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Smad4/Fascin index is highly prognostic in patients with diffuse type EBV-associated gastric cancer

Byoung Kwan Son[a,1], Dong-Hoon Kim[b,1], Kyueng-Whan Min[c,*], Eun-Kyung Kim[d], Mi Jung Kwon[e]

[a] Department of Internal Medicine, Eulji Hospital, Eulji University School of medicine, Seoul, Republic of Korea
[b] Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[c] Department of Pathology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Gyeonggi-do, Republic of Korea
[d] Department of Pathology, Eulji Hospital, Eulji University School of Medicine, Seoul, Republic of Korea
[e] Department of Pathology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Gyeonggi-do, Republic of Korea

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ABSTRACT

Gastric cancer is a heterogeneous disorder for which predicting clinical outcomes is challenging, although various biomarkers have been suggested. The Smad4 and Fascin proteins are known prognostic indicators of different types of malignancy. Smad4 primarily functions as a key regulator of tumor suppression, whereas Fascin exhibits oncogenic function by enhancing tumor infiltration. A combined marker based on these opposing roles may improve prognostic accuracy in gastric cancer.

Smad4 and Fascin expression was assessed in tissue microarrays obtained from 285 primary gastric adenocarcinoma, 201 normal tissue, and 51 metastatic adenocarcinoma samples. A Smad4/Fascin index based on the relative expression of each protein was divided into low- and high-expression groups using receiver operating characteristic curves. We compared normal tissue, primary adenocarcinoma, and metastatic adenocarcinoma in Smad4 and Fascin expression and the differences in clinicopathological findings between low Smad4/Fascin and high Smad4/Fascin expression in gastric adenocarcinoma.

High Smad4/Fascin expression was significantly associated with worse outcomes, such as old age, advanced T and N category, large tumor size, high histological grade, lymphatic and vascular invasion, and presence of Epstein–Barr virus (EBV) (all $p < 0.05$). Univariate and multivariate analyses revealed a significant relationship between disease-free or overall survival and Smad4/Fascin index in diffuse-type or EBV-associated gastric cancer (all $p < 0.05$).

A dual marker system using Smad4 and Fascin may be a reliable indicator for predicting clinical outcomes in patients with diffuse-type or EBV-associated gastric cancer.

1. Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer-associated death worldwide [1]. Its incidence is more common in lower socioeconomic groups and varies from country to country. High incidence rates are found in Japan, Chile, Costa Rica, and Eastern Europe, whereas other area such as North America, Northern Europe, North and East Africa, and Southeastern Asia show a low incidence [2].

Most gastric cancers are associated with infectious agents, including *Helicobacter pylori* [3] and Epstein-Barr virus (EBV) [4]. Gastric adenocarcinoma is the most common type of gastric cancer and is classified as intestinal-type (well-defined glandular structures associated with intestinal metaplasia and variable degree of atrophic gastritis) or diffuse-type (diffuse infiltration of individual or small groups of neoplastic cells) [5]. Presently, clinical management refers to the following prognostic indicators: American joint Committee on Cancer TNM stage, histological type and grade, depth of invasion, and vascular invasion. A recent study by The Cancer Genome Atlas Research Network described four subtypes with different clinical outcomes and therapeutic strategies as follows: Epstein-Barr virus-positive, microsatellite instability, genomically stable, and chromosomal instability

Abbreviation: EBV, Epstein-Barr virus; EBVaGC, EBV-associated gastric adenocarcinoma; AGC, advanced gastric cancer; IRS, immunoreactive score; ISH, In situ hybridization; DFS, Disease-free survival; OS, Overall survival; EGFR, epidermal growth factor receptor

* Corresponding author at: Department of Pathology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Kyoungchun－ro 153, Guri－si, Gyeonggi－do, 11923, Republic of Korea.
E-mail address: kyueng@hanyang.ac.kr (K.-W. Min).
[1] The authors contributed equally to this work.

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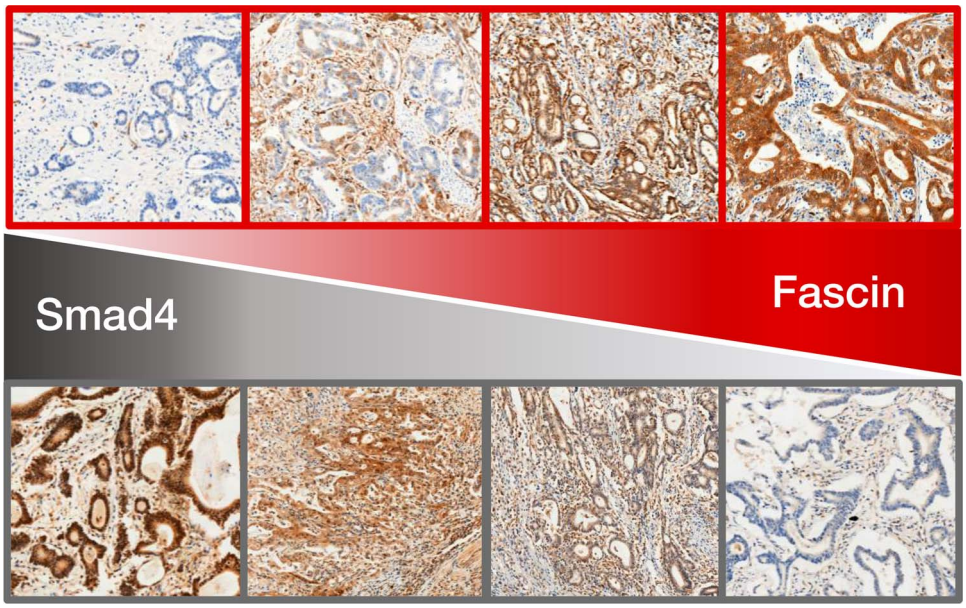

Fig. 1. Schematic illustration of the Smad4/Fascin index. The relative expression of Smad4 and Fascin in tumor cells could be a predictor of cancer progression. (top, negative, weak, moderate and strong intensity of Fascin; bottom, strong, moderate, weak and negative intensity of Smad4) (original magnification, × 200).

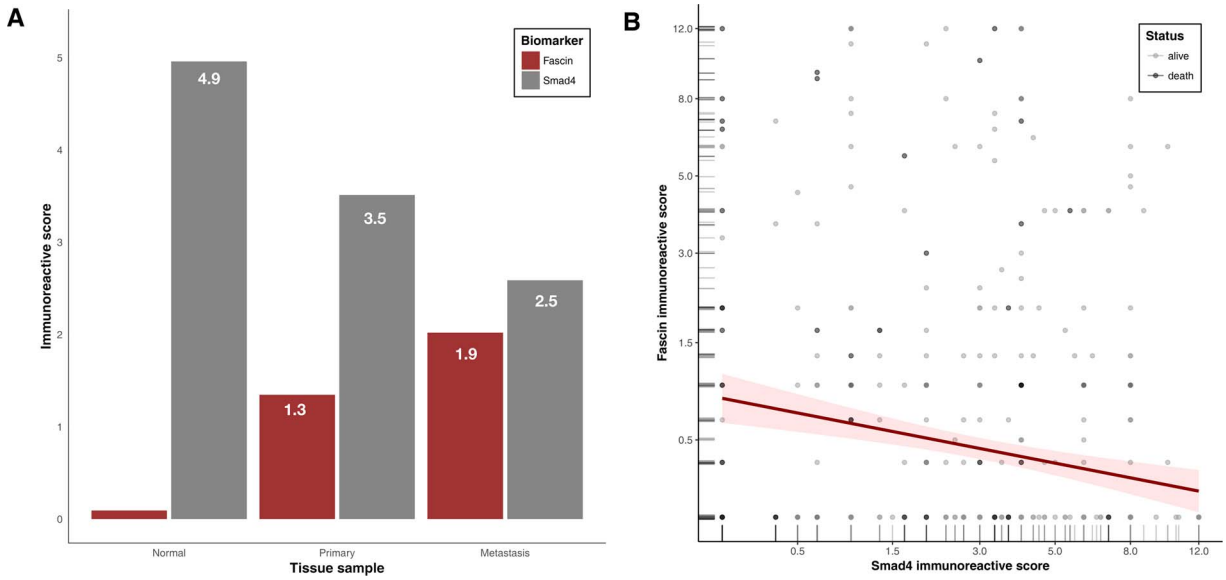

Fig. 2. Fascin was highly expressed in primary or metastatic lesions compared to in normal tissue. In contrast, Smad4 expression was higher in normal tissue than in primary or metastatic lesions (A) (all $p < 0.05$). There was an inverse correlation between Smad4 and Fascin expression (B) ($r = -0.168$, $p < 0.001$).

[6]. Notably, EBV-associated gastric adenocarcinoma (EBVaGC) presents a generally diffuse-type carcinoma associated with abundant lymphoid aggregates [7] and is related to the CD274 gene which encodes programmed death receptor-ligand 1 as well as PIK3CA mutations and DNA hypermethylation.

Molecular subtyping by genomic sequencing have improved the understanding of gastric cancer, but the clinical application of gene expression data remains difficult. Evaluation by immunohistochemistry remains a simple, rapid, sensitive, and cost-effective method compared to genomic analysis. Several studies have established single biomarkers that are associated with the clinical outcomes of patients with gastric cancer [8–10]. Many single makers were reported as predictors of prognosis in several types of malignancy, but there is a lack of research on combination markers. A few studies using dual markers in various cancers have recently been published [11–13].

The balance between infiltration and suppression of neoplastic cells plays an important role in malignant development. Fascin, a tumor invasiveness marker, is tightly linked to enhanced cell motility, migration, and adhesion as well as aggressive clinical behaviors [14,15]. Smad4, a tumor suppressor marker, regulates cell proliferation, differentiation, and extracellular matrix production and inhibits tumorigenesis [16]. Therefore, the combination use of Fascin as an invasion marker and Smad4 as a tumor suppressor marker may be more reliable for predicting clinical outcome using either marker alone.

The aim of this study was to investigate the relationships between Fascin and Smad4 in normal tissue, primary adenocarcinoma, and metastatic adenocarcinoma in patients with gastric cancer. We evaluated whether the Smad4/Fascin index based on Smad4-mediated Fascin levels was significantly related to clinical outcome in different types of gastric cancer.