Hem- and lymph-angiogenesis in cancer metastasis

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Petrénsalen, Nobels väg 12B

Fredagen Den 14 juni 2013, kl 13.00

av
Hong Ji

Huvudhandledare: Professor Yihai Cao Karolinska Institutet Institutionen för Mikrobiologi, Tumör och Cell Biologi

Bihandledare: Dr. Kayoko Hosaka Karolinska Institutet Institutionen för Mikrobiologi, Tumör och Cell Biologi

Fakultetsopponent: Professor Klaus Elenius University of Turku Medical biochemistry and genetics Institute of Biomedicine

Betygsämnd: Professor Manuel Patarroyo Karolinska Institutet Institutionen för odontologi

Associate Professor Teresa Pereira Karolinska Institutet Institutionen för molekylär medicin och kirurgi

Professor Ann-Kristin Östlund Farrants Stockholm University Wenner-Grens institut för experimentell biologi

Stockholm 2013
ABSTRACT
Angiogenesis, the process of sprouting new microvessels from the preexisting vasculature, is known to promote tumor growth. However, the role of tumor angiogenic vessels in facilitating metastasis remains poorly understood. In addition to hemangiogenesis, various types of tumors often contain lymphatic vessels, which may facilitate lymphatic metastasis. Cancer metastasis employs complex processes that are collectively termed as the metastatic cascade, which involves multiple-step defined mechanisms. A clinical detectable metastatic mass represents the ultimate consequence of the complex metastatic cascade that includes dissemination of tumor cell from the primary site; invadopodia of tumor cells into the circulation or lymphatic system; transport of tumor cells along blood circulation or lymphatic system to distal tissues or organs; extravasation of tumor cells from the circulation of lymphatic system; formation of the primary metastatic niche in distal tissues; manipulation of metastatic microenvironment; and regrowth of metastatic nodules to a visible metastatic mass. Although advances of imaging techniques allow detection of relatively small sizes of tumors in cancer patients and in experimental animal models, the early onset of metastatic processes remains unknown. As for lymphangiogenesis, there has been lacking appropriate and powerful in vivo assay systems that allow quantitatively study lymphangiogenesis. In this thesis work, we have: 1) developed a novel zebrafish model to study the early steps of the metastatic cascade. We take the advantage of the transparent nature of zebrafish embryos to visualize under normoxic and hypoxic conditions marked human or mouse tumor cell migration and invasion in association with tumor angiogenesis. We have found that tumor angiogenesis is essentially required for tumor cell invasion and dissemination. This study, for the first time, provide compelling evidence of tumor cell-tumor vessel interaction in promoting cancer cell dissemination to distal sites; 2) studied the interplay between FGF-2 and VEGF-C in promoting lymphatic metastasis. In the tumor microenvironment, various angiogenic factors often co-exist and they often cross-communicate with different signaling pathways. Although the individual factor-transduced vertical signals via their specific receptors are relatively well studied, their horizontal interplay with other signaling systems remains poorly characterized. We show that FGF-2-triggered lymphangiogenic signaling pathways synergistically promote lymphangiogenesis with the VEGF-C-VEGFR-3 system, leading to synergistic lymphangiogenic effects in various in vivo models. A clear lymphangiogenic synergism between FGF-2 and VEGF-C has been observed in the tumor microenvironment. Importantly, this synergistic lymphangiogenic activity leads to accelerated lymphatic metastasis in sentinel lymph nodes; 3) developed a unique in vivo model to study lymphangiogenesis induced by various factors. We take the advantage of the avascular nature of the mouse corneal tissue and implant various growth factors/cytokines alone or in combinations to quantitatively study lymphangiogenesis and lymphatic structures; and 4) have also studied the impact of clinical available antiangiogenic drugs on healthy vasculatures and revealed potential sites for antiangiogenic drug-related side effects.

ISBN 978-91-7549-205-6