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Value of expression of insulin-like growth factor-1 receptor in gastric adenocarcinomas and normal gastric tissues

STOMACH

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Original Article

ABSTRACT

Background/Aims: Insulin-like growth factor-1 receptor (IGF-1R) plays critical roles in cell proliferation, differentiation, apoptosis, and transformation. Suppression of IGF-1R by means of antisense methods and specific antibodies causes cell apoptosis and growth inhibition of cancer cells. The present study aims to investigate whether there is a difference between normal and cancerous tissue with respect to IGF-1R expression and to assess the relationship between IGF-1R expression and tumor stage, degree of differentiation, and lymph node metastasis by examining IGF-1R expression in cancerous and normal tissues of gastric adenocarcinoma cases of different stages.

Materials and Methods: By using immunohistochemical methods, IGF-1Rb (H-60) (1/100, Santa Cruz Biotechnology, SC-9038, Texas,USA) expression was investigated in paraffin-embedded blocks obtained from total/partial gastrectomy material pertaining to 47 gastric adenocarcinoma cases. IGF-1R expression was evaluated semi-quantitatively in terms of intensity and distribution in both normal and cancerous tissues.

Results: Insulin-like growth factor-1 receptor expression mean score was 5.38 and 8.40 for cancerous and for normal gastric tissues, respectively. IGF-1R expression decreased significantly in cancerous tissues compared normal tissue (p:0.001). When all cases with and without lymph node metastasis were analyzed, IGF-1R expression was observed to decrease for cases with lymph node metastasis compared to those without lymph node metastasis (p:0.035).

Conclusion: Insulin-like growth factor-1 receptor expression in gastric cancer tissue has proven to be considerably lower than IGF-1R expression in normal gastric mucosa. Metastatic progression reduces IGF-1R expression gradually in cancer tissue.

Keywords: Insulin-like growth factor-1 receptor, gastric cancer, metastasis

INTRODUCTION

Gastric adenocarcinoma is the second most important cause of cancer-related mortality on a global scale. Though its incidence is gradually decreasing, about 930,000 new cases are being detected every year. Despite the development of numerous new drug treatments recently, the median survival is around 7-10 months in inoperable or metastatic gastric cancers (1).

Many risk factors and premalignancy conditions were defined in the development of gastric cancer, but the process of cancer development has not been fully elucidated yet. In recent years, studies conducted on various cancer types have revealed the importance of growth factors in carcinogenesis. The establishment of the relationship between growth factors and oncogenes has given impetus to studies on this issue (2-4). Insulin-like growth factor-1 (IGF-I) and its receptor (IGF-1R) have a special place among growth factor systems. The presence of IGF-1R in particular was suggested to play a key role in the process of tumorigenesis. The finding that cells that do not express IGF-1R can not be subjected to transformation via viral and cellular oncogenes has made IGF-1R a new target in cancer treatment (5-8). Inhibition of IGF-1R expression leads to apoptosis of cancer cells and inhibition of cancer growth. The methods used for IGF-1R suppression are IGF-1R antisense oligonucleotides, IGF-1R antisense RNA-expressing

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plasmids, and IGF-1R-specific antibodies. Using these methods, it was possible to halt growth in lung cancer, breast cancer, glioblastoma, prostate cancer, cervical cancer, and melanoma cells (9-19).

The number of studies investigating the presence of IGF-1R in gastric cancer is quite limited, and the results are heterogeneous. This study aims to investigate whether there is a difference between normal and cancerous tissue with respect to IGF-1R expression and to assess the relationship between IGF-1R expression and tumor stage, degree of differentiation, and lymph node metastasis by examining IGF-1R expression in cancerous and normal tissues of gastric adenocarcinoma cases of different stages.

MATERIALS AND METHODS

Forty-seven cases diagnosed with gastric adenocarcinoma and operated on in our hospital were included in the study. Formalin-fixed and paraffin-embedded preserved tissues from these cases were used in the IGF-1R assay. In the study, the presence of IGF-1R in cancerous and normal tissues of gastric adenocarcinoma cases was investigated using an immunohistochemical method.

Immunohistochemical staining was performed with the streptavidin-biotin immunoperoxidase method using primary monoclonal antibodies developed against IGF-1Rβ (H-60) (1/100, Santa Cruz Biotechnology, SC-9038, Texas USA) on 5-micrometer sections transferred from paraffin blocks to poly-L-lysine-coated slides. The stages of the procedure are as follows:

The sections are deparaffinized in xylol for 20 minutes. Then, starting with 96% alcohol, they are dehydrated by passing through an alcohol series until 70% alcohol. After the sections are washed in TRIS (hydroxymethyl-aminomethane) solution with a pH of 7.2 for 5 minutes, they are boiled in citric acid solution in special containers for antigen extraction in a microwave oven. After the cooling procedure, they are flushed with TRIS, and the borders of the sections are marked with a limiting pen. Then, 3% hydrogen peroxide (H_2O_2) is dropped on the sections and kept there for 5 minutes. With this procedure, endogenous peroxidase activity is blocked. The sections are flushed with TRIS once again, and blocking (nonimmune serum) (ZYMED Histostatin Plus, 01062420, California, USA) solution is dropped and kept there for 10 minutes. After flushing with TRIS again, IGF-1RB (1/100, Santa Cruz Biotechnology, SC-9038 Texas, USA) is dropped on the sections and kept there at room temperature for 60 minutes. After the sections are flushed in TRIS solution for 5 minutes, binding biotinylated secondary antibody is dropped and kept there for 10 minutes. Then, they are flushed in TRIS solution for 5 minutes. Streptavidin-peroxidase solution is dropped on the sections and kept there for 10 minutes. After the sections are flushed in TRIS solution for 5 minutes, they are treated with Mayer's hematoxylin for 5 minutes for contrast staining. After the sections are washed in tap water, dehydrated by passing through ab increasing alcohol series from 70% ethyl alcohol to 96% alcohol and isopropyl alcohol, and kept in xylol for 20 minutes to make them transparent, they are covered with Entellan (Merck KGaA 107960, Darmstadt, Germany).

All of the preparations stained with the immunohistochemical method were assessed twice by two pathologists at different times using a Nikon E600 light microscope. Placenta was used as the positive control for the IGF-1R antibody.

Immunohistochemical assessment

For every cancer case, sections displaying tumorous and normal mucosal tissue were obtained and IGF-1R expression was investigated with the immunohistochemical method in these tissues. In these tissue sections, intensity and extent of cytoplasmic staining were examined separately and graded with scores ranging from 1 to 4. The intensity and extent of staining obtained for every different tissue were multiplied, and thus, the total score was obtained. Taking the total scores into consideration, the degree of staining was divided into three groups as weak positive (those with a total score of 1-4), moderate positive (those with a total score of 5-8), and strong positive (those with a total score of 9-16) (20).

Statistical analysis

Percentage calculations and averages were used for descriptive findings. Comparison of tumor tissue and normal mucosal tissue with respect to IGF-1R expression was made with student t-test and chi-square test. $P<0.05$ was accepted as statistically significant.

Chi-square test was used to determine the relationship between IGF-1R expression and cell differentiation and tumor stage, and Fisher's exact test was used to determine the relationship between lymph node metastasis and IGF-1R expression. These tests were based on the degrees of staining (weakly positive, moderately positive, and strongly positive) for IGF-1R in the tissues. However, the groups were merged because of the lack of an adequate number of cases in table cells. Cases with weakly or moderately positive staining pattern were merged to constitute the "weak" staining group, while the strongly positive staining group constituted the "strong" staining group.

"SPSS/PC V 10.0 (Chicago, IL, USA)" was used for the statistical analyses.

RESULTS

In the study, a total of 47 total-partial gastrectomy materials from gastric adenocarcinomas were used; 72.3% of the cases (34) were male and 27.7% (13) was female.

The average age of the cases was 62.8 (minimum:28, maximum:87). The average age of the male patients at the time of diagnosis was 63.6, and that of the female patients was 60.6.

Table 1. Comparison of IGF-1R expression in tumor tissue and normal mucosal tissue according to the average of total scores

	Number	Average	p
Tumor tissue	47	5.383	0.001
Normal mucosal tissue	47	8.404	

Table 2. Comparison of tumor tissue and normal mucosal tissue with respect to IGF-1R expression (X^2:23.936, p:0.001)

	Degree of Staining			
	Weak	Moderate	Strong	Total
Tumor tissue	27 (57.4%)	10 (21.3%)	10 (21.3%)	47 (100%)
Normal mucosal tissue	5 (10.6%)	27 (57.4%)	15 (31.9%)	47 (100%)
Total	32 (34.0%)	37 (39.4%)	25 (26.6%)	94 (100%)

Table 3. The relationship between tumor stage and IGF-1R expression (X^2:4.458, p:0615)

	Degree of Staining			
Stage	Weak	Moderate	Strong	Total
1				
Number	1	1	1	3
Percentage	33.3%	33.3%	33.3%	100%
2				
Number	5	1	4	10
Percentage	50.0%	10.0%	40.0%	100%
3				
Number	13	6	3	22
Percentage	59.1%	27.3%	13.6%	100%
4				
Number	8	2	2	12
Percentage	66.6%	16.7%	16.7%	100%
Total				
Number	27	10	10	47
Percentage	57.4%	21.3%	21.3%	100%

The distribution of tumors with respect to their stages was as follows: stage I: 3 patients (6.4%), stage II: 10 patients (21.3%), stage III: 22 patients (46.8%), and stage IV: 12 patients (25.5%). Of all the cancerous tissues, 25 were poorly differentiated (53.2%), 17 were moderately differentiated (36.2%), and 5 were well differentiated (10.6%).

In all sections of cancerous and normal mucosal tissue from gastric adenocarcinoma cases, staining for IGF-1R was observed. The total score average was found to be 5.38 in cancerous tissue and 8.40 in normal gastric tissue. IGF-1R expression in cancerous tissue was significantly decreased compared with normal tissue (p:0.001) (Table 1,2). IGF-IR expression in normal and cancer tissue are shown in Figure 1-3.

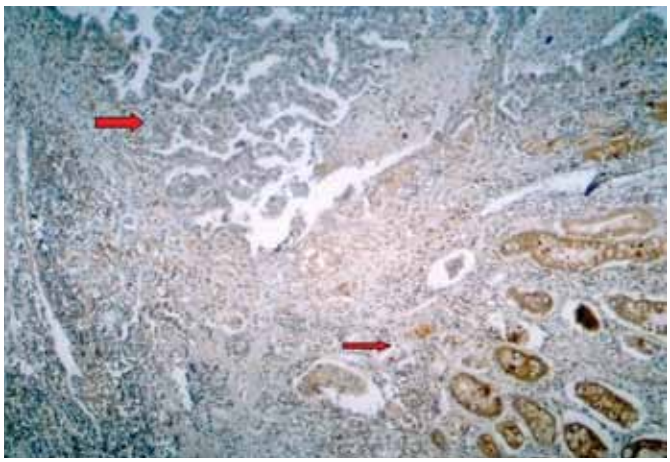

Figure 1. Strong positive staining for IGF-1R in normal gastric mucosa (thin arrow). Weak positive staining for IGF-1R in gastric cancer tissue (thick arrow).

Table 4. The relationship between tumor differentiation and IGF-1R expression (X^2:5.433, p:0.246)

	Degree of Staining			
Differentiation	Weak	Moderate	Strong	Total
Poor				
Number	16	5	4	25
Percentage	64%	20.0%	16.0%	100%
Moderate				
Number	10	4	3	17
Percentage	58.8%	23.5%	17.6%	100%
Well				
Number	1	1	3	5
Percentage	20.0%	20.0%	60.0%	100%
Total				
Number	27	10	10	47
Percentage	57.4%	21.3%	21.3%	100%

In the study, tumor tissues were divided into four groups according to their stages. The relationship between stage and IGF-1R expression was investigated. It was observed that the characteristic of weak staining for IGF-1R increased with increasing tumor stage. It was 33%, 50%, 59%, and 67% respectively, but this finding did not reach statistical significance (Table 3).

In this study, the relationship between tumor differentiation and IGF-1R expression was also investigated. While the strongly positive IGF-1R expression rate was 16.0% in poorly differentiated cancer tissue, it was 60.0% in well-differentiated cancer tissue. Though statistical significance was not detected, the strongly positive staining rate increased with increasing differentiation (Table 4).

Upon assessment of cases with and without lymph node metastasis, weak staining for IGF-1R was detected in 81.6% of

Table 5. The relationship between the presence of lymph node metastasis and IGF-1R expression (Fisher's exact test, p:0.035)

	Degree of Staining		
Lymph node metastasis	**Weak**	**Strong**	**Total**
Present			
Number	31	7	38
Percentage	81.6%	18.4%	100.00%
Absent			
Number	4	5	9
Percentage	44.4%	55.6%	100.00%
Total			
Number	35	12	47
Percentage	74.5%	25.5%	100.00%

cases with lymph node metastasis and in 44.4% of cases without lymph node metastasis. This result, revealing decreasing IGF-1R expression during the process of metastasis, was found to be statistically significant (p:0.035) (Table 5).

DISCUSSION

In recent years, the new target of studies conducted on cancer development has been growth factor systems. The relationship between these factors and cancer has become more important with the revelation of the connection between growth factors and oncogenes. It was determined with various studies that the IGF system in particular plays quite a significant role in cancer development.

The finding that R cells without IGF-1R expression can not be subjected to transformation via oncogenes has made the IGF system a new target of cancer treatment. IGF-1R suppression has caused apoptosis of cancer cells or inhibition of tumor growth in many human tumors (21). The most frequently used methods for this purpose are IGF-1R antisense oligonucleotides, IGF-1R antisense RNA-expressing plasmids, and IGF-1R-specific antibodies. Antisense approaches inhibit IGF-1R synthesis. When IGF-1R-specific antibodies are used, the relationship between IGF-1R and its ligands is impaired, and thus, IGF-I- and IGF-II-mediated signaling is blocked (22).

Baserga succeeded in decreasing IGF-1R numbers in glioblastoma cells using IGF-1R antisense RNA-expressing and observed massive apoptosis in cancer cells (23). Using specific antibodies, Sachdev demonstrated that breast cancer cells acquire resistance against the mitogenic effects of IGF-1 (12). In human prostate cancer cells, antisense oligonucleotide was applied against IGF-1R, and the growth of cancer cells was observed to be blocked at a rate of 90% (19). Using antisense RNA-expressing plasmid in a cervical cancer cell series, Nakamura achieved a drop in IGF-1R numbers at rates approaching 80% and prevented cancer cells from forming colonies in culture (14). Another feature of methods maintaining IGF-1R

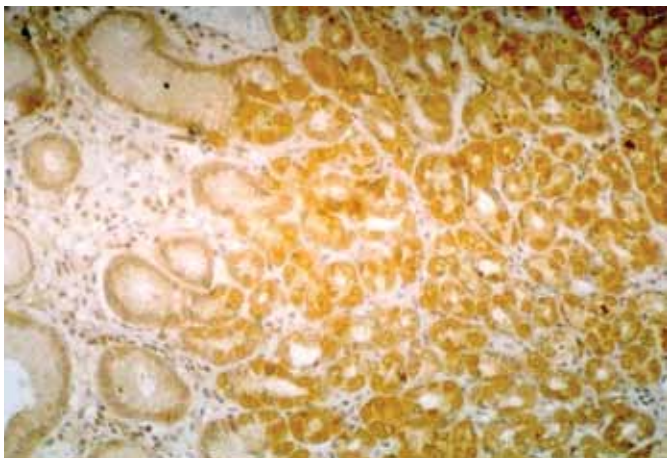

Figure 2. Strong positive staining for IGF-1R in normal gastric mucosa.

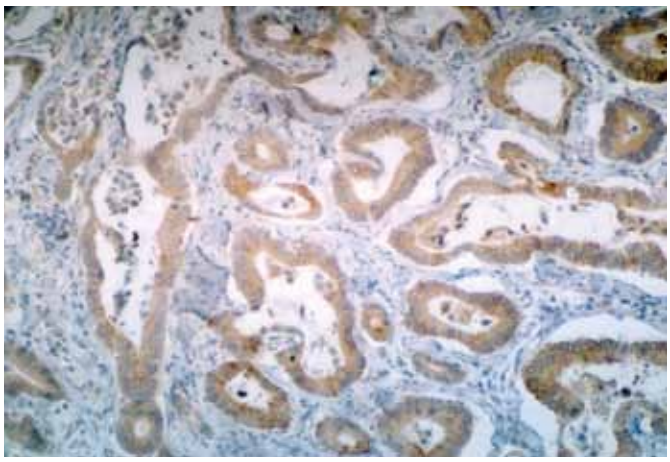

Figure 3. Strong positive staining for IGF-1R in gastric cancer tissue.

suppression is that with concomitant use, they enhance the effectiveness of routinely used chemotherapy and radiotherapy (18,19). However, the most exciting aspect of studies on this subject is that unlike many agents used in cancer treatment, changes in IGF-1R expression affect the normal tissue at a minimal level. When IGF-1R suppression is achieved, growth inhibition in normal cells is observed at a rate of 10%-15% (21). The reason for this is that IGF-1R activity does not play a critical role in normal cell growth (16). When suppression is applied to cancer cells with similar methods, it causes widespread apoptosis in cells and regression in cancer (13,17).

Studies conducted with the IGF system in gastric cancer are quite limited. IGF-1R expression was investigated in a limited number of studies, and different results were obtained. Using in situ hybridization and immunohistochemical methods, Chung detected IGF-1R expression in gastric cancer tissue and the surrounding non-malignant cells (24). Durrant demonstrated the presence of IGF-1R in three different gastric cancer cell series and performed their quantitative measurements (in St16 cell series 250/cell, in St42 cell series 190/cell, in MKN45 cell series 310/cell) (25). Quban detected IGF-1R positivity in five out of seven gastric adenocarcinomas with an immunohistochemical method. IGF-1R has not been detected in normal gastric mucosa (26).

In our study, we found IGF-1R expression in gastric adenocancer to be significantly decreased compared with normal gastric tissue (Table 1,2). When we divided the staining pattern for IGF-1R into three degrees as weak, moderate, and strong, we detected a weakly staining rate in tumor tissue of 57.4% and found this rate to be 10.6% in normal tissue (p:0.001). Upon assessment of the relationship between tumor stage and IGF-1R expression, we detected increased weak staining for IGF-1R in more advanced tumors. The rates were, respectively, 33%, 50%, 59%, and 67%, however; this finding did not reach statistical significance (Table 3).

Although a relationship was detected between increased IGF-1R expression in cancer cells and tumor progression in studies investigating the relationship between various cancer types and the IGF system (27-30), in the literature, there are a few studies that do not confirm this relationship, as is the case in our study. The most striking of these studies was conducted by Schnarr et al. (31). In that study, the intensity and extent of IGF-1R, IR, and IRS-1 expression were investigated in breast cancer tissue and the surrounding normal tissue with an immunohistochemical method. Sixty-nine breast cancer tissues and 21 normal breast tissues obtained from surgical resection materials were included in the study. It was striking to observe IGF-1R to be moderately-strongly expressed in all control breast tissues after immunohistochemical staining. A similar staining characteristic was also detected in the tissues surrounding the tumor. In well- and moderately differentiated ductal carcinomas, IGF-1R was moderately-strongly expressed. In poorly differentiated carcinomas, on the other hand, expression was observed to be significantly decreased.

In our study, we also investigated the relationship between IGF-1R expression and differentiation. We divided cancer tissue into three groups according to the degree of differentiation. Among these groups, we observed strong IGF-1R expression in 16.0% of poorly differentiated cancer cells, in 17.6% of moderately differentiated cancer cells, and in 60.0% of well-differentiated cancer cells. Although these findings did not reach statistically significant values, probably due to the number of patients (p:0.246), they showed IGF-1R expression to be increased with increasing differentiation.

Another important point is that IRS-1 plays an active role in cell adhesion by interacting with various integrins. As expected, a cancer cell that is preparing to metastasize may want to break free by decreasing the IRS-1 level and thus facilitate invasion to other tissues. However, an important point here is that the relatively increasing IGF-1R in response to decreasing IRS-1 levels may lead the cell to differentiation. In this case, the cell will decrease the number of IGF-1R and will be able to metastasize later (32).

In our study, we also investigated the relationship between lymph node metastasis and IGF-1R expression in tumor cases. In the group without lymph node metastasis, the rate of cases with strong staining was 55.6%. On the other hand, the rate of strong staining in tumor tissue with lymph node metastasis was found to be 18.4%. This result, which was statistically significant as well (p:0.035), is important, since it demonstrates that IGF-1R expression is decreased during metastasis.

In short, the presence of IGF-1R is required for malignant transformation. IGF-1R level is important in distinguishing cellular differentiation from transformation. A decrease in IGF-1R number leads to tumorigenesis and an increase in metastatic capacity in the presence of IRS-I, whereas an increase in IGF-1R level leads to the commencement of the differentiation process.

In conclusion, in our study, we have observed IGF-1R expression to be markedly decreased in gastric adenocancer tissue compared with normal gastric mucosa and detected a gradual decrease of IGF-1R expression in cancer tissue during the metastatic process. To further elucidate the relationship between IGF-1R and IRS-I during transformation and metastasis in gastric adenocancer, studies that concomitantly evaluate both parameters in the same cell are warranted.

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REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108. **[CrossRef]**
2. Vincent AM, Feldman EL. Control of cell survival by IGF signaling pathways. Growth Horm IGF Res 2002; 12: 193-7. **[CrossRef]**
3. Moschos SJ, Mantzoros CS. The role of the IGF system in cancer: From basic to clinical studies and clinical applications. Oncology 2002; 63: 317-32. **[CrossRef]**
4. Grothey A, Voigt W, Schöber C, Müller T, Dempke W, Schmoll HJ. The role of insulin-like growth factor I and its receptor in cell growth, transformation, apoptosis and chemoresistance in solid tumors. J Cancer Res Clin Oncol 1999; 125: 166-73. **[CrossRef]**
5. Wener H, Roberts CT Jr. The IGFI receptor gene: a molecular target for disrupted transcription factors. Genes Chromosomes Cancer 2003; 36: 113-20. **[CrossRef]**
6. Valentinis B, Porcu PL, Quinn K, Basserga R. The role of the insulin-like growth factor I receptor in the transformation by simian virus 40 T antigen. Oncogene 1994; 9: 825-31.
7. Sell C, Rubini M, Rubin R, Liu JP, Efstratiadis A, Baserga R. Simian virus 40 large tumor antigen is unable to transform mouse embryonic fibroblasts lacking type 1 insulin-like growth factor receptor. Proc Natl Acad Sci USA 1993; 90: 11217-21. **[CrossRef]**

8. Coppola D, Ferber A, Miura M et al. A functional insulin-like growth factor I receptor is required for the mitogenic and transforming activities of the epidermal growth factor receptor. Mol Cell Biol 1994; 14: 4588-95.
9. Jiang Y, Rom WN, Yie TA, Chi CX, Tchou-Wong KM. Induction of tumor suppression and glandular differentiation of A549 lung carcinoma cells by dominant-negative IGF-I receptor. Oncogene 1999; 18: 6071-7. **[CrossRef]**
10. Adachi Y, Lee CT, Coffee K et al. Effects of genetic blockade of the insulin-like growth factor receptor in human colon cancer cell lines. Gastroenterology 2002; 123: 1191-204. **[CrossRef]**
11. Reinmuth N, Fan F, Liu W et al. Impact of insulin-like growth factor receptor I function on angiogenesis, growth and metastasis of colon cancer. Lab Invest 2002; 82: 1377-99. **[CrossRef]**
12. Sachdev D, Li SL, Hartell JS, Fujita-Yamaguchi Y, Miller JS, Yee D. A chimeric humanized single-chain antibody against the type-1 IGF receptor renders breast cancer refractory to the mitogenic effect of IGF-I. 2003. Cancer Res 2003; 63: 627-35.
13. Resnicoff M, Coppola D, Sell C, Rubin R, Ferrone S, Baserga R. Growth inhibition of human melanoma cells in nude mice by antisense strategies to the type 1 IGF receptor. Cancer Res 1994; 54: 4848-50.
14. Nakamura K, Hongo A, Kodama J, Miyagi Y, Yoshinouchi M, Kudo T. Down-regulation of the IGF-1R by antisense RNA can reverse the transformed phenotype of human cervical cancer cell lines. Cancer Res 2000; 60: 760-5.
15. Long L, Rubin R, Baserga R, Brodt P. Loss of the metastatic phenotype in murine carcinoma cells expressing an antisense RNA to the insulin-like growth factor receptor. Cancer Res 1995; 55: 1006-9.
16. Baserga R, Hongo A, Rubini M, Prisco M, Valentinis B. TheIGF-1R in cell growth, transformation and apoptosis. Biochim Biophys Acta 1997; 1332: 105-26.
17. Resnicoff M, Sell C, Rubini M. Rat glioblastoma cells expressing an antisense RNA to the IGF-1R are non-tumorigenic and induce regression of wild-type tumors. Cancer Res 1994; 54: 2218-22.
18. Macaulay VM, Salisbury AJ, Bohula EA, Playford MP, Smorodinsky NI, Shiloh Y. Downregulation of the type-1 IGFR in mouse melanoma cells is associated with enhanced radiosensitivity and impaired activation of Atm kinase. Oncogene 2001; 20: 4029-40. **[CrossRef]**
19. Hellawell GO, Ferguson DJ, Brewster SF, Macaulay VM. Chemosensitization of human prostate cancer using antisense agents targeting the type 1 insulin-like growth factor receptor. BJU Int 2003; 91: 271-7. **[CrossRef]**
20. Gilcrease MZ, Truong L, Brown RW. Correlation of very late activation integrin and CD44 expression with extrarenal invasion and metastasis of renal cell carcinomas. Hum Pathol 1996; 27: 1355-60. **[CrossRef]**
21. Baserga R, Peruzzi F, Reis K. The IGF-1R in cancer biology. Int J Cancer 2003; 107: 873-7. **[CrossRef]**
22. Pavelic K, Kolak T, Kapitonovic S, et al. Gastric cancer: The role of insulin-like growth factor 2 (IGF 2) and its receptors (IGF 1R and M6-P/IGF 2R). J Pathol 2003; 201: 430-8. **[CrossRef]**
23. Baserga R. The contradictions of IGF-1R. Oncogene 2000; 19: 5574-81. **[CrossRef]**
24. Chung CK, Antoniades HN. Expressionof c-sis/platelet derived growth factor B, IGF-I and transforming grovth factor alpha m-RNA and their respective receptor mRNA in primary human gastric carcinomas: invivo studies with insitu hybridiidzation and immunocytochemistry. Cancer Res 1992; 15: 3453-9.
25. Durrant LG, Watson SA, Hall A, Morris DL. Co-stimulation of gastrointestinal tumour cell growth by gastrin, transforming growth factor alpha and insulin like growth factor-I. Br J Cancer 1991; 63: 67-70. **[CrossRef]**
26. Ouban A, Muraca P, Yeatman T, Coppola D. Expression and distribution of IGF-1R in human carcinomas. Hum Pathol 2003; 34: 803-8. **[CrossRef]**
27. All-Ericsson C, Girnita L, Seregard S, Bartolazzi A, Jager MJ, Larsson O. Insulin-like growth factor-1 receptor in uveal melanoma: a predictor for metastatic disease and a potential therapeutic target. Invest Ophthalmol Vis Sci 2002; 43: 1-8.
28. Long L, Rubin R, Brodt P. Enhanced invasion and liver colonization by lung carcinoma cells overexpressing the type 1 insulin-like growth factor receptor. Exp Cell Res 1998; 238: 116-21. **[CrossRef]**
29. Parker AS, Cheville JC, Janney CA, Cerhan JR. High expression levels of IGF-1R predict poor survival among women with clear-cell renal cell carcinomas. Hum Pathol 2002; 33: 801-5. **[CrossRef]**
30. Weber MM, Fottner C, Liu SB, Jung MC, Engelhardt D, Baretton GB. Overexpression of the insulin-like growth factor I receptor in human colon carcinomas. Cancer 2002; 95: 2086-95. **[CrossRef]**
31. Schnarr B, Strunz K, Ohsam J, Benner A, Wacker J, Mayer D. Down-regulation of insulin-like growth factor-I receptor and insulin receptor substrate-1 expression in advanced human breast cancer. Int J Cancer 2000; 89: 506-13. **[CrossRef]**
32. Baserga R. The IGF-I receptor in cancer research. Exp Cell Res 1999; 253: 1-6. **[CrossRef]**