Clinical significance of S100A4 and E-cadherin related adhesion molecules

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S100A4, a member of the S100 calcium-binding protein family, has been suggested to be a metastasis-associated molecule. Its overexpression is observed not only in primary and metastatic tumors but also in normal cells with enhanced invasiveness such as macrophages, neutrophils, and T-lymphocytes. E-cadherin has an important role in the homophilic cell-cell adhesion and is an invasion suppressor gene. In the current study, we investigated the histological type and metastatic potential of gastric, non-small cell lung cancer NSCLC and esophageal squamous cell carcinoma from the aspect of the interrelationship of E-cadherin and S100A4 expression. S100A4 protein and E-cadherin were expressed in five of eight gastric cancer cell lines, and inverse expression of the two proteins was found in four cell lines. In the clinical specimens, E-cadherin mRNA expression in differentiated adenocarcinomas (88%, 14 of 16) was significantly more frequent than that in poorly differentiated adenocarcinomas (50%, 22 of 44; p=0.015). Western blot analysis demonstrated that S100A4 protein expression in poorly differentiated adenocarcinomas was 1.6-fold higher than in well differentiated adenocarcinoma. Immunohistochemically, S100A4 expression was detected in 51 (55%) of 92 primary gastric cancers. Reduced expression of E-cadherin in primary tumor was found in 66 (72%) of 92 tumors. S100A4 expression in the poorly differentiated adenocarcinomas had a strong relation to positive lymph node involvement or peritoneal dissemination. Also, the S100A4 protein level was significantly higher in tumor tissue than in corresponding normal esophageal mucosa ($p<0.05$) in 22 cases of esophageal carcinoma by western blot analysis. Patients with S100A4-positive carcinoma had significantly poorer prognosis than those with S100A4-negative carcinoma, which was also true in the cases with deep invasion of the primary cancer (T3, T4) ($p<0.01$ and $p<0.05$, respectively). Expression of S100A4 was observed in 81 (60%) of 135 NSCLCs and correlated with progression of the pathological T factor ($p<0.001$), Lymph node metastasis ($p<0.005$), and poor survival ($p<0.05$). The expression of E-cadherin closely correlated with differentiation and inversely with that of S100A4. These results indicate that S100A4 plays a role in the progression and metastasis of various cancers and that simultaneous immunohistochemical detection of S100A4 and E-cadherin may be useful to define subpopulation of lung cancer patients with a possible poor prognosis.

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