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Circulating levels of IGF-I and IGFBP-3 in gastric cancer

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Aim: To explore the causative mechanism of gastric carcinoma and to investigate the roles of circulating IGF-I and IGFBP-3 in gastric cancer.

Materials and methods: Serum IGF-I and IGFBP-3 concentrations were measured using a 2-site coated tube immunoradiometric assay.

Results: Serum IGF-I and IGFBP-3 values in gastric cancer patients were significantly lower compared to those in the control group. The difference between serum IGF-I/IGFBP-3 in patients and the control group was not significant.

Conclusion: The low serum IGF-I and IGFBP-3 levels detected in patients with gastric cancer could be due to decreased synthesis or increased catabolism of IGF-I or both. It could be suggested that these parameters may be important in the development and prognosis of gastric cancer.

Key words: Insulin-like growth factors, insulin-like growth factor-1, stage, gastric cancer

Introduction

The insulin-like growth factor (IGF) family of peptide ligands (IGF-I and IGF-II), the IGF-I and IGF-II receptors, the 6 IGF-binding proteins (IGFBPs), and the IGFBP proteases are fundamentally involved in the regulation of somatic growth, cell proliferation, transformation, and apoptosis. The biological activities of the IGFs are modulated by IGFBPs, which have higher affinity for IGFs than for the IGF receptors (1–3). The IGF system is widely involved in human carcinogenesis (4,5). Numerous studies have demonstrated that IGFs and IGFBPs are produced by tumor cell lines and tumors, acting as an autocrine growth factor (6,7), and circulating concentrations of IGF-I may be associated with an increased risk of cancer (8,9), whereas IGFBP-3 concentrations may be associated with a decreased cancer risk (10,11). A number of prospective studies have identified high plasma levels of IGF-I as a potential risk factor for several malignancies, and showed associations between IGF-I and prostate cancer, premenopausal breast cancer, and colon cancer (12–14).

Normal growth and the differentiation of cells in the gastrointestinal tract are regulated by autocrine and paracrine secretion of peptide growth factors, which are responsible for controlling maturation, differentiation, and apoptosis (15). Gastric cancer is one of the most common neoplasms and a leading cause of death worldwide (15). According to data from the Turkish Ministry of Health, gastric cancer occupies first place among cancer incidence in males and second place in females around Erzurum and Van (16). There is evidence that the upregulation of certain growth factors could play an important role in the promotion and development of gastric cancer. IGFs and their receptors may be important in the regulation of epithelial cell growth, but few data are available on the expression and biological function of

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the IGF system in gastric cancer. Durrant et al. (17) have reported that IGF-I could facilitate the growth of 3 cell strains of gastric carcinoma in vitro.

The aim of the present work was to investigate the roles of circulating IGF-I and IGFBP-3 in gastric cancer.

Materials and methods

Patients

Thirty patients (16 males; with mean age ± SD of 57.3 ± 14.3 years) and 35 clinically healthy subjects (17 males; with mean age ± SD of 56.8 ± 9.7 years) were included in the study. Informed consent was obtained from all patients. None of the patients were receiving chemotherapy and all were newly diagnosed. Tumors were classified according to UICC criteria (18). Thirty had adenocarcinoma. All patients were in stage IV and had distant organ–tissue metastases. Tables 1 and 2 show the localization and metastatic sites of patients with gastric cancer.

Biochemical assay

Blood samples were drawn into nonadditive vacutainer tubes and centrifuged at 3000 × *g* at 4 °C for 10 min, and sera were stored at –80 °C until analysis. Serum IGF-I and IGFBP-3 concentrations were measured using a 2-site coated tube immunoradiometric assay (IRMA; Diagnostics Systems Laboratories, Webster, TX, USA). Assays were performed according to the manufacturer's instructions. These assays are based on noncompetitive IRMA in which the analyte to be measured is sandwiched between 2 antibodies. The IGF-I IRMA has a minimum detection limit of 2.06 ng/mL and intra- and interassay coefficients of variation of 4.4% and 5.1%, and the IGFBP-3 IRMA has a minimum detection limit of 0.5 ng/mL and intra- and interassay coefficients of variation of 3.3% and 3.9%, respectively.

Statistics

All data were entered into an SPSS database (SPSS, version 10.0, Chicago, IL, USA). IGF-I and IGFBP-3 values were expressed as mean ± SD. The significance of differences between groups was assessed using Student's t test. A P value < 0.05 was considered significant.

Results

Table 3 shows levels of IGF-I and IGFBP-3 in the serum of patients with gastric cancer and of the controls. In this study, serum IGF-I and IGFBP-3 values in gastric cancer patients were significantly lower compared to those in the control group but the difference in the serum IGF-I/IGFBP-3 ratio between patients and controls was not significant.

Discussion

Gastric cancer is one of the most frequent neoplasms and a leading cause of death worldwide. With developments in molecular biology technology, research on the mechanism of gastric carcinoma has gone into deep molecular levels. Carcinogenesis is a complicate process that includes many steps; many gene abnormities may be involved in this process. There was evidence that the effect of protooncologenes, the inactivation of many antioncogenes, the regulation of many growth factors and their receptors, the accumulation of gene mutations, and imperfection of the DNA rehabilitation system might play important roles in the carcinogenesis and development of gastric carcinoma. It is thought that the upregulation of certain growth factors could play an important role in the promotion and development of gastric cancer (19,20).

Table 1. Patient characteristics regarding localization of gastric cancer.

Localization	Patient number
Corpus	11
Cardia	13
Antrum	6

Table 2. Patient characteristics regarding metastatic site of gastric cancer.

Metastasis	Patient number
Liver + brain + lung	1
Peritoneum	7
Liver	18
Liver + lung	1
Spleen + lymph	1
Pancreas	1
Pancreas + surrenal gland	1

Most of the circulating IGF-I and IGFBP-3 are synthesized in the liver, where expression of each is increased by growth hormone. IGFBP-3 binds more than 95% of the IGF in serum and influences cell proliferation by modulating access of IGFs to the IGF receptors. IGFBP-3 also apparently inhibits growth and induces apoptosis through IGF- independent mechanisms (21). There is considerable between-person variability in blood levels of IGF-I, IGF-II, and IGFBP-3. Tissue IGF bioactivity is influenced by circulating IGF levels and by local expression of IGFs, IGFBPs, and IGFBP proteases. At the tissue level, IGFBP-3 may regulate the interaction of IGF-I with its receptor by inhibiting or augmenting the interaction (2). Pollak et al. reported a strong positive association between baseline plasma IGF-I levels and subsequent risk of prostate cancer (22) or premenopausal breast cancer (23). Results of some (24,25) but not all (26) previous epidemiological studies have suggested a possible direct relationship between circulating IGF-I and colorectal cancer risk. The serum IGF-I and IGFBP-3 levels were significantly elevated in patients with esophageal cancer compared with the control group and there was a positive correlation between IGF-I and IGFBP-3 (27). Franciosi et al. (28) showed that baseline IGF-I and IGFBP-3 levels were significantly higher in patients with gastric cancer than in healthy controls. This report showed that tumor extension was not related to baseline IGF-I levels. On postoperative day 14 in the patient group a significant decrease in IGF-I levels was observed versus baseline values. These data suggested that surgical ablation of tumors may be able to reduce IGF-I levels and this difference is present even in the late postoperative period (day 50), showing that the reduction in tumor load is closely related to IGF-I decrease. IGFBP-3 levels after surgery were not significantly different. In the present study, all patients were in stage IV and had distant organ-tissue metastases. The serum IGF-I and IGFBP-3 levels were measured before the chemotherapy.

IGF-I might increase the risk of cancer through its anti-apoptotic activity. In this case it prevents the programmed death of cells that have been transformed, thus interrupting an important process that retards the development of cancer. Experiments using animal and cell cultures have shown that the anti-apoptotic activity of IGF-I is counterbalanced by the activity of IGFBP-3, which may have a direct and independent stimulatory action on apoptosis (29).

Table 3. Mean ± SD of IGF-I and IGFBP-3 in serum of patients with gastric cancer and controls.

	IGF-I	IGFBP-3	IGF-I/IGFBP-3
Control group	228.3 ± 84.0	3284.4 ± 741.1	0.069 ± 0.016
Patient group	143.9 ± 60.1[b]	2476.3 ± 1180.4[a]	0.065 ± 0.028

a: $P < 0.001$, b: $P < 0.0001$ vs. control group

In our study, the low serum IGF-I and IGFBP-3 levels detected in patients with gastric cancer could be due to decreased synthesis and/or increased catabolism of IGF-I.

Dae-Yeol et al. (30) reported that the serum IGF-I level in gastric cancer was significantly lower than in control subjects, and was further decreased after surgery. They found that the serum IGFBP-3 level was not significantly different from those in control subjects, and a decreased level of serum IGFBP-3 was found after surgery.

In summary, we showed that serum IGF-I and IGFBP-3 values in gastric cancer patients are significantly decreased compared to the controls. The difference between serum IGF-I/IGFBP-3 in patients and controls was not significant. One may suggest that these parameters are important in the development and prognosis of gastric cancer and a well-designed follow-up study is needed to confirm these findings.

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