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Mini-review

Cancer stem cells, lymphangiogenesis, and lymphatic metastasis

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ABSTRACT

Although current opinion indicates that tumor-induced lymphangiogenesis plays a key role in promoting the initial spread of malignant tumors, the mechanism that underlies lymphatic spread is not clear. The recent discovery of cancer stem cells (CSCs) in human tumors has challenged our current understanding of tumor recurrence, drug resistance, and metastasis, and opens up new research directions on how cancer cells are capable of switching from dormancy to malignancy. CSCs can be directly and indirectly involved in tumor-induced lymphangiogenesis and ultimately promote lymphatic metastasis. However, the details and the possible relationship between CSCs, lymphangiogenesis, and lymphatic metastasis remain ambiguous, and the origin of tumor lymphatic endothelial cells is controversial. Elucidation of these factors may provide useful information for future research and cancer treatment. In this article, we summarize current knowledge of CSCs, tumor-induced lymphangiogenesis, and lymphatic metastasis and attempt to find an association between key molecular and cellular mechanisms. We provide an overview of CSCs and lymphatic vasculature as potential therapeutic targets. CSC- and lymphatic vasculature-targeted therapy may bring new hope for cancer treatment.

Introduction

Metastasis is a characteristic trait of most tumor types and the cause of the majority of cancer deaths; over 90% of cancer suffering and death is associated with metastatic spread. As such, a significant aim of cancer research is to understand the molecular and cellular mechanisms that underlie the processes of metastasis.

It is widely accepted that solid tumor growth and spread involve angiogenesis and the blood vessels (hematogenous spread). However, increasing evidence suggests that this is a secondary event in metastasis, and that an important initial event involves the lymphatic system (lymphanogenous spread) [1]. Tumor-induced lymphangiogenesis both locally and in regional lymph nodes has been correlatively and functionally associated with metastasis formation [2,3], and many tumor types, including melanoma, breast, and prostate cancers, first metastasize via lymphatic vessels to their regional lymph nodes. Clinically, regional lymph node metastasis is considered a prognostic indicator and a critical determinant of cancer management and therapy [1]. Despite this, the molecular and cellular mechanisms that underlie lymphatic spread remain largely unknown.

Recently, the cancer stem cell (CSC) theory has emerged as an attractive hypothesis for tumor development and progression. In the CSC model, tumors consist of subsets of cells with functional heterogeneity, and one small subset of cancer cells has the characteristics of stem cells. These CSCs have the capability of both self-renewal and multi-lineage differentiation into diverse cancer cells, which play a decisive role in maintaining the capacity for malignant proliferation, invasion, metastasis, and tumor recurrence [4,5]. CSCs, also termed tumor-initiating cells (TICs) or cancer metastasis-initiating cells (CMICs), are known to exhibit aggressive phenotypes and resistance to most anticancer agents, including chemo- and/or radiotherapy, and DNA damage-induced apoptosis [6]. Therefore, the discovery of CSCs challenges our current understanding of tumor recurrence, drug resistance, and metastasis [7]. Assuming that CSCs are relatively refractory to the therapies developed to eradicate the non-stem cell component of tumors, the CSC model provides a theoretical basis for developing therapies that target the minority CSC population and presents a new perspective for the treatment of cancer [5].

To date, accumulating evidence suggests that CSCs closely correlate with tumor metastasis [5–8]. This idea is supported by previous experimental observations including: (a) CSCs can induce cancer metastasis through multiple pathways; (b) lymphangiogenesis is a significant pathological change in the process of tumor metastasis; and (c) CSCs participate in lymphangiogenesis directly and

Abbreviations: CSC, cancer stem cell; LEC, lymphatic endothelial cell; BEC, blood endothelial cell; NOS, nitric oxide synthase; LEPC, lymphatic endothelial progenitor cell; MCSC, migrating cancer stem cell; MSCs, mesenchymal stem cells; EMT, epithelial-to-mesenchymal transition; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TAMs, tumor-associated macrophages; ALDH, aldehyde dehydrogenase; VM, vasculogenic mimicry.

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indirectly [9]. Therefore, there remains an urgent need to understand the role of CSCs in tumorigenesis and tumor metastasis.

In this review, the possible relationship between CSCs, tumor-induced lymphangiogenesis, and lymphatic metastasis is discussed to reveal the cellular and molecular mechanisms responsible for metastatic spread and to inform research on approaches to block tumor lymphatic metastasis. Such strategies may overcome the current clinical problems associated with anti-angiogenic therapy and could result in the development of breakthrough anticancer therapies.

Biomarkers of lymphatic metastasis

Lymphatic spread is an important clinical determinant in cancer prognosis. Early detection of lymph node metastasis and the identification of key protein targets for the treatment of metastatic cancer remain a challenge in current cancer research. With the developments of molecular analysis technologies, such as DNA and proteomic microarray analyses, detection of metastatic signatures in primary tumors has been possible, opening new avenues toward the molecular diagnosis and prognosis of cancers [10].

Cabioglu et al. studied the differential expression of CCR7 and CXCR4, as well as the biomarker HER2-neu, to evaluate whether these biomarkers can predict axillary lymph node metastasis in breast cancer. The results suggest that the chemokine receptor CCR7 is a novel biomarker that can predict lymph node metastases in breast cancer. Utilization of additional markers, such as CXCR4 and HER2-neu, further improves the prediction of the presence and extent of lymph node involvement [11].

To find new markers, Cerutti et al. performed serial analyses of gene expression on three samples from the same patient, including normal thyroid tissue, primary papillary thyroid cancer (PTC), and PTC lymph node metastasis. LIMD2 and PTPRC (CD45) showed a statistically significant difference in expression between tumor and metastatic samples, and an additional gene (LTB) had borderline significance. PTPRC and LTB were tested by immunohistochemistry in an independent set of paired samples, with both markers showing a difference in protein expression [12].

To determine which markers may be helpful for improving the specificity of molecular diagnosis of nodal involvement, Samouelian et al. studied the expression of CK19, MUC1, HER1-HER4, VEGF, VEGF-C, uPA, MMP9, and PRAD1 in uterine cervical tumors and in histologically nonmetastatic lymph nodes. They suggested that CK19, MUC1, HER1-3, uPA, and VEGF are biomarkers that have a higher expression in tumoral cervical tissues compared with negative lymph nodes, and may be useful to diagnose nodal involvement in uterine cervical carcinoma [13]. Another study demonstrated that CD44v6, MMP-7, and nuclear Cdx2 were independent predictors for lymph node status [14].

A recent study detected the pretreatment serum protein profiles of breast cancer patients by mass spectrometry (MS) to screen candidate tumor biomarkers to find a simple, accurate, and minimally invasive method to predict axillary lymph node metastasis in breast cancer. Four proteins were used to construct a diagnosis model, and cross-validation indicated that breast cancer with and without axillary node metastasis was identified with 87.04% sensitivity, 87.23% specificity, and 87.13% accuracy. These proteins can potentially be used as predictive biomarkers to distinguish between breast cancer patients with or without lymph node metastasis [15].

Targeted therapy for lymphatic metastasis

Many strategies have been used to prevent lymphatic metastasis. In addition to VEGF inhibiting antibodies, new therapeutic approaches are in clinical development. The latest therapeutic approaches or new targets that may be used on a regular basis in the future to improve cancer treatment include targeting molecules of signaling pathways, gene therapy, immunotherapy, and subverting tumor microenvironments and niches.

Kashima et al. found that a novel anti-VEGF-D monoclonal antibody cVE199, with specific reactivity against human VEGF-D, prevents lymphatic metastasis of neuroblastoma through the inhibition of lymphangiogenesis in an animal model [16]. Sennino et al. showed that c-Met blockade by the selective inhibitor PF-04217903 significantly reduced metastasis to local lymph nodes. Prevention of lymph node metastasis by PF-04217903 in this setting implicates c-Met signaling in tumor cell spread to lymph nodes. Inhibition of c-Met signaling reduced tumor cells inside lymphatics and lymph node metastasis [17]. Karadayı et al. showed that iNOS-mediated NO formation plays an important role in gastric carcinogenesis, tumor lymphangiogenesis, and the development of lymphatic metastases. Inhibition of the NO pathway may be an alternative treatment for gastric carcinomas [18]. IPI-926, an inhibitor of the Hedgehog signaling pathway, can deplete tumor-associated stromal tissue, and it was observed that coadministration with gemcitabine improved the delivery and efficacy of gemcitabine, obtaining transient stabilization of disease in a mouse model of pancreatic cancer [19].

The strategy of immunotherapy for cancer was put forward as early as the 1950s [20]. Immunotherapeutic strategies, including programmed death ligand 1 (PDL1, an immune regulator) [21], cancer immunotherapy using dendritic cells [22], genetically modified autologous T-Cells [23,24], anti-CTLA4 antibodies [25,26] or CCR7-CCL19/21 [27,28], were shown to be feasible for cancer treatment. Further studies are justified to determine their efficacy and precise role in blocking lymphangiogenesis and preventing lymphatic metastasis.

Tumor-induced lymphangiogenesis

Tumor-induced lymphangiogenesis plays an important role in promoting tumor growth and metastasis [29,30]. Evidence suggests that tumor-associated lymphatic vessel density is correlated with metastasis to draining lymph nodes, distant metastases, and poor prognosis [31–33]. Lymphangiogenic growth factors produced by tumor cells induce lymphangiogenesis, which promotes metastasis to draining lymph nodes and beyond [34–37]. Beasley et al. analyzed samples from human head and neck cancers by immunohistochemical staining for the lymphatic endothelial marker LYVE-1, CD34, and the proliferation marker pKi67, and they quantified the lymphangiogenic growth factor, vascular endothelial growth factor C (VEGF-C), by real-time polymerase chain reaction. Their study provided evidence that proliferating lymphatics occur in human malignant tumors, and they reported that a high intratumoral lymph vessel density was significantly correlated with cervical node metastases and an infiltrating margin of tumor invasion [38]. Similarly, He et al. showed that the initiation of lymphatic metastasis correlated with tumor lymphangiogenesis in a human lung cancer xenograft model in mice. This study investigated how tumor cells gain access to lymphatic vessels and at what stage tumor cells initiate metastasis. The results showed that VEGF-C produced by tumor cells induced extensive lymphatic sprouting toward the tumor cells, as well as dilation of the draining lymphatic vessels, suggesting an active role for lymphatic endothelial cells (LECs) in lymphatic metastasis. A significant increase in lymphatic vessel growth occurred between 2 and 3 weeks after tumor xenotransplantation, and lymph node metastasis occurred at the same stage [37]. Notably, tumor-associated lymphangiogenesis has potential significance not only at the primary site, but also in lymph nodes and at distant sites. Primary tumors induce new lymphatic vessel growth in draining lymph nodes before metastasis [39]. Expansion of the lymphatic vasculature in premetastatic lymph nodes has been confirmed in mouse