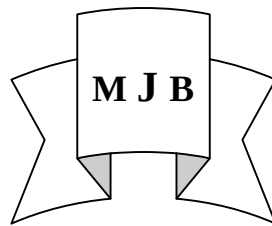


Editorial

Tumor suppressor gene(E-cadherin)and its role in normal and Malignant cells (Part Two)

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Role of Tumor suppressor gene(E-cadherin) in malignant cells

Progressive accumulation of somatic mutations in a number of different genes characterizes the process of tumorigenesis. Many genes involved in the process of tumorigenesis are components of one of a great many signal transduction pathways through which signals traffic via molecular networks. It is now apparent that epithelial malignancy can in certain aspects be explained by alterations in the adhesive properties of neoplastic cells. Epithelial-mesenchymal conversion is also observed in malignant tumors of epithelial origin. This process is similar to developmental events but with the important difference that it is uncontrolled. Malignant carcinoma cells are characterized in general by poor intercellular adhesion, loss of the differentiated epithelial morphology and increased cellular motility. Downregulation or a complete shutdown of E-cadherin expression, mutation of the E-cadherin gene, or other mechanisms that interfere with the

integrity of the adherens junctions, are observed in carcinoma cells. In human tumors, the loss of E-cadherin-mediated cell adhesion correlates with the loss of the epithelial morphology and with the acquisition of metastatic potential by the carcinoma cells [12]. Thus, a tumor invasion/suppressor role has been assigned to this gene. Additional data also support this role. Loss of heterozygosity on 16q is detected frequently in metastasizing malignancies derived from the liver, prostate, and breast [31]. Mutations in CDH1 have been described in a number of human cancers including breast, stomach, endometrium, ovary and thyroid [32,33]. Transgenic mouse model with loss of E-cadherin expression developed invasive carcinoma from well-differentiated adenomas [34] and finally germ-line mutations have recently been reported in early onset, diffuse-type stomach cancers [35].

Many immunohistochemical studies have examined changes in expression of the E-cadherin gene in human malignancies. In almost all non-

colonic tumors examined, the patterns of changes in the expression of this gene have been similar to that seen in colorectal cancer, i. e. loss of protein expression is positively correlated to loss of tumor differentiation. In oesophageal, pulmonary, squamous head and neck tumors, pancreatic and cervical tumors, loss of expression has been correlated with a high grade and an advanced stage of the disorder, with poor prognosis [2]. It has been reported that inactivating mutations of E-cadherin gene are highly frequent in infiltrating lobular breast carcinomas [38] and diffuse gastric carcinomas [32,33]. These mutations mostly occur in combination with loss of heterozygosity of the wild-type allele.

Another interesting paper [37] on E-cadherin expression demonstrates its reappearance in metastatic cells. Significant increase in re-expression of E-cadherin, together with alpha and beta-catenin, was observed in metastatic deposit of primary lobular breast cancers. This protein product was missing in the primary tumors of the same origin. Lobular breast cancers harbour E-cadherin mutations as well as losses of the gene locus, even *in situ* disease. That suggests that the mutated protein has a role even before invasion process started. The findings reveal another dimension of adhesion molecules in tumor metastasis: reestablishment of cellular contact may prevent apoptosis. I would like to cite M. Iiyas [38] "adhesion molecule expression is the phoenix in tumor metastasis".

And finally, let us not forget yet another level of CDH1 expression regulation, i. e. E-cadherin promotor hypermethylation. This process has been known to be an inactivating event in some tumors and is currently extensively researched [39].

Mutation reports

Most interesting genetic mutations and their consequences are

listed in this section. Becker *et al.* [40] suggested that E-cadherin mutations contribute to the histopathologic appearance of stomach cancer because 13 of 26 diffuse gastric carcinomas, which had reduced homophilic cell-to-cell interactions, had abnormal gene transcripts that were not seen in non-cancerous tissue from same patients. Berx *et al.* [32] reported of 69 somatic mutations of the CDH1 gene. In addition to a few missense mutations, those were mainly splice site and truncation mutations caused by insertions, deletions, and nonsense mutations. There was a major difference in mutation type between diffuse gastric and infiltrative lobular breast cancers. In diffuse gastric tumors, the predominant defects were exon skippings, which caused in-frame deletions. In contrast, most mutations found in infiltrating lobular breast cancers were out-of-frame mutations, which yield secreted truncated E-cadherin products. In most cases these mutations occurred in combination with loss of heterozygosity.

Guilford *et al.* [35] reported germline mutations in the CDH1 gene in 3 familial gastric cancer kindreds of Maori origin from New Zealand. Furthermore, Richards *et al.* [41] analyzed 8 UK gastric cancer kindreds and identified novel germline CDH1 mutations (a nonsense and a splice site mutation) in 2 families. Both mutations were predicted to truncate the E-cadherin protein in the signal peptide domain. Gayther *et al.* [42] also described germline CDH1 mutations in familial gastric cancer. In a family with a strong history of diffuse gastric carcinoma, Chun *et al.* [43] found the 1558insC germline mutation in the CDH1 gene. The gastric cancer was of the early onset, histologically diffuse type. In another family with early onset diffuse gastric cancer, Guilford *et al.* [35] found that the 30-year-old proband was heterozygous for A-to-T transition at nucleotide 2095, which resulted in a