News Release

Title

Discovery of synaptotagmin 7 as a driver of liver metastasis formation of gastric cancer

Key Points

- We identified synaptotagmin 7 overexpressing in clinical gastric cancer tissues with synchronous liver metastasis from global expression profiling of 57749 molecules
- Knockout of synaptotagmin 7 attenuated abilities of gastric cancer cells, and inhibited formation of subcutaneous and liver tumors in mouse xenograft models
- Tissue synaptotagmin 7 level serves as a predictive biomarker for liver metastasis of gastric cancer

Summary

Prof. Yasuhiro Kodera (Department of Gastroenterological Surgery (Surgery II)) in Nagoya University Graduate School of Medicine (Dean: Dr. Kenji Kadomatsu) and Dr. Mitsuro Kanda (Clinical Department of Gastroenterological Surgery 2 in Nagoya University Hospital (Director: Dr. Naoki Ishiguro) identified synaptotagmin 7 (SYT7) overexpressing in clinical gastric cancer tissues with synchronous liver metastasis from global expression profiling of 57749 molecules. SYT7 knockout inhibited the proliferation of gastric cancer cells, indicated by increased apoptosis with activated caspase and loss of mitochondria membrane potential, G2/M cell cycle arrest and attenuated cell migration, invasion, and adhesion. The tumorigenicity of SYT7 knockout cells was moderately reduced in a mouse model of subcutaneous metastasis and was more strikingly attenuated in a model of liver metastasis. The SYT7 levels in the primary gastric cancer tissues were significantly associated with liver recurrence and metastasis. SYT7 represents a tool for prediction and monitoring of liver metastasis from gastric cancer as well as being a promising therapeutic target. This work was published online in Oncogene on June 1, 2018.

Research Background

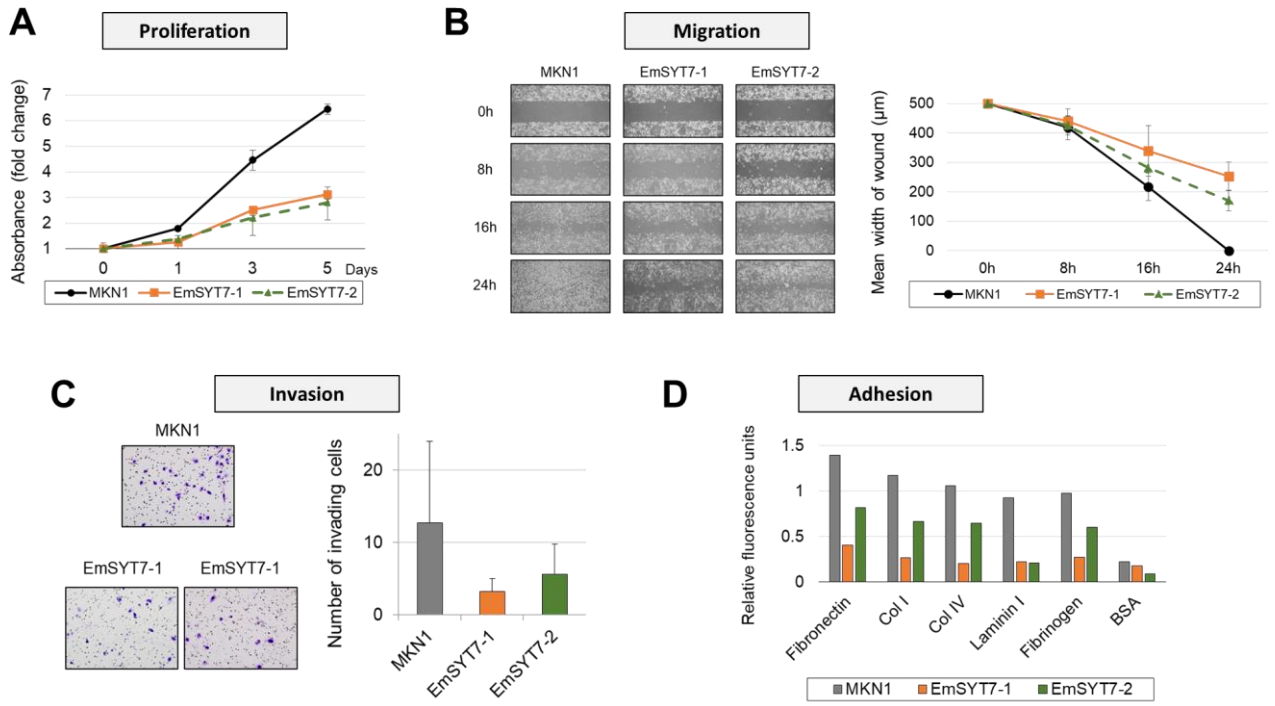
Gastric cancer is one of the most common carcinomas in the world, constituting approximately 10% of newly diagnosed cancer each year, and is associated with high mortality. Liver metastasis, the most common site of the hematogenous metastasis, has recently attracted attention since the incidence of differentiated-type gastric cancers located in the upper stomach or esophagogastric junction, which are more often associated with liver metastasis, has increased worldwide. Establishment of liver metastasis is considered to require a complex set of cellular functions that mediate local invasion, entrance into the blood stream, survival in the circulation, extravasation, survival in the liver's microenvironment, and eventually colonization. Growing body of evidence indicates that a liver metastasis cascade depends on intrinsic molecular signatures of the tumor cells and their subsequent responses

to multiple stimuli. Identification of the key molecular mechanisms that contribute to such signaling cascade is warranted. We used transcriptome analysis and identified synaptotagmin VII (SYT7) as a putative molecule involved in the liver metastasis of gastric cancer. We subsequently conducted functional analyses of SYT7 in vitro and in vivo to evaluate its value as a novel molecular therapeutic target.

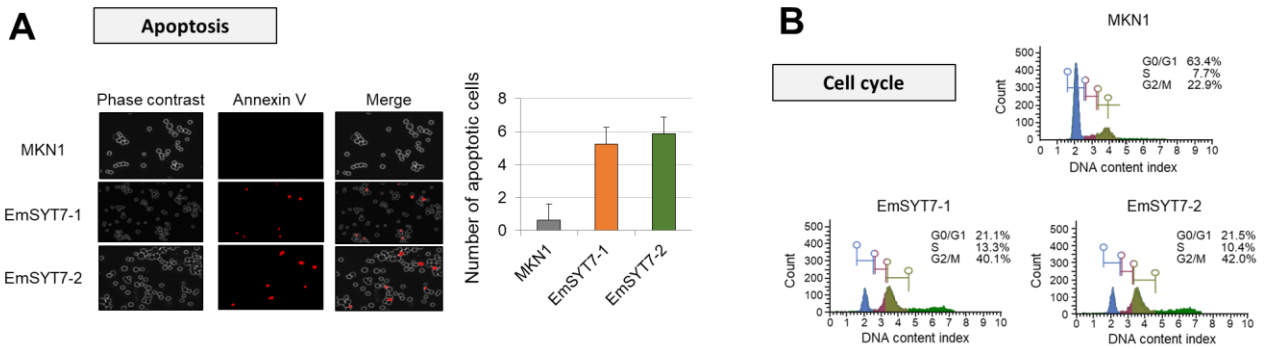
Research Results

We conducted a transcriptome analysis and identified SYT7 as a candidate drivers for liver metastasis of gastric cancer. Stable SYT7-knockout gastric cancer cells (EmSYT7-1 and EmSYT7-2) were established by a genome editing method. SYT7 knockout inhibited the proliferation of gastric cancer cells (Figure 1A) and attenuated cell migration (Figure 1B), invasion (Figure 1C), and adhesion (Figure 1D).

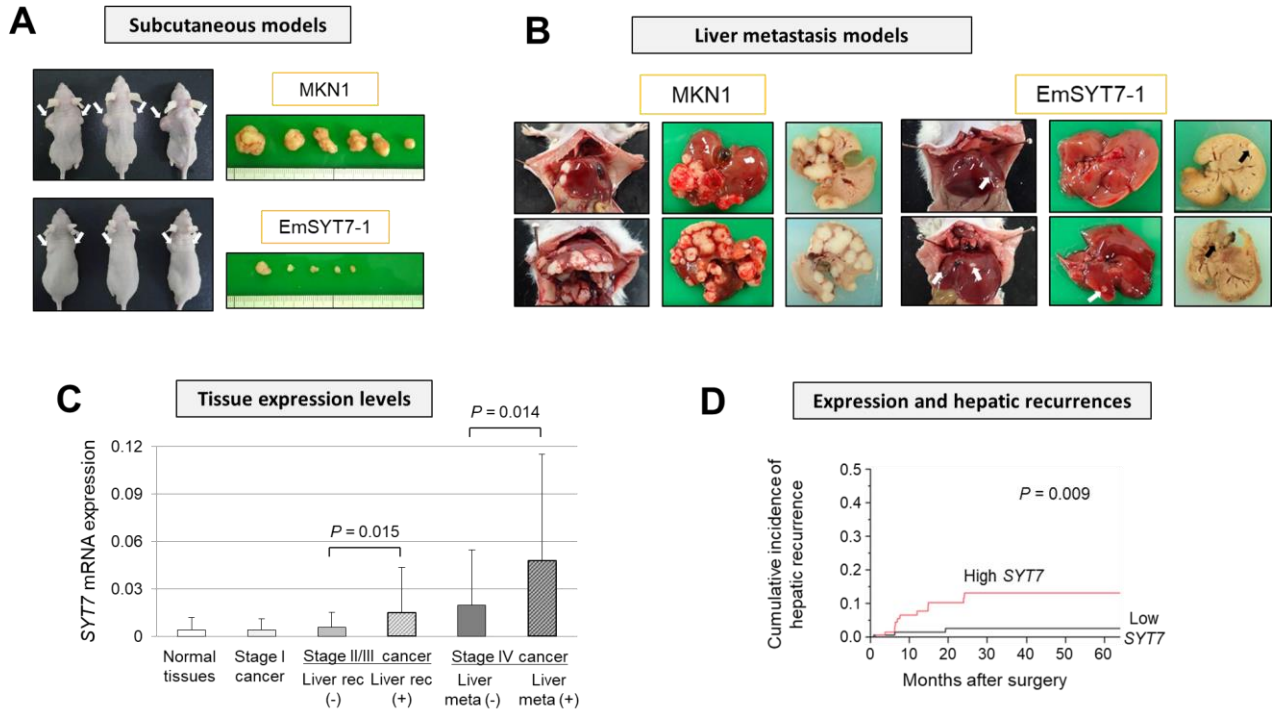
The Annexin V assay data revealed that cultures of SYT7-knockout (EmSYT7-1 and EmSYT7-2) cells harbored significantly more annexin V-positive cells compared with MKN1 cultures, indicating that SYT7 knockout cells were more susceptible to apoptosis (Figure 2A). With respect to effect of SYT7 knockout on the cell cycle progression, an increase of the amount



of cells in G2/M phase was exhibited in EmSYT7-1 and EmSYT7-2 cells (Figure 2B).



We determined whether knockout of SYT7 influences the growth of tumors formed by gastric cancer cells in vivo. The subcutaneous tumors grew progressively in the MKN1 group while only slightly in the EmSYT7-1 group (Figure 3A). We used mouse liver metastasis models to evaluate the involvement of SYT7 in the metastasis of gastric cancer cells to the liver. The macroscopic appearance (laparotomy and specimens) of liver metastases 12 weeks after cell implantation is shown in Figure 3B. Multiple tumor nodules were observed in the liver of the MKN1-implanted mice. In contrast, the number and size of the tumors observed in mice implanted with the EmSYT7-1 were smaller. The tissue SYT7 expression levels were significantly higher in patients with stage II/III gastric cancer who developed liver recurrence than those did not. Moreover, among stage IV patients who harbored concomitant distant metastasis, SYT7 expression levels in the cancerous tissues were significantly higher in patients with liver metastasis than those without (Figure 3C). The cumulative incidence of liver recurrences after curative resection was significantly higher in the high SYT7 group than the low SYT7 group (Figure 3D).



Research Summary and Future Perspective

SYT7 is a promising diagnostic and predictive biomarker for liver metastasis of gastric cancer. Inhibition of SYT7 may represent a key of treatment strategy to overcome uncontrolled liver metastasis from gastric cancer. Since anti-SYT7 treatment is based on quite different mechanisms of action from existing molecularly targeted therapies, it can open new frontiers in treatment of gastric cancer and possibly other malignancies overexpressing SYT7 including breast, colon, prostate, ovarian and pancreatic cancer.

Publication

Kanda M, Tanaka H, Shimizu D, Miwa T, Umeda S, Tanaka C, Kobayashi D, Hattori N, Suenaga M, Hayashi M, Iwata N, Yamada S, Fujiwara M, Kodera Y. SYT7 acts as a driver of liver metastasis formation of gastric cancer cells. Oncogene 2018 in press.
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Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Oncogene_20180604.pdf