Molecular Markers in Gastric Cancer: Can They Predict Prognosis?

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Gastric cancer is one of the most common cancers in the world, which ranks first in frequency among Koreans. Curative surgery is the treatment of choice, with recent improvements in the overall survival rate. However, the mortality of patients diagnosed with gastric cancer still remains high, due to many patients being diagnosed in the advanced stages of the disease. The TNM staging system has been found to be the most reliable prognostic indicator of the clinical outcome. As the malignant potential can be different, even at the same disease stage; it is difficult to precisely predict the prognosis of each patient, especially in the cases of stage II and III gastric cancers. Much effort has been made to precisely estimate the malignant potential, and establish better prognostic indicators.

Developments in molecular biology have enhanced our understanding of many cancers, including that of gastric cancer. Although the molecular mechanisms underlying gastric cancer are still unknown, some interesting molecular markers have been suggested as prognostic markers in such patients. These include, growth factors and their receptors, such as EGF and EGFR, tumor suppressor genes, such as p53, cell cycle regulatory factors, such as p16 or p27, matrix metalloproteinases (MMPs), cell adhesion molecules and proliferating cell nuclear antigen to name but a few (1). The clinical significance of prognostic markers is to discriminate those patients whose risk of recurrence is sufficiently high, as justification for the application of aggressive treatment strategies. However, the expressions of these markers are not very high, and are inconsistent between patients, due to the contribution of various prognostic factors, which is an obstacle requiring a solution.

In this issue of journal, Yoo et al examined the prognostic value of CD44 molecules in a series of 116 gastric cancer patients. The CD44 molecules are a group of transmembrane glycoproteins, encoded by the CD44 gene, and have been proposed to function in extracellular matrix binding, hyaluronan degradation, cell migration and lymphocyte activation. Alternative splicing has generated a number of different CD44 isoforms, whose functions are dependent on the level of the expressions of the CD44 molecules in the tissue, and the form of the molecule, that is the standard or a variant form. Although there have been many studies on the correlations between various CD44 expressions and the clinical, or pathological, features of cancers, the results were inconsistent. The expression of CD44v6, one of the variant forms of the CD44 gene in gastric cancer tissue, has been reported to correlate with the tumor progression and the long-term prognosis (2). With regard to this issue, Yoo et al has demonstrated that soluble CD44v6 in serum had a similar prognostic value in gastric cancer patients to that of the tissue expression of the CD44v6. However, the soluble CD44 standard, and CD44v5, failed to indicate prognosis in this study. Setala et al reported similar results using an immunohistochemistry method in 198 stage I-IV gastric cancer patients. The expressions of CD44 and CD44v3 showed no prognostic significance in gastric cancer in Setala et al studies (3). Nevertheless, the serological measurement of soluble CD44 molecules may have a potential in the prediction of the presence of a malignancy or in the prognosis. Questions regarding the discrepancy between the relationship of the clinicopathological features and the various CD44 expressions should be addressed in future.

E-cadherin, another cell adhesion molecule, binds with catenin to form an E-cadherin/catenin complex. Thus, mutations of E-cadherin can result in reduced cell adhesion with enhanced cellular motility, and it has also been reported to contribute to the invasiveness and metastasis of cancers. Although the prognostic studies have been inconsistent, many have reported the E-cadherin mutation to be associated with poor survival rates. With regard to this issue, Joo et al reported that the E-cadherin/(c-catenin) complex expression did not correlate with the depth of tumor invasion, or lymph node metastasis, in the early stages of gastric cancer. Similar results, showing a lack of correlation between these, have been reported in another study (4). However, Pan et al suggested a relationship between the depth of invasion, lymph node metastasis and the low expression of E-cadherin, in the early stages of gastric cancer (5). This discrepancy could be explained by several factors. Firstly, the expression of E-cadherin has been studied at the protein level using immunohistochemistry, but the interpretations of the results are often difficult, and differ between investigators. Secondly, the number of samples in each of the studies was different, which could affect the significance of the results. Despite these limitations, the expression patterns of E-cadherin could be used as a reliable indicator of the malignant potential in gastric cancers; especially in the early stages of gastric cancer. In addition, Joo et al detected E-cadherin mutations, predominantly in diffuse-type early gastric cancers, suggesting these mutations may contribute to the morphological appearance of the cancers, and might occur in the early stages.
of carcinogenesis. Thus, mutant E-cadherin could be an attractive target for the novel therapeutic interventions, and cancer prevention, in a subgroup of gastric cancer patients. 

Degradation of the extracellular matrix is an essential step for invasion and metastasis. In this step, tumor-associated proteases, such as metalloproteinases and serine proteases, play crucial roles. These enzymes have also been studied to evaluate their correlations with the prognosis. Urokinase-type plasminogen activator (uPA) is one of the serine proteases, and is known to be secreted in many solid cancers, including those of the stomach, colon and breast. It has ability to convert plasminogen to plasmin, which degrades most proteins in the extracellular matrix. The independent prognostic impact of the uPA in the survival of gastric cancer patients has been demonstrated (6). The uPA is activated, after binding with uPAR (uPA receptor), via the epidural growth factor-like domain of the uPA. Thus, the expression of uPAR has also been reported to be involved in tumor cell invasion and metastasis. uPAR, rather than the expression of uPA, may better reflect a tumor cell’s malignant potential, as uPA enzymatic activity is affected more by stroma than by cancer cells. However, there was no significant difference in the level of serum uPAR between the gastric cancer and control groups in the study of Oh et al. on this issue. This might be explained by the fact most cases studied were early stage gastric cancers. However, the reduction in the serum uPAR after a tumor resection implies uPAR has the potential as a predictive factor for recurrence. Oh et al also measured the expression of c-met in 50 patients with gastric cancer, and reported a significant correlation between the overexpression of c-met and overall survival. The c-met gene codes for a tyrosine kinase receptor, and acts as a receptor for hepatocyte growth factor (HGF), which is a potent mitogenic factor. Many studies have demonstrated that c-met was preferentially overexpressed in diffuse-type gastric cancers, and that its amplification had a close association with the stage, and prognosis, of gastric cancer (7). Furthermore, Amemiya et al demonstrated a correlation between the overexpression of c-met in gastric cancers and liver metastasis, suggesting its expression might be a useful indicator of liver metastasis in gastric cancer (8). Taniguchi et al studied the relationship between the survival rate and the expression patterns of c-met, autocrine motility factor receptor (AMFR) and uPAR, in gastric cancers. Of 102 cases, 43 (42%) had overexpressed c-met, with 41 and 38 cases showing AMFR and uPAR immunoreactivity, respectively. They reported that the overexpression of uPAR alone was associated with peritoneal dissemination and lymphatic invasion, but was not associated with the overall survival. The reason for this could be explained by uPAR mainly being involved in the local invasion, rather than the distant metastasis (9). However, a significant correlation between the prognosis and the co-expression of these three markers was observed, suggesting the need for an assessment of multiple molecular markers as a prognostic indicator.

Many previous studies used one, or a few, selected molecules to analyze the malignancy, and to predict the prognosis of cancer patients, but unlikely that only a few of those molecules could define the all the characteristics of a tumor. There are many other prognostic factors during the course of cancer treatment, such as stage, method of treatment, physical status of the patient, immunity of patient and the underlying disease. Heterogeneous cancer cells, with different genetic changes, have been found to compose a single mass. Also, there are many cross-talks between the cancer cells and host as surveillance and survival signals. Thus, the study the malignant potential of a tumor, from a viewpoint of the total expression profile of many genes has been recommended. Recent advances in high-throughout gene expression and protein technologies has enable the analyses of gene expression profiles in cancers, and efforts have been made to predict the prognosis of gastric cancers using a cDNA microarray or proteomic analysis (10). Considering the heterogeneity of the characteristics of gastric cancers, and a variety of gene expressions, we should analyze individual gastric cancers on the basis of their tumor molecular profile. Thus, while single-marker investigations have been the mainstay of molecular approaches, the development of multiplex strategies could help in the prediction of the prognosis, and help determine treatment strategies in the near future.

REFERENCES