Gastrointestinal Cancer Metastasis and Lymphatic Advancement

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Abstract

The role of angiogenesis in the growth of solid tumors is well established, but the role of lymphatic vessels and the relationship between lymphangiogenesis and tumor spread are less clear. Recently, the molecular pathway that signals lymphangiogenesis and specific markers for lymphatic endothelium have been discovered; however, the lymphatic pathway of cancer metastasis is only partly clarified. Several investigators from the mid 20th century indicated the existence of lymphatico-venous communications, and some observed the retrograde filling of lymph flow and lymphatico-venous communication in obstructive lymphopathy. In the 1960s Burn reported the importance of lymphovenous communication in his clinical and animal experimental data. Thus, the role of potential peripheral lymphatico-venous communication must be considered in the mechanism of cancer metastasis. We observed the lymphatico-venous (portal) communication, as well as lymph retention and reflux, in a rat model of mesenteric lymph vessel obstruction. Based on the phenomenon of lymphatico-venous communication and lymph flow reflux by lymphatic obstruction, we speculate that tumor cell obstruction in the lymph system will lead to the establishment of liver and/or peritoneal metastasis. Clinically, we observed extranodal cancer invasion in a model of lymphatic obstruction, and noted a strong relationship between extranodal invasion and liver or peritoneal metastasis. Thus, the existence of peritoneal and liver metastasis via a lymphatic pathway should be considered.

Key words Lymphogenous metastasis · Lymphatico-venous communication · Lymph reflux · Extranodal invasion

Introduction

Cancer cells from malignant primary tumors spread from their sites of origin to invade local tissue and enter the systemic circulation. This spread can occur directly into local tissue, via blood vessels (hematogenous spread) and lymphatics (lymphogenous spread), or via the invasion of body cavities such as the pleura or peritoneum (peritoneal metastasis, pleural metastasis). The role of angiogenesis in promoting the growth of solid tumors is well established, but the roles of lymphatic vessels and lymphangiogenesis in tumor spread are unclear. The molecular pathway that signals lymphangiogenesis and specific markers for lymphatic endothelium have recently been described, allowing tumor lymphangiogenesis to be analyzed in animal models. In practice, clinicopathological data suggest that lymphatics are an initial route for the metastasis of solid tumors. This idea forms the basis for surgical intervention. Lymphatics are thin-walled, low-pressure vessels that collect fluid and cells from the interstitium and return them to the circulation via the thoracic duct. The thoracic duct is the classic pathway from lymphatic to blood circulation. As far back as the 1960s, investigators discussed the existence of lymphatico-venous communication. In this article, we review lymphatic advancement from the viewpoint of the lymphatic system.

Historical Review of Cancer Metastasis

In the 19th century, the pathologist Rudolf Virchow presented the concept of cancer metastases as hematogenous and lymphogenous spread. Towards the end of that century, several mechanisms of cancer metastasis were proposed. The relationship between primary tumors and their metastatic tropisms had already been recognized, including the relationship between prostate...
cancer and bone metastasis, colon cancer and liver metastasis, and breast cancer and lung metastasis.

This predilection to form macrometastases in a particular organ site was noted in 1889 by the British pathologist, Stephen Paget. He proposed the “seed and soil” hypothesis, in which he analogized the seeding of cancer cells to the dispersal of plant seeds. After studying the clinical course of breast cancer patients, Paget concluded that the patterns of metastasis formation could not be explained either by random scattering throughout the body or by dispersal from the breast through the general circulation. Thus, he proposed that the metastasizing cancer cells (the seed) find a compatible home only in certain especially hospitable tissues (the soil). He wrote “a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenital soil.” However, this hypothesis cannot explain the metastatic patterns of all types of human cancer. Rather, it seems that the predilection to metastasize to a certain target organ is dictated by the layout of the vessels connecting the site of the primary tumor and the site of metastasis. For example, the strong tendency of colon carcinoma cells to metastasize to the liver may simply reflect the fact that these cancer cells leave the gut via the portal vein and almost inevitably become lodged in the capillary beds of the liver, which are fed by this vein. Even if individual metastasizing colon cancer cells colonize the liver with low efficiency, the sheer number of cancer cells trapped in the liver guarantee that over time, substantial metastases will arise in this target organ. This is the anatomical-mechanical theory.

These two theories for cancer metastases are still widely accepted today. It has been postulated that peritoneal metastasis develops when cancer cells in the gastrointestinal serosa become capable of implantation on exposure to the abdominal cavity. They then detach from the gastrointestinal wall and float within the abdominal cavity until they make contact with the peritoneal mesothelium, stomata milky spots, where they implant and proliferate within the host tissue. This mechanism has been supported by clinicopathological analysis, including electron microscopy studies, of resected specimens, and a molecular pathway has recently been developed that includes adhesion molecules, chemokines, growth factors, and angiogenetic factors.

Fidler proposed the experimental model of metastasis in 1973, since when molecular biology as a tool to study the metastatic mechanism has developed remarkably. In 1986 Liotta proposed a three-step hypothesis for the sequence of biochemical events during tumor cell invasion of the extracellular matrix. The first step is tumor cell attachment via cell-surface receptors that bind specifically to components of the matrix, such as laminin and fibronectin. The anchored tumor cell next secretes hydrolytic enzymes that can degrade the matrix locally. Matrix lysis probably takes place in a highly localized region close to the surface of the tumor cell. The third step is tumor cell locomotion into the region of the matrix modified by proteolysis. Continued invasion of the matrix may take place by cyclic repetition of these three steps. This theory led to the recognition of many of the molecular components of the metastatic process.

Cancer cells must first invade either blood or lymphatic vessels to enter the circulation. In blood vessels, this requires penetration of the basement membrane and migration through the cellular layers of the vessel. It has been proposed that the entry of tumor cells into the lymphatic circulation might be easier due to the nature of lymphatic vessels: the thin, discontinuous basement membrane of lymphatics might not provide a strong barrier to the entry of tumor cells.

Previous studies have established the role of angiogenesis in solid tumor growth and there is some evidence indicating a direct role of angiogenesis in hematogenous cancer spread. However, little is known about the role of tumor lymphangiogenesis, namely, the growth and production of new lymphatic vessels, in the spread of tumors and whether this process is important in the overall context of lymphatic spread.

**Progress in the Study of Lymphatic Metastasis**

The extended discussion on hematogenous cancer spread reflects the important role of the blood circulation in metastatic dissemination; however, the contribution of lymphatic vessels to the dispersion of cancer cells is less obvious. Almost all tissues in the body carry networks of lymphatic vessels, which are responsible for continuously draining the interstitial fluid that accumulates in the spaces between cells. The fact that the walls of lymphatic vessels are thinner than those of blood vessels is, in part, due to the highly attenuated cytoplasm of lymphatic endothelial cells. The endothelium of lymphatic vessels contains fewer tight junctions than that of blood vessels, and it is speculated that this may be the cause of the greater permeability of the lymphatic vessels. Clinical-pathological data point to the spread of solid tumors via the lymphatics as an important early event in metastatic disease. The detection of tumor cells in lymphatic vessels and regional lymph nodes is a key factor in the staging of human tumors, and forms the basis for treatment of regional lymph nodes by surgery and radiation therapy. However, the exact mechanism by which tumor cells enter the lymphatic system is uncertain, despite our knowledge of lymphatic vessel structure.