IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 10 Ver. I (Oct. 2017), PP 09-15
www.iosrjournals.org

Expression of Autocrine Motility Factor Receptor and E-Cadherin in Gastric Adenocarcinoma-A Correlative study

[1]*Dr. Debashis Roy Burman, [2]Dr.DibyenduGoutam
1Associate professor,Department of Laboratory Oncology(Oncopathology),Medical College, Kolkata,
2.Professor,Department of Surgery,R.G.KarMedical College,Kolkata
*Corresponding Author: *Dr. Debashis Roy Burman*

Abstract: *Carcinoma of the stomach is still remained among the most common cause of cancer death worldwide. In an effort to understand interaction between force of Intercellular adhesion and its disruption by propagating cancer cells we have selected 46 caresses of Gastric adenocarcinomas. As E-cadherin (ECD) is the strongest intercellular adhesion molecule in nonmalignant Gastric mucosal epithelial cell and Autocrine motility Factor (AMF) is an established propagator of its malignant counterpart, we have studied simultaneous expression of ECD and AMFR (Autocrine motility Factor Receptor).With aid of immunohistochemical technique, strong or weak expression of ECD and AMFR was determined according to predetermined parameters .Normal Gastric mucosal cell (the control cases) strongly express ECD whereas reverse was true with AFMR. We find decrease ECD and simultaneous increase of AMFR in gastric adenocarcinomas. Furthermore, more aggressive morphologic variant showed varied expression in comparison to its less aggressive type. Diffuse type of Gastric adenocarcinoma show weak ECD (61.5% vs 40%) and more AFMR (53.8% vs 30%)expression in comparison to Intestinal type. Strong AMFR expression is correlated positively with increasing depth of invasive tumor. As both ECD and AMFR are involved in the pathway of tumor progression as well as development of more aggressive type of Gastric Adenocarcinomas, their simultaneous examination is necessary to evaluate biologic potential of this tumor.*

Key words: *Gastric Adenocrnomas; E-Cadherin: Autocrine motility Factor Receptor*

Date of Submission: 31-08-2017 Date of acceptance: 07-10-2017

I. Introduction

Adenocarcinoma of the stomach, a leading cause of cancer death worldwide is the second and fourth most common cancer in males and females respectively(1,2). In Asia.such incidence in male is similar ,whereas it ranked third among female .(3)Globally, gastric cancer accounts for about 1 lakh new cases and close to 0.8 lakh deaths annually. The case-fatality ratio of gastric cancer is higher than for common malignancies like colon, breast, and prostate cancers (4). Despite advances in diagnosis, the disease is usually detected after invasion of the muscularispropria, because most patients experience vague and nonspecific symptoms in the early stages and the classic triad of anemia, weight loss, and refusal of meat-based foods is seen only in advanced stages. Furthermore, surgery and chemotherapy have limited value in advanced disease and there is a paucity of molecular markers for targeted therapy. Since cancer of the stomach has a very poor prognosis and the 5-year survival rate is only around 20 per cent, a new look at the results of epidemiological and experimental studies is important to establish strategies for early precise detection and prognosis . (5)

Obviously,Despite such prevalence of malignant lesions, modern science yet to find complete curative treatment protocol of neoplasm.Limited success of medical science in such curative treatment is restricted to mostly early staged and low graded lesions.At cellular level,progression of malignancy is dependent variably on many cellular properties including intercellular adhesion, motility and proteolysis,(17)for infiltration of malignant cell into surrounding stroma , reduction of intercellular adhesion and increment of cell motility appeared two necessary simultaneous incidents.

It is established that E-cadherin(ECD) is strongest intercellular adhesion molecule in epithelial cell.(36)and such adhesion is regulated by ECD and ECD associated proteins including cateninin.(18,19).Many researchers has indicated correlation between of infiltration of malignant cell and diminished ECD and cateninsboth in vitro and in vivo in malignant lesion of various organs(18,19)including esophagous, stomach, Breast and Colon.(20-23)

As previous researchers already confirmed that Malignant cell infiltration is modulated by property of cell motility-which in turns is affected by various motility factors like Hepatocyte Growth factor, Epidermal growth factors(24-26) and as Silleti et el found that loss of intercellular adhesion up regulate the protine

expression and opromoter activity of AMFR(35),we intend find efficacy of AMFR in malignant cell progression.

AutocrineMotility Factor (AMF) has been purified from the culture media of various tumor cells as a specific motility modifier.(27,28) The receptor for AMF (AMFR) has been identified as a cell surface glycoprotein (gp78; molecular weight,78,000) on the B16-F1 melanoma cell line with high metastatic ability.(27,28)AutocrineMotility Factor Receptor (AMFR) concentrates on the leading edge of the cell surface, then is phosphorylated and internalized by binding with AMF.(29) Finally, it induces rearrangement of integrin, causing cells to move.(30) In this pathway, G protein might be involved, since cell motility is inhibited by a Bordetella pertussis toxin.(30) Up-regulation of AMFR and its implication in cancer progression in human cancers of various origin, including the large intestine,(31) placenta,(32)esophagus,(33) and stomach,(31-34) has been reported.

We intend to study simultaneous destruction of cellular adhesion and effect of motility factors in propagation malignant cell of epithelial origin. Review of literature reveled in epithelial cell, ECD is strongest intercellular adhesion molecule(36),association between ECD and AMFR is studied in various epithelial malignancies i.e. carcinomas and simultaneous loss of ECD and increase in AMFR is found in cultured cell lines of Urinary Bladder carcinomas.(37)This simultaneous alteration of ECD and AMFR, if they are situated on the common signal, enables us to understand that cancer progression more fluently leads to invasion and metastasis.

It is established thatGastric carcinomas depending on their diverse morphology, cellular origin and prognosis are divided into two categories.-namely Intestinal and Diffuse type.

In our study, we have evaluated expression of ECD and AMFR gene with aids of Immunohistochemistry. We found that the difference in natural history of these two type of gastric carcinomas can be partially explained by behavioral pattern of ECD and AMFR.

II. Materials And Methods

The study population consisted of 46 patients who were finally treated with total or distal gastrectomy with or without regional lymph node dissection. In this retrospective study (conducted between 2010 to 2015),in Medical College, Kolkata,we selected only those patients who underwent endoscopic evaluation followed by Final surgery. Interval between endoscopy and final surgery in our study varied from 22 to 166 days. Most patients underwent Final surgery within 50 days of the endoscopic evaluation. To reduce influence on natural history the disease, we selected only patients who have received no anticancer therapy prior to the surgery.

Stomach cancer incidence is known to increase with age with the peak incidence occurring at 60-80 years. Cases in patients younger than 30 years are very rare (6,7). In India, the age range for stomach cancer is 35-55 years in the South and 45-55 years in the North. The disease shows a male preponderance in almost all countries, with rates two to four times higher among males than females(8). In the present study,Age of the patients ranged between 36 to 74 years(male n=35 and female n=11),roughly in accordance to the previous results.

Clinical data including copy of histopathology requisition slips were collected from tertiary treatment center in Kolkata. Fresh Copy of Hematoxylene and Eosin stained tissue sections of endoscopic biopsy and total or distal gastrectomy with or without regional lymph node dissection specimens were prepared from paraffin blocks. Team of physicians, surgeons and Pathologist in Medical College, Kolkata went through the clinical data and tissue sections as per previously fixed protocol and parameters.

Cases in which histologic slides from endoscopic biopsy were not available for review were excluded. Pathologic Staging and Grading was performed by the team pathologist according to the WHO classification system TNM (tumor, lymph nodes, and metastasis) system.

Such representative Hematoxylene and Eosin stained tissue 0.5 micrometer thick sections were studied andTumour was designated intestinal or diffuse type based on histomorphology. Depth of Tumour invasion was noted following established WHO Guideline. Sections for immunohistochemistry was selected among the paraffin blocks which were taken from invasive margins of tumor, and had tumor in 50% or more of total section area.

Immunohistochemistry was performed on sections obtained from representativeblock of formalin-fixed paraffin-embedded tissue using the Avidin-biotin complex technique. The sections were deparaffinized in xylene, and rehydrated in a graded ethanol series. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide. The slides were subsequently incubated at room temperature with reagents. After washing in a 0.05-mol/L concentration of phosphate-buffered saline (PBS), they were incubated with3% normal rabbit serum for AMFR or 3% normal mouse serum for ECD for 30 minutes to block nonspecific conjugation in the tissues. The specimens were incubated sequentially with the primary anti-AMFR monoclonal antibody, 3F3A19, or antihuman ECD antibody, HECD1 (Takara Shuzo, Kyoto, Japan), at 4°C overnight. After washing with PBS, they were incubated with biotinylated rabbit antiratIgG for AMFR or rabbit antimouseIgG (Vectastain ABC Kit, Vector, Burlingame, CA), diluted1:250 in PBS, for 30 minutes at room temperature and with ABC reagent

(Vectastain ABC Kit) for 30 minutes at room temperature. The immune conjugate was visualized with a 0.05-mol/L concentration of tris(hydroxymethyl)- aminomethane (Tris)–hydrochloric acid (pH 7.6) containing0.02% (wt/vol) 3,3´-diaminobenzidine tetrahydrochloride and 0.03% (vol/vol) hydrogen peroxide, and counterstaining was performed with Meyer`shematoxylin.

During immunohistochemical evaluation of ECD and AFMR tumour cell were designated positive or negative as per predetermined criteria(Table 1).For statistical analysis, differences between the 2 groups were assessed by the Mann-Whitney U test, and correlations between 2 parameters were evaluated by the Spearman rank correlation test.

III. Results

In non malignant gastric mucosa, ECD is strongly expressed at intercellular border. Incontrast to ECD expression ,AMFR, in such cases is seen in some foci of proliferating zone.(Image 1,2,3)

In gastric cancer cells, AMFR frequently was expressed in the cell surface and cytoplasm,(image 4,5) and ECD expression frequently was reduced in a homogenous or heterogeneous fashion(Image 6,7). Thus, the alteration in gastric cancers was follows: 20 cases (43.4%) showed strong expression of AMFR, and 24 cases (52.1%) showed weak ECD expression.

The expressions of AMFR and ECD molecules were correlated with morphologic variant as well as depth of tumor invasion in Gastric Adenocarcinoma [Table 2]. Strong expression of AMFR was observed more frequently in diffuse-type carcinomas (14/26 [53.8%]) than in intestinal- type carcinomas (6/20 [30%]). Likewise, the frequency of weak expression of ECD was higher in diffuse type carcinomas (16/26 [61.5%]) than in intestinal-type carcinomas (8/20 [40%]). The alterations of these molecules were associated with diffuse-type carcinomas, which imply a loss of differentiation (P = .005 and P = .0223 for AMFR and ECD respectively). Strong expression of AMFR was observed less frequently in superficial (T1) cancer (5/18 [27.7%]) than those with deeper infiltration (T2,3) (14/26 [53.8%]). There was a significant positive correlation between the depth of invasion and the expression of AMFR (P = .0382); however, the proportion of ECD reduction (weak expression) was similar in superficial and deep infiltrating tumors.

When the expression of ECD and AMFR are compared(Table 3), strong expression of AMFR was more frequent in tumors with weak expression of ECD (14/24 [58.3%]) than in tumors with strong expression of ECD (6/22 [27.2%]), thereby showing a significant negative correlation (P =.0033). When other morphometric parameters were reevaluated according to the coexpression pattern of these molecules, tumors with strong AMFR and weak ECD expression showed deep tumor invasion (T2,3) more frequently than tumors with weak AMFR and strong ECD expression.

Table 1

Evaluation of Autocrine Motility Factor Inhibitor Receptor(AMFR) and E-Cadherin(ECD) Expression		
	Strong Expression	Weak Expression
Autocrine Motility Factor Inhibitor Receptor(AMFR)	50% or more tumor cell stained	Less than 50% of tumor cell stained
E-Cadherin(ECD)	90% or more tumor cell stained	Less than 90% of tumor cell stained

Table 2

Expression of Autocrine Motility Factor Inhibitor Receptor(AMFR) and E-Cadherin(ECD)				
	AMFR		ECD	
	Strong	weak	Strong	Weak
Histopathologic Type				
Intestinal (n=20)	6	14	12	8
Diffuse(n=26)	14	12	10	16
Depth of Invasion				
T1(n=18)	5	13	9	9
T2(n=17)	10	7	9	8
T3(n=9)	4	5	3	6

Table 3

Relationship Between Autocrine Motility Factor Inhibitor Receptor(AMFR) and E-Cadherin(ECD) Expression			
	ECD Strong	ECD Weak	Total
AMFR Strong	6	14	20
AMFR Weak	16	10	26
Total	22	24	46

IV. Discussion

Histologically, gastric cancers are classified into intestinal type and diffuse type. The former arises from intestinal metaplasia of foveolar epithelium and from the tubules, and the latter arises from the proper gastric gland and shows a diffuse growth pattern.(38)

The E-cadherins (ECD), or "classical" cadherins of type I, belong to the large family of cadherins, transmembrane or membrane-associated glycoproteins, mediating cell-cell adhesion and playing a pivotal role in epithelial cell behavior and tissue morphogenesis or remodeling (9–15). Transcriptional ECD reprogramming in epithelial cells leads to decreased adhesion and enhanced migration or invasion at the epithelial-to-mesenchymal transition (EMT) interface during cancer progression (16).

As for ECD, it is the characteristic of diffuse type tumors that the function of ECD is disturbed, even in the presence of its protein expression,(21) because of ECD gene mutation or tyrosine phosphorylation of ECD binding proteins.(19) Accordingly, as mentioned previously, loss of cell- cell adhesion induces transcription of the AMFR gene. In the present study, we found more AMFR overexpression in diffuse-type tumors than in intestinal-type tumors. This probably is a consequence of a functional or expression disorder of ECD.

As ECD is normally expressed on cell surface, it was advantageous to set the cutoff line at 90% for ECD expression.(31,39) However, as AMFR was expressed only slightly in normal epithelium and gradually increased in cancer cells, a 50% cutoff was sufficient for separating AMFR expression into 2 groups.(19)

In the present study, we found overexpression of AMFR in about half of the patients with gastric cancer and association of AMFR with dedifferentiation and deep tumor infiltration. In 1 study that examined the role of AMFR in gastric cancers,(34) the observations were consistent with ours.

The mechanism for regulation of AMFR is yet to be known in detail. The AMFR gene is located on 16q2130. In cultured cell lines, cell- cell contact dramatically down-regulated the protein expression and messenger RNA transcription of the AMFR gene.(35) Researchers performed an AMFR promoter assay and found it was suppressed by high cell density. They could not identify the transcription factor but speculated that c- Myc was a candidate, since the amount of c-Myc was correlated inversely with cell density.(40) There is another report that retinoic acid down-regulates AMFR expression.(41) Since retinoic acid induces differentiation in various types of cells, differentiation might be another factor that regulates AMFR expression.

These phenomena convinced us that ECD is involved in transcriptional regulation of AMFR. For example, ECD is the strongest cell-cell adhesion molecule(36) and beta-catenin, an ECD binding protein, is reported to be associated with c- Myc transcription.(42) Retinoic acid is known to up-regulate ECD expression.(43) Although the suppression of AMFR transcription by ECD has not been proven directly, the inverse correlation of ECD and AMFR expression has been reported in bladder carcinomas.(44) and we found the same relationship in human gastric cancers.Since ECD itself is a strong repressor of cancer invasion and metastasis, the reduction of ECD induces cancer invasion and metastasis, both by the function itself and by the regulatory mechanism for AMFR expression.

In conclusion ,complicated histologic types in gastric cancers and their properties could be understood partly by the expression of ECD and AMFR in the present study. We find importance of evaluation of both molecules simultaneously, and the synergistic effect of these molecules seems to be a crucial step for progression of malignancy of epithelial origin.

Images

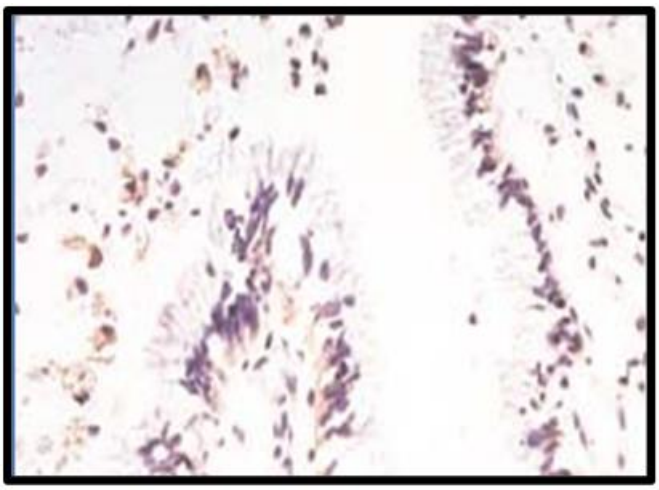

Figure 1: (Magnification = x400) Normal AMFR expression in gastric mucosa

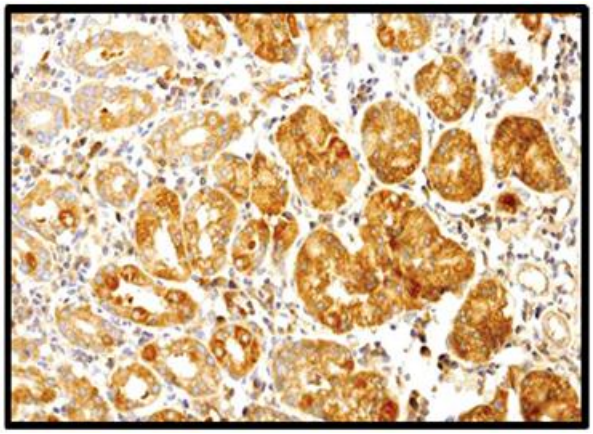

Figure 2: (Magnification = x400) Normal ECD expression in gastric mucosa

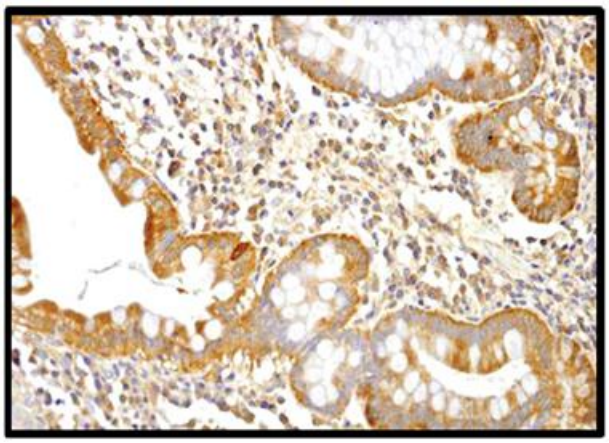

Figure 3: (Magnification = x400) Normal ECD expression in gastric mucosa with Intestinal Metaplaisa

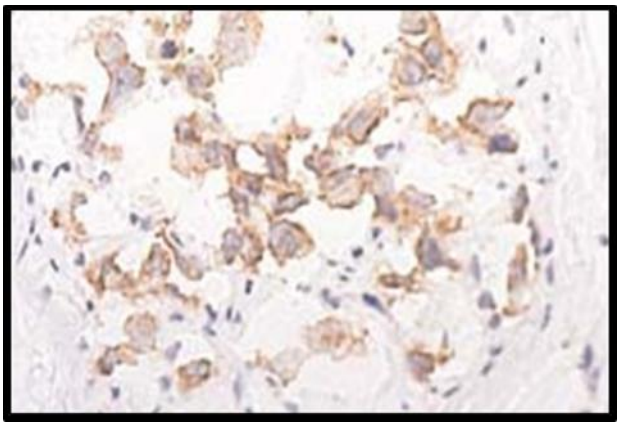

Image 4: (Magnification = x400) AMFR expression in Diffuse type of Gastric Carcinoma

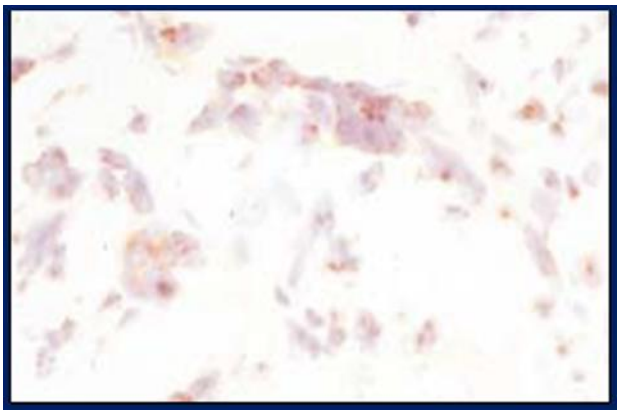

Image 5: (Magnification = x400) AMFR expression in Intestinal type of Gastric Carcinoma

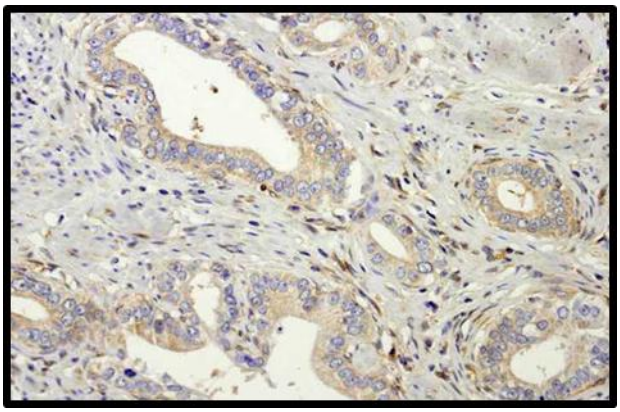

Image 6: (Magnification = x400) ECD expression in Intestinal type of Gastric Carcinoma

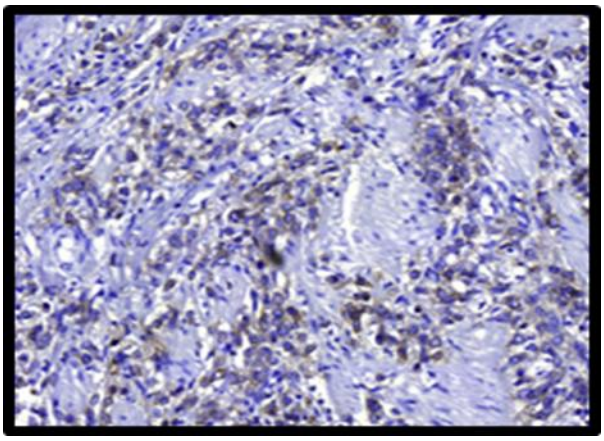

Image 7: (Magnification = x400) ECD expression in Diffuse type of Gastric Carcinoma

Reference

[1]. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Peter Boyle, Bernard Levin., editors. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. Lyon, France: International Agency for Research on Cancer. 2010.

[2]. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366:1784–1793.

[3]. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev OncolHematol. 2009;71:127–164.

[4]. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.

[5]. SiddavaramNagini. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrotest.Oncol.2012 Jul 15; 4(7): 156–169.

[6]. Theuer CP, de Virgilio C, Keese G, French S, Arnell T, Tolmos J, Klein S, Powers W, Oh T, Stabile BE. Gastric adenocarcinoma in patients 40 years of age or younger. Am J Surg. 1996;172:473–476; discussion 473-476;.

[7]. Nakamura T, Yao T, Niho Y, Tsuneyoshi M. A clinicopathological study in young patients with gastric carcinoma.J SurgOncol. 1999;71:214–219.

[8]. Yeole BB. Trends in cancer incidence in esophagus, stomach, colon, rectum and liver in males in India. Asian Pac J Cancer Prev. 2008;9:97–100. [PubMed]

[9]. W. J. Nelson, D. J. Dickinson, and W. I. Weis, "Roles of cadherins and catenins in cell-cell adhesion and epithelial cell polarity," Progress in Molecular Biology and Translational Science, vol. 116, pp. 3–23, 2013.
[10]. F. Twiss and J. De Rooij, "Cadherin mechanotransduction in tissue remodeling," Cellular and Molecular Life Sciences, vol. 70, no. 21, pp. 4101–4116, 2013.
[11]. E. Tsanou, D. Peschos, A. Batistatou, A. Charalabopoulos, and K. Charalabopoulos, "The E-cadherin adhesion molecule and colorectal cancer. A global literature approach," Anticancer Research, vol. 28, no. 6, pp. 3815–3826, 2008.
[12]. F. van Roy and G. Berx, "The cell-cell adhesion molecule E-cadherin," Cellular and Molecular Life Sciences, vol. 65, no. 23, pp. 3756–3788, 2008.
[13]. J. M. Halbleib and W. J. Nelson, "Cadherins in development: cell adhesion, sorting, and tissue morphogenesis," Genes and Development, vol. 20, no. 23, pp. 3199–3214, 2006
[14]. W.-H. Lien, O. Klezovitch, and V. Vasioukhin, "Cadherin-catenin proteins in vertebrate development," Current Opinion in Cell Biology, vol. 18, no. 5, pp. 499–506, 2006.
[15]. B. M. Gumbiner, "Regulation of cadherin-mediated adhesion in morphogenesis," Nature Reviews Molecular Cell Biology, vol. 6, no. 8, pp. 622–634, 2005. View at Publisher • View at Google Scholar • View at Scopus
[16]. A. Gheldof and G. Berx, "Cadherins and epithelial-to-mesenchymal transition," Progress in Molecular Biology and Translational Science, vol. 116, pp. 317–336, 2013.
[17]. Calabresi P, Schein PS. Medical Oncology. 2nd ed. New York, NY: McGraw-Hill; 1993.
[18]. Shiozaki H, Tahara H, Oka H, et al. Expression of immunoreactive E-cadherin adhesion molecules in human cancers. Am J Pathol. 1991;139:17-23.
[19]. Shiozaki H, Oka H, Inoue M, et al. E-cadherin mediated adhesion system in cancer cells.Cancer. 1996;77:1605-1613.
[20]. Kadowaki T, Shiozaki H, Inoue M, et al. E-cadherin and alpha-catenin expression in human esophageal cancer. Cancer Res. 1994;54:291-296.
[21]. Matsui S, Shiozaki H, Inoue M, et al. Immunohistochemical evaluation of alpha-catenin expression in human gastric cancer. Virchows Arch. 1994;424:375-381.
[22]. Oka H, Shiozaki H, Kobayashi K, et al. Expression of E- cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. Cancer Res.1993;53:1696-1701.
[23]. Takayama T, Shiozaki H, Doki Y, et al. Aberrant expression and phosphorylation of beta-catenin in human colorectal cancer. Br J Cancer. 1998;77:605-613.
[24]. Iwazawa T, Shiozaki H, Doki Y, et al. Primary human fibroblasts induce diverse tumor invasiveness: involvement of HGF as an important paracrine factor. Jpn J Cancer Res.1996;87:1134-1142.
[25]. Yano H, Shiozaki H, Kobayashi K, et al. Immunohistologic detection of the epidermal growth factor receptor in human esophageal squamous cell carcinoma. Cancer. 1991;67:91-98.
[26]. Shiozaki H, Kadowaki T, Doki Y, et al. Effect of epidermal growth factor on cadherin-mediated adhesion in a human esophageal cancer cell line. Br J Cancer. 1995;71:250-258.
[27]. Liotta LA, Mandler R, Murano G, et al. Tumor cell autocrine motility factor. Proc Nat AcadSci U S A.1986;83:3302-3306.
[28]. Evans CP, Walsh DS, Kohn EC. An autocrine motility factor secreted by the Dunning R-3327 rat prostatic adenocarcinoma cell sub-type AT2.1.Int J Cancer.1991;49:109-113.
[29]. Watanabe H, Carmi P, Hogan V, et al. Purification of human tumor cell autocrine motility factor and molecular cloning of its receptor. J Biol Chem. 1991;266:13442-13448.
[30]. Silletti S, Paku S, Raz A. Tumor autocrine motility factor responses are mediated through cell contact and focal adhesion rearrangement in the absence of new tyrosine phosphorylation in metastatic cells. Am J Pathol.1996;148:1649-1660.
[31]. Nakamori S, Watanabe H, Kameyama M, et al. Expressionofautocrine motility factor receptor in colorectal cancer as a predictor for disease recurrence. Cancer. 1994;74:1855-1862.
[32]. Yelian FD, Liu A, Todt JC, et al. Expression and function of autocrine motility factor receptor in human choriocarcinoma. GynecolOncol. 1996;62:159-165.
[33]. Maruyama K, Watanabe H, Shiozaki H, et al. Expression of autocrine motility factor receptor in human esophageal squamous cell carcinoma. Int J Cancer. 1995;64:316-321.
[34]. Hirono Y, Fushida S, Yonemura Y, et al. Expression of autocrine motility factor receptor correlates with disease progression in human gastric cancer. Br J Cancer.1996;74:2003-2007.
[35]. Silletti S, Yao JP, Pienta KJ, et al. Loss of cell-contact regulation and altered responses to autocrine motility factor correlate with increased malignancy in prostate cancer cells. Int J Cancer. 1995;63:100-105.
[36]. Takeichi M. Cadherin cell adhesion receptors as a morphogentic regulator.Science.1991; 251:1451-1455.
[37]. Otto T, Bex A, Schmidt U, et al. Improved prognosis assessment for patients with bladder carcinoma. Am J Pathol.1997;150:1919-1923.
[38]. Lauren P. The two histological main types of gastric carcinoma-diffuse and so-called intestinal type carcinoma. ActaPatholMicrobiol Scand. 1965;64:31-49.
[39]. Oka H, Shiozaki H, Kobayashi K, et al. Immunohisto- chemical evaluation of E-cadherin adhesion molecule expression in human gastric cancer. Virchows Arch A PatholAnatHistopathol. 1992;421:149-156.
[40]. Huang B, Xie Y, Raz A. Identification of an upstream region that controls the transcription of the human autocrine motility factor receptor. BiochemBiophys Res Commun.1995;212:727-742.
[41]. Zhu WY, Fang WG, Zheng J. Effects of retinoic acid on the adhesion and motility of metastatic human lung cancer cell subline (PGCL3). Chung Hua Chung Liu Tsa Chih.1994;16:323-326.
[42]. He TC, Sparks AB, Rago C, et al. Identification of c-MYC as a target of the APC pathway.Science. 1998;281:1509-1512.
[43]. Vermeulen SJ, Bruyneel EA, van-Roy FM, et al. Activation of the E-cadherin/catenin complex in human MCF-7 breast cancer cells by all-trans-retinoic acid. Br J Cancer.1995;72:1447-1453.
[44]. Otto T, Birchmeier W, Schmidt U, et al. Inverse relation ofE-cadherin and autocrine motility factor receptor expression as a prognostic factor in patients with bladder carcinomas.Cancer Res. 1994;54:3120-3123.

*Dr. Debashis Roy Burman. "Expression of Autocrine Motility Factor Receptor and E-Cadherin in Gastric Adenocarcinoma-A Correlative study." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.10 (2017): 09-15