News Release

Title

Identification of stromal cell-derived factor 4 as a liquid biopsy-based diagnostic marker in solid cancers

Key Points

- We have a novel serum tumor marker for early detection of multiple cancers including gastric cancer, esophageal cancer, colorectal cancer, pancreatic cancer, breast cancer, and liver cancer.
- The sensitivity and specificity of this marker were 89% and 99%, respectively, for diagnosis of gastric cancer.
- The diagnostic performance of this marker demonstrated a greater performance than conventional serum tumor markers (CEA and CA19-9).

Summary

A research team led by Prof. Yasuhiro Kodera, Dr. Mitsuro Kanda, and Dr. Takahiro Shinozuka (Department of Gastroenterological Surgery) have revealed the high diagnostic accuracy of a protein called stromal cell-derived factor 4 (SDF-4) as a novel blood cancer marker, measurable via blood tests, capable of early detection of various cancers, starting with gastric cancer. For many years, blood tests to detect cancers such as gastric, colorectal, and breast cancer have utilized tumor markers like CEA and CA19-9. However, these tumor markers do not always accurately detect all cancers, and their accuracy has been less than satisfactory. Given that early detection of cancer boosts treatment success rates, the development of more accurate blood tumor markers has been a pressing need. In this study, proteins secreted by cancer cells were investigated using the latest research results and public databases, identifying the protein SDF-4, which shows potential for mass screenings. Upon measuring the concentration of SDF-4 in blood samples from various cancer patients and healthy individuals, elevated levels were observed in various cancers including gastric, esophageal, colorectal, pancreatic, breast, and liver cancer. Notably, in the case of gastric cancer, a sensitivity of 89% and a specificity of 99% were recorded, surpassing conventional tumor markers. Even in patients with stage I gastric cancer, higher levels than in healthy individuals were noted, suggesting its potential for early cancer detection. Experiments were conducted to elucidate how the blood concentration of SDF-4 increases in cancer patients. Cultivating cancer cells and measuring the concentration in the culture fluid

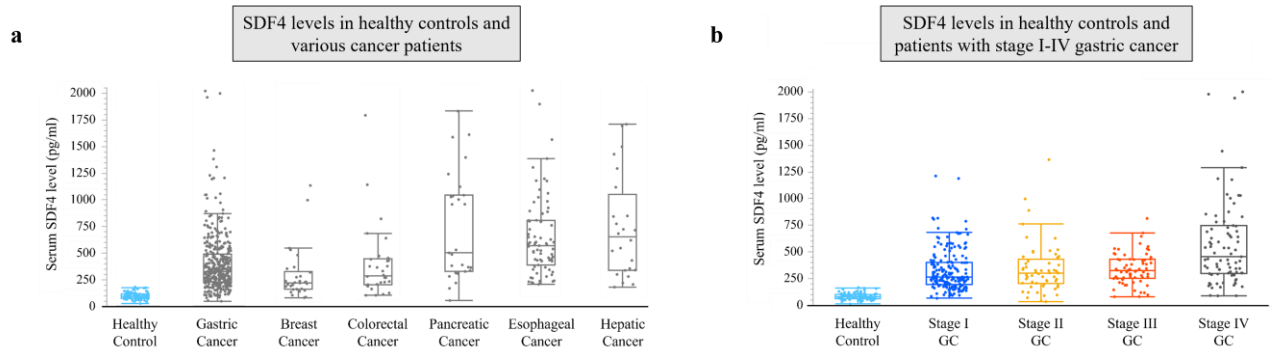
revealed an increase in SDF-4 levels, indicating the cancer cells themselves were secreting SDF-4. Moreover, crushing cancer cells and assessing the SDF-4 levels also showed a rise, suggesting that the degradation of cancer cells could elevate SDF-4 levels in a patient's bloodstream. Further, using immunohistochemical staining with tissues obtained from gastric cancer patients, it was demonstrated that SDF-4 was present in the cancerous tissue but absent in normal tissue. This was consistent for both early stage and advanced gastric cancer patients. These findings suggest that SDF-4 offers new potential for early diagnosis of various cancers. Future collaborative international research plans include validating the diagnostic accuracy of this tumor marker in a larger patient cohort. Development of an original diagnostic measurement kit is also underway, aiming to make this new testing method accessible to mass screening. This research was published online in the British scientific journal, "Scientific Reports," on September 20, 2023.

Research Background

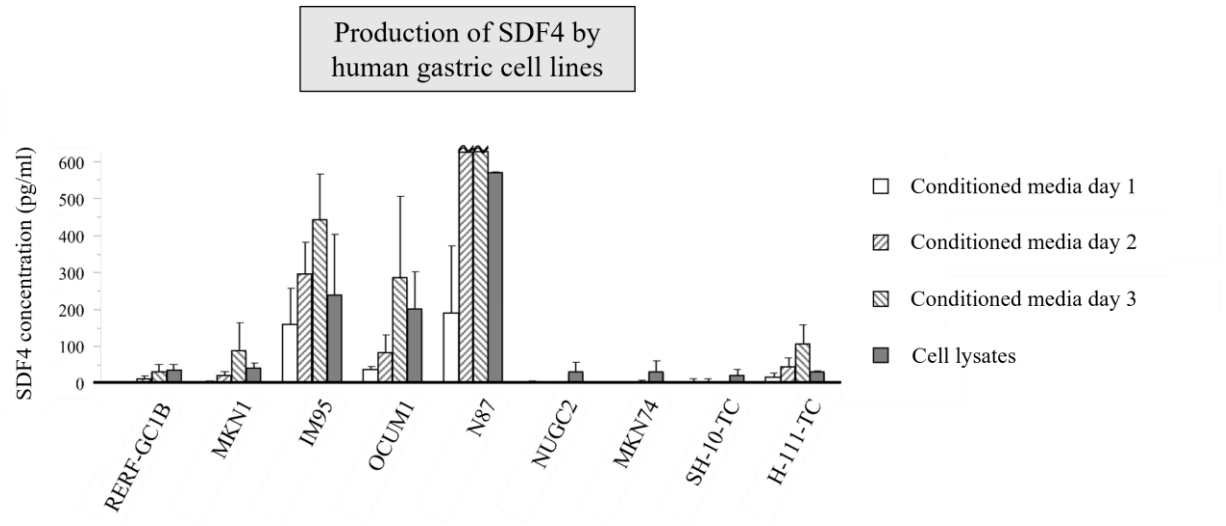
According to statistics from the National Cancer Center Japan, one in four Japanese men and one in six Japanese women die from cancer. To achieve a complete cure for gastrointestinal cancers such as esophageal, gastric, colorectal, liver, and pancreatic cancer, a complete resection through surgery or endoscopy is often required. However, when these cancers are detected in advanced stages, they often fall outside the scope of these therapeutic options, making a complete cure challenging. On the other hand, the therapeutic outcomes in the early stages of these cancers are generally favorable, leading to a high likelihood of a cure. For instance, the 5-year survival rate for advanced gastric cancer with distant metastasis is 6.6%, while for early stage gastric cancer, it stands 96.7%. Therefore, early detection of cancer significantly improves therapeutic outcomes. Currently, various blood tumor markers such as CEA and CA19-9 are used for the diagnosis of cancer. However, they do not adapt to every type of cancer, and their diagnostic accuracy is not always satisfactory. In recent years, there have been research reports on new tumor markers that enable early diagnosis of cancer. However, many of these proposed markers present challenges such as intricate, costly measurement procedures, or invasive testing methods, preventing their widespread use in mass cancer screenings. Consequently, there is an urgent need to develop new tumor markers that can detect various cancers at early stages and can be determined through non-invasive, cost-effective, and highly versatile testing methods.

Research Results

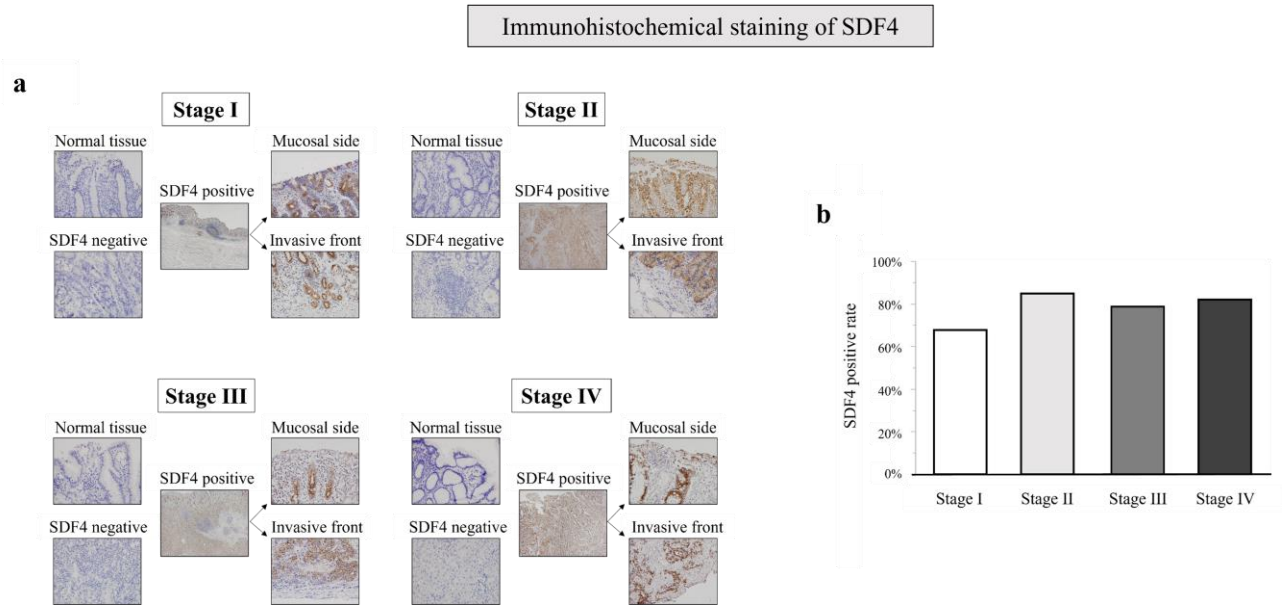
Upon examining the concentration of SDF-4 in the blood of cancer patients treated at our institution for gastric cancer, breast cancer, colorectal cancer, pancreatic cancer, esophageal cancer, and liver cancer, as well as in healthy individuals, we found that all cancer patients exhibited elevated levels of SDF-4 (Figure 1a). Furthermore, when comparing the SDF-4 concentrations in healthy individuals to those of gastric cancer patients based on the progression stage, even those at stage I, an early stage, showed values as high as those with advanced stages. The sensitivity for distinguishing between the gastric cancer patients and healthy individuals in our study was 0.889 for SDF-4, which was notably higher compared to 0.131 for CEA and 0.169 for CA19-9.



To investigate the mechanism behind the elevation of SDF-4 in the blood of cancer patients, we conducted experiments using nine types of human gastric cancer cell lines. SDF-4 was present in the conditioned media, and its concentration increased over time. Additionally, SDF-4 was also detected in the cell lysates produced by crushing the cancer cells (Figure 2). Based on these results, it's suggested that cancer cells secrete SDF-4 and also contain it intracellularly. Thus, the breakdown of cancer cells might result in the release of SDF-4 into the extracellular environment, possibly leading to its migration into the bloodstream



We performed immunohistochemical staining for SDF-4 using gastric cancer tissues excised by surgery and the adjacent normal tissues. SDF-4 was not observed in the normal tissue at any stage but was uniformly stained within the tumor tissue (Figure 3a). Additionally, when examining the positive staining rates among every stage, it was found that the positive rates were nearly consistent for all stages (Figure 3b).



Research Summary and Future Perspective

For the complete cure of gastric cancer and other gastrointestinal cancers, it's crucial to detect the disease early and intervene with treatment. Our study indicates the potential of SDF-4 to serve as a novel blood tumor marker that can detect various types of cancers at an early stage. Moving forward, we plan to evaluate the diagnostic accuracy of SDF-4 in a larger number of patients through international collaborative study. Moreover, with an aim to apply it in mass cancer screenings, we are working towards developing an

original test kit to measure SDF-4 concentrations using blood samples.

Publication

Takahiro Shinozuka, Mitsuro Kanda, Dai Shimizu, Shinichi Umeda, Hideki Takami, Yoshikuni Inokawa, Norifumi Hattori, Masamichi Hayashi, Chie Tanaka, Goro Nakayama, Yasuhiro Kodera. Identification of stromal cell-derived factor 4 as a liquid biopsy-based diagnostic marker in solid cancers. Scientific Reports. September 20, 2023
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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_230927.pdf