Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Serum CD10 is associated with liver metastasis in colorectal cancer

Takamitsu Sasaki, MD, PhD,[a] *Hiroki Kuniyasu, MD, PhD,*[b,*] *Yi Luo, MD, PhD,*[b] *Rina Fujiwara, MD,*[b] *Misaho Kitayoshi, PhB,*[b] *Eriko Tanabe, PhB,*[b] *Daisuke Kato, MD,*[a] *Satoshi Shinya, MD,*[a] *Kiyomu Fujii, MD, PhD,*[b] *Hitoshi Ohmori, MD, PhD,*[b] *and Yuichi Yamashita, MD, PhD*[a]

[a] *Department of Gastroenterological Surgery, Fukuoka University School of Medicine, Fukuoka, Japan*
[b] *Department of Molecular Pathology, Nara Medical University, Kashihara, Japan*

ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form
15 April 2014
Accepted 23 May 2014
Available online 2 June 2014

Keywords:
Colorectal cancer
CD10
Liver metastasis
Serum marker

ABSTRACT

Introduction: Colorectal cancer (CRC) is the third leading cause of cancer death in Japan. CD10 expression is closely associated with liver metastasis. In the present study, we explored the possibility of serum CD10 as a marker of liver metastasis in CRC.
Methodology: BALB/c mouse with subcutaneous tumor of syngeneic CT26 CRC cells were examined serum CD10. In 84 CRC patients and patients undergoing hemodialysis, serum CD10 was examined. CD10 concentration was measured by enzyme-linked immunosorbent assay.
Results: In a mouse subcutaneous tumor model, serum CD10 correlated with the weight of the tumors. Serum CD10 was examined in 84 patients with CRC. The serum levels of CD10 were higher in patients with more advanced cancer stages. Patients with liver metastasis showed the highest levels of serum CD10 among all patients. Importantly, patients with high serum CD10 levels had metachronous liver metastasis. Healthy volunteers showed low levels of CD10; however, serum CD10 levels in patients undergoing hemodialysis showed levels as high as those with stage II and III CRC. A cutoff of serum CD10 set to >1000 pg/mL showed 70% sensitivity and 93% specificity for liver metastasis in CRC. This cutoff included all cases of metachronous liver metastasis.
Conclusions: With the exclusion of mimicking factors, serum CD10 levels might serve as a useful marker of synchronous and metachronous liver metastasis in CRC.
© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer death in Japan [1]. CRC incidence is on the rise with increasing western life styles, especially high-fat and high-glucose diets. Most of the CRC cases are managed through resection with endoscopy or surgery. However, the metastatic disease shows poor prognosis. One-fourth of advanced cases are associated with liver metastasis, which is a life-threatening event in 30% of CRC deaths [2,3]. The prompt adjuvant chemotherapy based on the evidence of the liver metastasis might improve patient prognosis.

CD10 (enkephalinase or neprilysin) is a neutral endopeptidase [4], which is closely associated with liver metastasis in

* *Corresponding author*. Department of Molecular Pathology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8521, Japan. Tel.: +81 744 22 3051; fax +81 744 25 7308.
E-mail address: cooninh@zb4.so-net.ne.jp (H. Kuniyasu).
0022-4804/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2014.05.071

CRC [2,5,6]. CD10 expression in CRC detected through immunohistochemistry is a good marker for the liver metastasis in CRC. CD10-positive CRC is associated with the liver metastasis in 60%–70% of the cases [5,7]. The levels of CD10 messenger RNA are also associated with tumor invasion depth, lymph node status, and tumor-nodes-metastasis classification system (TNM) stage [8].

CD10 not only is a marker for liver metastasis but also is a pathognomonic factor for the process [7,9]. CD10 degrades enkephalins, which are secreted from CRC cells and are known to suppress CRC growth and promote apoptosis of T lymphocytes [10–12]. Thus, CD10-positive CRC cells avoid prosuppression signaling and thereby enhance their ability to metastasize.

CRC cell-inhibitory enkephalins are secreted from hepatocytes stressed by bile stasis, hepatitis, and cancer metastasis, and might have anti-inflammatory and antitumorigenic properties [7,13–15]. In such cases, CD10-positive CRC cells show an enhanced ability for establishing liver metastases.

CD10 is localized mainly on the apical plasma membrane; however, we detected CD10 in the stromal space among cancer nests, which suggests that CD10 is secreted from CRC cells [7]. Increased levels of CD10 are reported in allergic diseases such as bronchial asthma or hemodialysis conditions [16,17]. These findings suggest that serum CD10 might be a good marker for the liver metastasis in CRCs. In the present study, we explored the potential of serum CD10 as a marker for CRC liver metastasis.

2. Materials and methods

2.1. Cell culture and reagents

CT26 mouse colon cancer cell line was provided by Professor I. J. Fidler (M.D. Anderson Cancer Center) and was maintained in Dulbecco modified eagle's medium (Sigma Chemical Co, St. Louis, MO) containing 10% fetal bovine serum (Sigma Chemical Co) under the conditions of 5% CO_2 at 37°C.

2.2. Animal model

BALB/c mice were purchased from Japan SLC Inc (Shizuoka, Japan). The mice were maintained according to the institutional guidelines approved by the Committee for Animal Experimentation of Nara Medical University, in accordance with the current regulations and standards of the Ministry of Health, Labour and Welfare. The mice were used according to the institutional guidelines when they were 5 wk old. CT26 cells were briefly trypsinized and washed thrice with Hank balanced saline solution. The cells (1×10^7) were suspended in Hank balanced saline solution and injected into the subcutaneous region. The mice were euthanized by performing cervical dislocation at 2 wk after inoculation of cancer cells, and tumors were excised for measurements (size and weight).

2.3. Serum specimens

Serum specimens from eight patients with CRC and four patients with noncancerous diseases examined in the first set of experiments were obtained at Fukuoka University Hospital in 2008. Serum specimens from 75 patients with CRC examined in the second set of experiments were obtained at Fukuoka University Hospital before 2008 with subsequent follow-up of the disease recurrence. Serum specimens from 19 patients undergoing hemodialysis and 26 healthy volunteers examined in the second set of experiments were obtained at Tanaka Urology Clinic. The classification of the disease was according to TNM classification [20]: stage II, tumor invades beyond the muscularis propria without lymph node metastasis; stage III, any cases with lymph node metastasis; and stage IV, any case with or without lymph node metastases but with distant metastases (all cases metastasized to the liver). All cases were negative for hepatitis virus type B or type C and negative for inflammatory changes or renal dysfunction. Because written informed consent was not obtained, identifying information for all samples was removed before analysis for strict privacy protection; the procedure was in accordance with the Ethical Guidelines for Human Genome/Gene Research enacted by the Japanese Government.

2.4. Enzyme-linked immunosorbent assay

Sera were used for enzyme-linked immunosorbent assay. Concentrations of CD10 (neprilysin) were detected using Neprilysin Human Duo Kit (R&D Systems Inc, Minneapolis, MN) according to the provider's instructions.

2.5. Statistical analysis

Statistical analyses of experimental data were performed using the Mann–Whitney *U* test and analysis of variance test. Statistical significance was defined as a two-sided *P* value of <0.05.

3. Results

3.1. Serum CD10 concentration in tumor-burden mice

CT26 mouse colon cancer cells were inoculated in the subcutaneous tissues of syngeneic BALB/c mice. The tumor sizes were compared with mouse serum CD10 concentrations (Fig. 1). Serum CD10 concentrations were significantly correlated with the tumor sizes.

3.2. Serum CD10 concentrations in patients with CRC

The first set of the patients included four patients without CRC, five patients with pT3, and three patients with liver metastasis, which were not followed-up after resection. Patients had no history of liver or renal diseases (Fig. 2). The serum levels of CD10 were higher in patients with more advanced stage cancer. Patients with liver metastasis, especially, showed highest CD10 concentrations.

The second set of patients included 29 stage II, 29 stage III, and 17 stage IV patients who were followed-up for >5 y after resection of the primary tumors. Healthy volunteers and patients undergoing hemodialysis were also examined. Serum CD10 levels in patients with CRC were higher than those in healthy volunteers. Within patients with CRC, the CD10 levels

Download English Version:

https://daneshyari.com/en/article/4300010

Download Persian Version:

https://daneshyari.com/article/4300010

Daneshyari.com