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Orthotopic gastric cancer mouse model identifies trajectory of lymphatic metastasis

Huafeng Fu, Qinbo Cai, Zhijun Zhou, Yulong He, Min Li, Dongjie Yang

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To the Editor: Gastric cancer remains a major global health challenge. Lymph node metastasis is prevalent in gastric cancer and is associated with worse prognosis. Even in patients with early-stage gastric cancer, the prevalence of lymph node metastasis is high, ranging from 22.1% to 27.3% (1). The mechanism of lymph node metastasis in gastric cancer remains poorly understood. The mouse footpad tumor model and subcutaneous xenograft model are commonly used for in vivo studies of lymph node metastasis in gastric cancer (2, 3). However, these models cannot fully recapitulate the tumor microenvironment, invasive growth pattern, or lymph node invasion sequence of gastric cancer in patients (4–6). In this study, we investigated the perigastric lymphatic drainage network in mice and established an orthotopic xenograft tumor model to explore the trajectory of lymphatic metastasis (Supplemental Methods). We injected nanocarbon particles into the subserous layer of the stomach at multiple sites (Figure 1A). The particles entered the lymphatic vessels, flowing to the corresponding perigastric lymph nodes (Figure 1B). Lymph fluid from the body and antrum of stomach flows into a lymph node next to the gastric lesser curvature, which we defined as lymph nodes along the lesser curvature (lcLN). Lymph fluid from the greater curvature flows into a lymph node located at the roots of the right gastroomental artery and vein (RGOA/V), which […]

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We injected nanocarbon particles into the subserous layer of the stomach at multiple sites (Figure 1A). The particles entered the lymphatic vessels, flowing to the corresponding perigastric lymph nodes (Figure 1B). Lymph fluid from the body and antrum of stomach flows into a lymph node next to the gastric lesser curvature, which we defined as lymph nodes along the lesser curvature (lcLN). Lymph fluid from the greater curvature flows into a lymph node located at the roots of the right gastroomental artery and vein (RGOA/V), which we defined as lymph nodes along the greater curvature (gcLN). The gcLN and lcLN are the first stations for perigastric lymphatic drainage. The particles then flowed into the lymph nodes located next to the celiac artery. This group of lymph nodes, consisting of 2–3 small nodes, are defined as lymph nodes along the celiac artery (caLNs). The caLNs constitute the second station for perigastric lymphatic drainage. The particles then flowed into a lymph node located next to the abdominal aorta, which is defined as the paraaortic lymph node (paLN). The paLN is the third station for perigastric lymphatic drainage. The particles from the paLN flowed into the superior paramesenteric lymph nodes under compression, which we defined as lymph nodes along the superior mesenteric artery (smaLN). These findings show the trajectory of perigastric lymphatic drainage in mice (Figure 1, B–D).

Direct inoculation of tumor cells into stomach wall may lead to perforation and tumor dissemination during gastric contraction. To recapitulate the process of gastric cancer metastasis in patients, we implanted tumor tissue into the submucosa of mice stomaches (Figure 1E). Bioluminescence and MR imaging tracked tumor growth and lymph node metastasis (Figure 1, F and G). We observed a significant increase in the size of perigastric draining lymph nodes, gcLN, lcLN, and caLNs, in tumor-bearing mice compared with the control group using MR imaging (Figure 1H). This orthotopic gastric cancer mouse model showed extensive thickening and local bulging of the glandular stomach (Figure 1I). At week 8 after tumor transplantation, we collected the perigastric draining lymph nodes. Consistently, we found the increased size of lymph nodes, including gcLN, lcLN, and caLNs in tumor-bearing mice compared with the control group (Figure 1I). At week 8 after tumor transplantation, we collected the perigastric draining lymph nodes. Examination of the first station (gcLN, lcLN) and the second station (caLNs) of the lymph nodes showed that all mice had metastasis (4 of 4), while there were no metastases at the third station (paLN; 0 of 4). The metastases exhibited mass-like growth with clear boundaries from the surrounding lymphoid tissue, closely recapitulating human lymphatic metastases (Figure 1J). Collectively, this study identifies the perigastric lymphatic network and the trajectory of lymph node metastasis in gastric cancer, which can be applied to study the mechanism and treatment of lymphatic metastasis (Figure 1K).

In conclusion, this study provides an invaluable mouse model to dissect the mechanism of lymphatic metastasis in gastric cancer. Future studies may use this model to delve deeper into the genetic and molecular alterations associated with lymph node metastasis, exploring the impact of the tumor microenvironment and testing potential therapeutic interventions.

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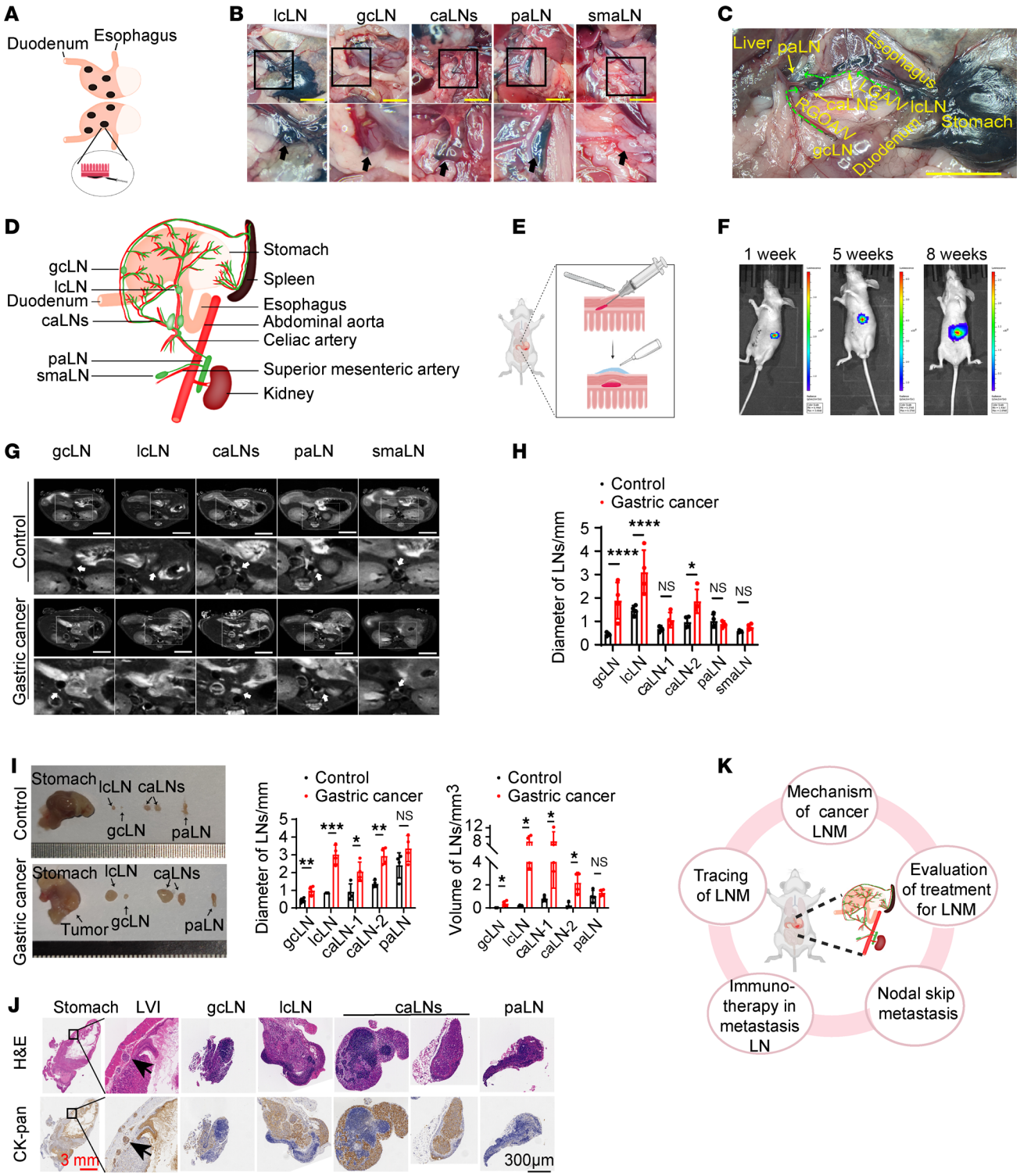

Figure 1. Conserved perigastric lymphatic drainage network and lymph node metastasis in an orthotopic gastric cancer mouse model. (**A**) Schematic diagram showing the injection of nanocarbon particles into the subserous layer of the stomach at multiple sites. (**B**–**D**) Perigastric lymphatic drainage network. LGA/V, left gastric artery/vein; smaLN, lymph node along the superior mesenteric artery. Scale bars: 5 mm. (**E**) Schematic diagram of orthotopic xenograft tumor model. A small piece of tumor tissue was implanted to the submucosal layer by an implantation needle. (**F**) Bioluminescence imaging was used to track tumor growth. (**G**) MR imaging was used to track tumor growth and lymphatic metastasis. Scale bar: 5 mm. (**H**) Statistics analysis on the size of lymph nodes in MR imaging (n = 4). (**I**) Gross images of the stomach and perigastric drainage lymph node of mice, and statistics analysis of the volume of lymph nodes (n = 4). (**J**) H&E and pan-cytokeratin (CK-pan) staining of stomach and perigastric lymph nodes. LVI, lymphovascular invasion. The magnification of representative images of gcLN, lcLN, caLNs and paLN were the same. (**K**) Schematic diagram showing the broad application of this orthotopic gastric cancer mouse model. LNM, lymph node metastasis. The arrows (**B**, **G**, **I**, and **J**) indicate the position of lymph nodes. Multiple unpaired 2-tailed t test was performed for statistical analysis. *P < 0.05 and ****P < 0.0001. Data represent mean ± SEM.

Huafeng Fu,[1,2,3] Qinbo Cai,[3,4] Zhijun Zhou,[5] Yulong He,[1,2,4,6] Min Li,[5] and Dongjie Yang[1,2,6]

[1]Digestive Medicine Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China. [2]Guangdong Provincial Key Laboratory of Digestive Cancer Research, Shenzhen, Guangdong, China. [3]General Surgery Laboratory and [4]Center for Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China. [5]Department of Medicine, Department of Surgery, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA. [6]Research Center for Diagnosis and Treatment of Gastric Cancer, Sun Yat-sen University, Guangzhou, Guangdong, China.

Address correspondence to: Dongjie Yang, Digestive Medicine Center, The Seventh Affiliated Hospital, Sun Yat-sen University, 628 Zhenyuan Road, Shenzhen, Guangdong 518107, China. Email: ydongj@mail.sysu.edu.cn. Or to: Min Li, Department of Medicine, Department of Surgery, The University of Oklahoma Health Sciences Center, 975 NE 10th Street, BRC 1262A, Oklahoma City, Oklahoma 73104, USA. Email: Min-Li@ouhsc.edu. Or to: Yulong He, Digestive Medicine Center, The Seventh Affiliated Hospital, Sun Yat-sen University, 628 Zhenyuan Road, Shenzhen, Guangdong 518107, China. Email: heyulong@mail.sysu.edu.cn

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