News Release

Title

Discovery of synaptotagmin 8 as a novel molecular target specific to peritoneal metastasis from gastric cancer

Key Points

- We identified synaptotagmin 8 overexpressing specifically in gastric cancer tissues with peritoneal metastasis from global expression profiling of 57751 molecules
- Inhibition of synaptotagmin 8 led to decreased invasion and migration ability of gastric cancer cells, and formation of peritoneal metastasis in mouse xenograft models
- Overexpression of synaptotagmin 8 serves as diagnostic and predictive biomarker for peritoneal metastasis from gastric cancer

Summary

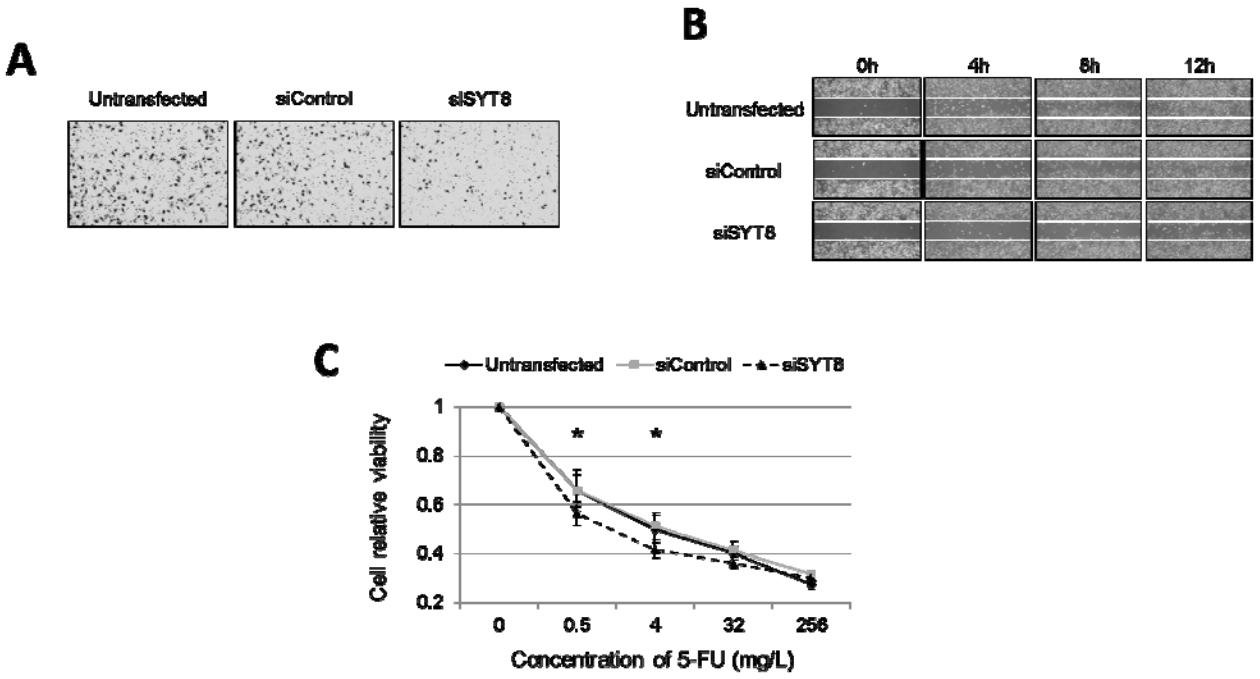
Prof. Yasuhiro Kodera and Dr. Mitsuro Kanda (Department of Gastroenterological Surgery (Surgery II)) in Nagoya University Graduate School of Medicine (Dean: Dr. Masahide Takahashi) identified synaptotagmin 8 overexpressing specifically in gastric cancer tissues with peritoneal metastasis from global expression profiling of 57751 molecules. In vitro studies revealed that inhibition of SYT8 expression inhibited the migration and invasive properties of gastric cancer cell lines, which are important for free gastric cancer cells present in the peritoneum to adhere to the distant peritoneum and form nodules by invading the sub-peritoneal space. When we next used a mouse xenograft model, we found that intraperitoneal administration of SYT8-siRNA significantly reduced the loss of body weight, inhibited the growth of peritoneal tumors, and prolonged survival. These findings support the conclusion that SYT8 serves as a biomarker as well as a therapeutic target for peritoneal metastasis of gastric cancer. SYT8 expression was found to serve as a novel diagnostic and predictive biomarker for peritoneal metastasis in patients with gastric cancer and therefore may be useful for preoperative staging, disease monitoring, and selection of optimal multimodal management strategies. This work was published online in Annals of Surgery on December 6, 2016.

Research Background

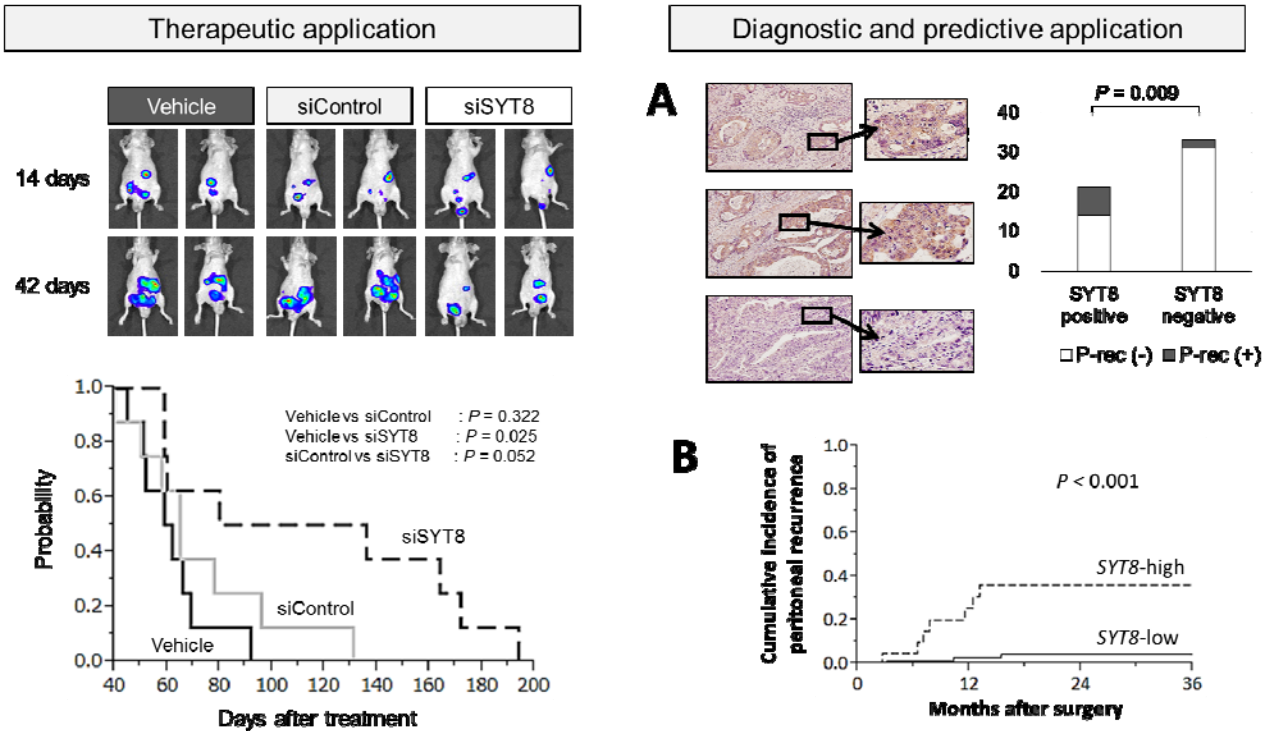
Advanced gastric cancer frequently recurs because of undetected micrometastases even after resection with curative intent. Peritoneal metastasis has been the most frequent pattern of disease recurrence after D2 dissection and is incurable. We aimed to develop novel diagnostic and therapeutic targets specific for peritoneal metastasis of gastric cancer to improve management.

Research Results

We conducted a recurrence pattern-specific transcriptome analysis to identify candidate biomarkers for peritoneal metastasis. The mRNA and protein levels of the molecule in primary gastric cancer tissues were compared with patients' clinical characteristics and survival in 340 patients with gastric cancer. The effects of siRNA-mediated knockdown on phenotype and fluorouracil sensitivity of gastric cancer cells were evaluated in vitro, and the therapeutic effects of siRNAs were evaluated using a mouse xenograft model. Synaptotagmin 8 (SYT8) was identified as a candidate biomarker specific to peritoneal metastasis. Inhibition of SYT8 expression by gastric cancer cells correlated with decreased invasion (Figure 1A), migration (Figure 1B), and fluorouracil resistance (Figure 1C).



Intraperitoneal administration of SYT8-siRNA inhibited the growth of peritoneal nodules and prolonged survival of mice engrafted with gastric cancer cells (Figure 2, left). High SYT8 levels were significantly and specifically associated with peritoneal metastasis (Figure 2, right A), and served as an independent prognostic marker for peritoneal recurrence-free survival of patients with stage II/III GC (Figure 2, right B).



Research Summary and Future Perspective

SYT8 is a promising diagnostic and predictive biomarker for peritoneal metastasis of gastric cancer and may affect sensitivity of gastric cancer cells to 5FU. Inhibition of SYT8 may represent a key of treatment strategy to overcome uncontrolled peritoneal metastasis from gastric cancer. Since anti-SYT8 treatment is based on quite different mechanisms of action from existing molecularly targeted therapies, it can open new medical frontiers in the field of gastric cancer treatment, and possibly other malignancies involving peritoneal metastasis.

Publication

Kanda M, Shimizu D, Tanaka H, Tanaka C, Kobayashi D, Hayashi M, Iwata N, Niwa Y, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M, Kodera Y. Significance of SYT8 for the Detection, Prediction, and Treatment of Peritoneal Metastasis from Gastric Cancer. Annals of Surgery, Dec.6, 2016.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2016/synaptotagmin8_20161206jp.pdf