six cases (10%, score 2+) and strong in two cases (3%, score 3+, Table 2). Immunostaining of IQGAP1 was observed at the cellular membrane and in the cytoplasm of tumor cells (Figure 1e–h). Lymphocytes and granulocytes showed membranous IQGAP1 expression.

Tiam1 reactivity was absent in five cases (7%, score 0), weak in 26 cases (37%, score 1+), moderate in 32 cases (45%, score 2+) and strong

Table 1 Clinicopathologic features of 76 patients with gastric cancer

	<i>n</i>	%
<i>Age</i>		
Mean	65.0	
Median	69.0	
s.d.	12.5	
Range	30–86	
<i>Gender</i>		
Female	20	26
Male	56	74
<i>Histotype (Laurén)</i>		
Intestinal	53	70
Diffuse and mixed	23	30
<i>Tumor stage</i>		
pT1	12	16
pT2a and pT2b	42	58
pT3	17	23
pT4	2	3
<i>Perigastric lymph node status</i>		
N0	24	33
N1	28	39
N2	20	28
<i>Grading</i>		
1	2	3
2	26	36
3	44	61
<i>Residual disease</i>		
R0	72	99
R1	1	1

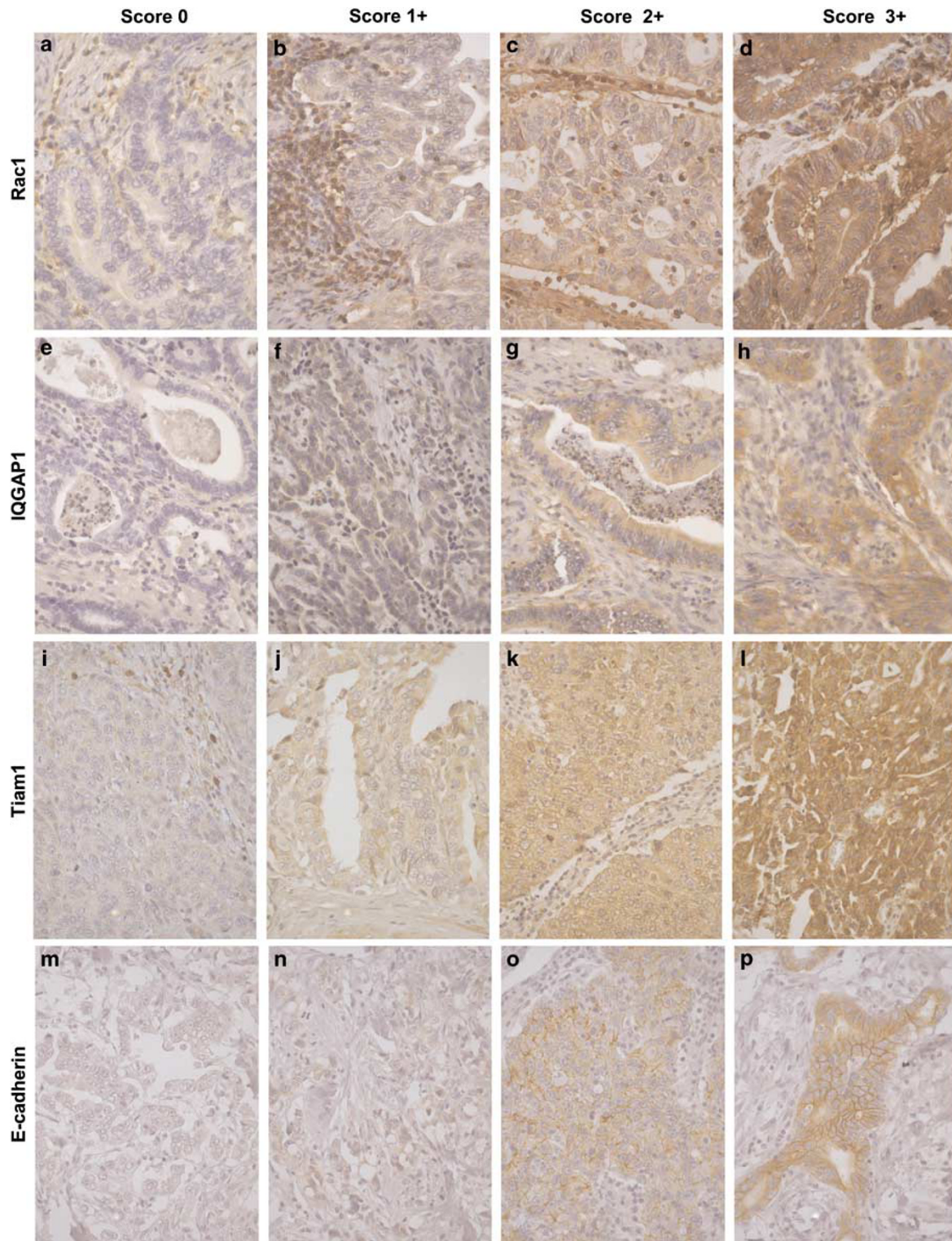


Figure 1 Immunohistochemical staining for Rac1, IQGAP1, Tiam1 and E-cadherin in gastric adenocarcinoma. Adenocarcinoma negative for Rac1 (a) or displaying weak cytoplasmic staining of Rac1 with an intensity of 1+ (b), an example Rac1 for expression with a moderate intensity of 2+ (c) or strong Rac1 staining with an intensity of 3+ (d) are shown. Gastric cancer samples negative for IQGAP1 (e) or showing weak cytoplasmic or membranous staining of IQGAP1 with an intensity of 1+ (f), an example for IQGAP1 expression with a moderate intensity of 2+ (g) or strong IQGAP1 staining with an intensity of 3+ (h) are depicted. Adenocarcinoma negative for Tiam1 (i) or displaying weak membranous staining of Tiam1 with an intensity of 1+ (j), an example for Tiam1 expression with a moderate intensity of 2+ (k) or strong Tiam1 staining with an intensity of 3+ (l) are shown. Gastric adenocarcinoma negative for E-cadherin (m) or displaying weak membranous staining of E-cadherin with an intensity of 1+ (n), an example for E-cadherin expression with a moderate intensity of 2+ (o) or strong E-cadherin staining with an intensity of 3+ (p) are depicted. Original magnification $\times 400$.

Table 2 Rac1, IQGAP1, Tiam1 and E-cadherin reactivity and its correlation with clinicopathologic features

Score	Rac1					IQGAP1					Tiam1					E-cadherin				
	0	1+	2+	3+	Total	0	1+	2+	3+	Total	0	1+	2+	3+	Total	0	1+	2+	3+	Total
Reactivity																				
n	2	34	26	5	67	26	29	6	2	63	5	26	32	8	71	9	18	23	19	69
%	3	51	39	7		41	46	10	3		7	37	45	11	13	26	33	28		
Histotype (Laurén)																				
Intestinal	2	23	18	5	48	17	22	5	2	46	3	22	21	5	51	3	14	15	16	48
Diffuse and mixed	0	11	8	0	19	9	7	1	0	17	2	4	11	3	20	6	4	8	3	21
	<i>P</i> =0.375					<i>P</i> =0.583					<i>P</i> =0.334					<i>P</i>=0.040				
Perigastric lymph node status																				
pN0	1	9	7	2	19	9	4	3	1	17	2	8	10	2	22	2	5	5	7	19
pN1	0	15	10	2	27	8	16	2	1	27	3	10	10	4	27	4	5	9	9	27
pN2	1	8	8	1	18	6	8	1	0	15	0	7	10	1	18	1	8	7	3	19
	<i>P</i> =0.895					<i>P</i> =0.364					<i>P</i> =0.718					<i>P</i> =0.512				
Tumor stage																				
pT1	1	5	2	2	10	4	3	0	1	8	1	4	5	1	11	2	2	1	4	9
pT2	1	17	19	1	37	14	19	3	1	37	2	13	22	3	40	1	12	16	11	40
pT3/4	1	10	5	2	18	5	7	3	0	15	2	8	4	3	17	4	4	5	4	17
	<i>P</i> =0.143					<i>P</i> =0.464					<i>P</i> =0.507					<i>P</i> =0.148				
Grading																				
G1	0	0	0	2	2	0	1	0	1	2	0	0	1	1	2	0	0	0	2	2
G2	1	11	10	0	22	8	10	4	0	22	2	10	10	3	25	3	4	8	8	23
G3	1	19	18	2	40	15	17	2	1	35	3	15	19	3	40	4	14	14	8	40
	<i>P</i>=0.022					<i>P</i>=0.010					<i>P</i> =0.603					<i>P</i> =0.217				

P-values were obtained by Pearson χ^2 or Fisher's exact test; significant values are in bold.

in eight cases (11%, score 3+, Table 2). Expression of Tiam1 was found at the cellular membrane of tumor cells (Figure 1i–l).

E-cadherin reactivity was absent in nine cases (13%, score 0), weak in 18 cases (26%, score 1+), moderate in 23 cases (33%, score 2+) and strong in 19 cases (28%, score 3+, Table 2). Expression of E-cadherin was detected at the cellular membrane of tumor cells (Figure 4m–p).

Correlation Analysis Between Expression Levels

Correlation analysis between expression levels of Rac1, IQGAP1, Tiam1 and E-cadherin using the Spearman's rho test revealed a significant correlation between Rac1 and IQGAP1 expression (*P*=0.007, *r*=0.343) and a trend suggesting an inverse correlation between Rac1 and E-cadherin expression (*P*=0.055, *r*=−0.245) (Figure 2).

Correlations with Clinical Data

A significant correlation was observed between the presence of Rac1 and grading (*P*=0.022) as well as between IQGAP1 and grading (*P*=0.010, Table 2). No association was observed between Tiam1 and pT, pN, grading and classification (Table 2). E-cadherin staining was more prominent in intestinal-type

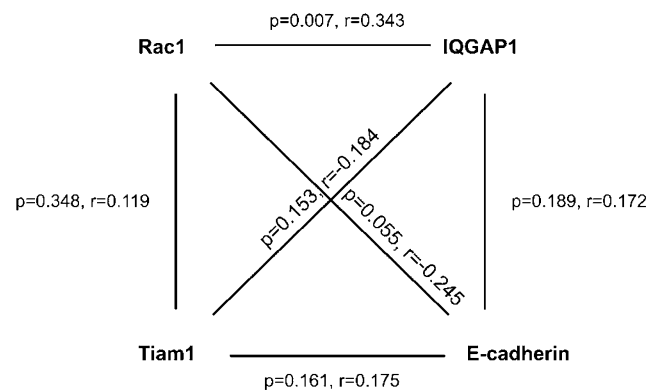


Figure 2 Correlation analysis. Correlation analysis was performed between the expression levels of Rac1, IQGAP1, Tiam1 and E-cadherin in gastric adenocarcinomas.

compared to diffuse- or mixed-type gastric cancer. The correlation between reactivity for E-cadherin and classification was significant (*P*=0.040, Table 2).

Prognostic Significance of Rac1, IQGAP1, Tiam1 and E-cadherin

Kaplan–Meier method was used to correlate the expression of Rac1, IQGAP1, Tiam1 and E-cadherin

with patient survival. The mean and median of the overall patient follow-up were 57.9 or 38.8 months, respectively (range, 0.2–183.8 months, s.d. 51.7 months). No significant correlation with prognosis was observed for expression of Rac1 (Figure 3, log-rank 0.252). Trends were observed when the prognostic significance of IQGAP1 (Figure 4, log-rank 0.088) or Tiam1 expression (Figure 5, log-rank 0.097) was investigated. No significant correlation between the expression of E-cadherin and prognosis was observed (Figure 6, log-rank 0.502).

Expression of Rac1, IQGAP1 and Tiam1 in Gastric Cancer with E-cadherin Mutations

Expression of Rac1, IQGAP1 and Tiam1 was also investigated in selected gastric cancer cases with E-cadherin mutations. The clinicopathological features of two patients with deletion of exon 9 of E-cadherin are shown in Table 3. In patients with E-cadherin mutations, expression of Rac1, IQGAP1 and Tiam1 was low or absent (Table 4).

Discussion

We examined the expression in Rac1, the effector protein IQGAP1 and the activator Tiam1 in relation to E-cadherin in a series of 76 gastric adenocarcinomas in a tissue microarray study. Immunohistochemical investigation revealed increased expression (score 2+ or 3+) of Rac1 in 46% and of Tiam1 in 56% of tumors. Expression (score 1–3+) of IQGAP1 was observed in 59% and of E-cadherin in 87% of tumors. From our results, the following conclusions were drawn: (1) Rac1 and E-cadherin expression were not related to prognosis, while

trends for a favorable prognosis of patients with Tiam1 expression and a lack of IQGAP1 expression were observed. (2) The expression levels of Rac1 and IQGAP1 were significantly correlated. (3) Tumors with E-cadherin mutations showed reduced levels or absence of Rac1, IQGAP1 and Tiam1.

The Rho GTPase Rac1

In this study, we detected increased expression of Rac1 in around half of the investigated gastric adenocarcinomas, a link between Rac1 expression and grading and a correlation between Rac1 and

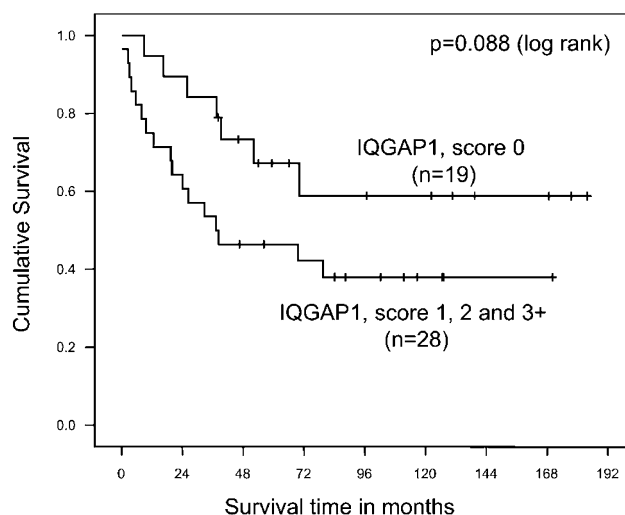


Figure 4 Survival impact of IQGAP1 expression. Kaplan–Meier survival curve for gastric carcinoma patients stratified according to the IQGAP1 expression status (score 0 vs score 1+, 2+ and 3+) in gastric carcinoma cells. A cutoff of 10% was used. The log-rank test statistical analysis indicates a $P=0.088$ (trend).

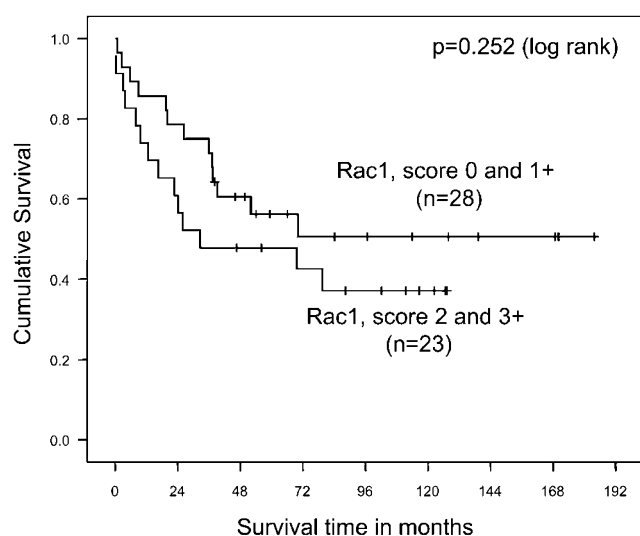


Figure 3 Survival impact of Rac1 expression. Kaplan–Meier survival curve for the gastric carcinoma patients stratified according to the Rac1 expression status in gastric carcinoma cells. The log-rank test statistical analysis indicates a $P=0.252$ (not significant).

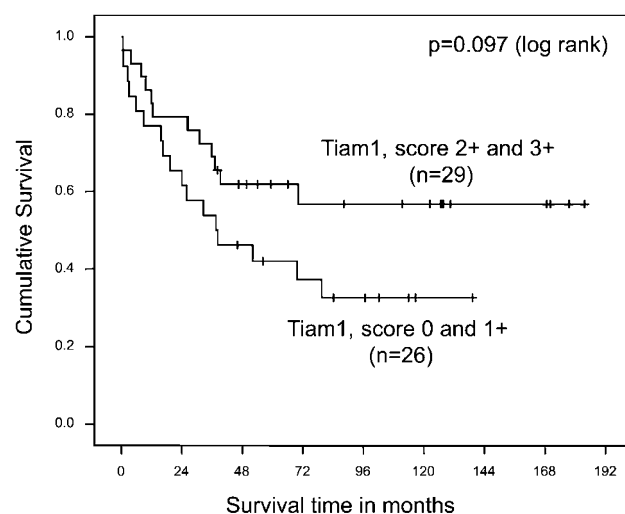


Figure 5 Survival impact of Tiam1 expression. Kaplan–Meier survival curve for gastric carcinoma patients stratified according to the Tiam1 expression status (score 0 and 1+ vs score 2+ and 3+) in gastric carcinoma cells. A cutoff of 10% was used. The log-rank test statistical analysis indicates a $P=0.097$ (trend).

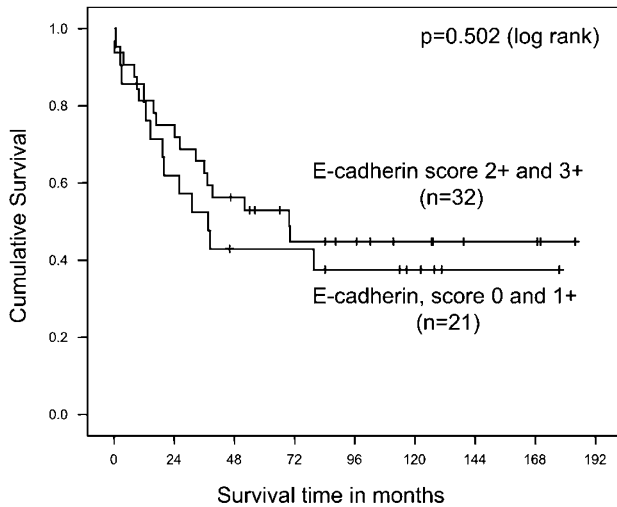


Figure 6 Survival impact of E-cadherin expression. Kaplan–Meier survival curve for gastric carcinoma patients stratified according to the E-cadherin expression status (score 0 and 1+ vs score 2+ or 3+) in gastric carcinoma cells. The log-rank test statistical analysis indicates a $P=0.502$ (not significant).

Table 3 Clinicopathologic features of patients with diffuse-type gastric adenocarcinomas with *del 9* E-cadherin mutations

Patient	1	2
E-cadherin mutation	<i>del 9</i>	<i>del 9</i>
Age	73	42
Gender	Male	Female
Histotype (Laurén)	Diffuse-type signet ring cell carcinoma	Diffuse-type
T stage	pT2b	pT1
N stage	N0	N0
G	3	3
Residual disease	R0	R0
Survival status	Dead	Alive
Survival time (month)	12.0	—

IQGAP1 expression. Only few data are available in the literature that refers to the role of Rac1 in gastric cancer. Recent findings indicate that Rac1 may play an important role in the carcinogenesis and progression of gastric carcinoma, because increased Rac1 expression was related to higher TNM stages.²² Genetic deletion of Rac1 has revealed its critical role in cell survival regulation²³ suggesting that increased expression of Rac1 in tumors may protect cells from apoptosis and lead to an increase of cell–matrix-interaction and cell spread. However, despite these important functions that are attributed to Rac1, no association of expression of Rac1 with prognosis was found in our study of gastric carcinomas. Of note, the investigated cohort was of relatively small size, limiting the conclusions that can be drawn.

Table 4 Expression of Rac1, Tiam1 and IQGAP1 in diffuse-type gastric adenocarcinomas with *del 9* E-cadherin mutations

Patient	1	2
E-cadherin mutation	<i>del 9</i>	<i>del 9</i>
E-cadherin	3+	3+
Rac1	0	1+
IQGAP1	1+	1+
Tiam1	1+	1+

The Rac1 Downstream Effector IQGAP1

We provide evidence that IQGAP1, a downstream effector of Rac1, is expressed in more than half of the examined gastric carcinomas and that its expression is linked to grading. Further, we demonstrate a trend that a lack of expression of IQGAP1 is beneficial for the patient’s survival. These results are consistent with *in vitro* data, showing that IQGAP1 negatively regulates E-cadherin-mediated cell–cell adhesion by interacting with β -catenin and displacing α -catenin from the adherens complex. In its activated GTP-bound form, Rac1 sequesters IQGAP1 and prevents its binding to β -catenin, thereby stabilizing cadherin-mediated cell adhesion.²⁴ The role of IQGAP1 in gastric carcinogenesis has been studied by several other groups, but to our knowledge, data on the prognostic significance of IQGAP1 in gastric cancer has not been reported. An inverse correlation of IQGAP1 with intercellular adhesion was shown in gastric cancers with cytoplasmic localization of IQGAP1 in intestinal type gastric cancer and membranous localization of IQGAP1 at the cellular membrane in diffuse type gastric cancer cells without cell–cell contact.²⁵ IQGAP1 expression has also been studied in other types of tumors. In colorectal cancer, overexpression of IQGAP1 in carcinomas and its association with invasion fronts has been detected.²⁶ In ovarian cancer, overexpression and diffuse expression pattern of IQGAP1 at invasion fronts are independent prognostic parameters.²⁷ To conclude, these reports and our own results converge at a negative role for IQGAP1 in tumorigenesis.

The Rac1-activator Tiam1

Here we report increased expression of the Rac1-activator Tiam1 in half of the examined gastric carcinomas. Further, increased positivity of tumor cells for Tiam1 tended to be associated with favorable prognosis. Tiam1 is required for the establishment and maintenance of E-cadherin-based adhesions,²⁸ hence it seems to play a role in conserving the epithelial phenotype of cells. In line with this, Tiam1-mediated activation of Rac1 stimulates cadherin-mediated cell adhesion, thereby limiting the capacity of cells to migrate and to

invade.⁶ On the other side, the function of Tiam1 strongly depends on the cellular context, because Tiam1 has originally been identified as an invasion- and metastasis-inducing gene in a murine T-lymphoma cell line.²⁹ Concerning cancer onset, Tiam1 has been found to correlate both positively and negatively with tumor progression, depending on the type of cancer.³ Tiam1 expression correlated inversely with renal tumor invasion *in vitro* and mutations in Tiam1 have been found in renal cell carcinoma.³⁰ However, Tiam1 plays an important role in the progression and metastasis of cancers, including colon and breast carcinomas.³¹

E-cadherin

In this study, we found expression of E-cadherin in the majority of cases. In accordance with previous results, the protein level has low impact on patient survival.²¹ Here we show that there was a tendency towards an inverse correlation between expression of E-cadherin and Rac1. Mutation of E-cadherin is frequently observed in diffuse-type gastric carcinoma.¹⁷ We recently demonstrated that patients carrying deletions of exons 8 or 9, observed in 5% of tumors in a Mexican series of gastric carcinomas, had a worse prognosis than patients without these alterations.²¹ Here we report that expression of Rac1, IQGAP1 and Tiam1 was low or absent in tumor cases with E-cadherin mutations. This result indicates that the trend for the inverse correlation between expression of E-cadherin and Rac1 is preserved in the presence of the mutation.

Taken together, in this study we investigated whether expression of Rac1, IQGAP1 and Tiam1 is deregulated in gastric cancer. We present evidence that upregulation (for Rac1 and IQGAP1) as well as downregulation (for Tiam1 and E-cadherin) occurs. Expression of Rac1 was positively linked to IQGAP1 and tended to be inversely linked to E-cadherin. Further studies with larger numbers of tumors are necessary to finally establish the role of the investigated markers in gastric carcinogenesis.

Acknowledgements

We thank C Hartmann, M Beckesch and A Voss for excellent technical assistance. Our study was supported by a grant to B Lubber from the Deutsche Krebshilfe (Nr 106148).

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