Pre-metastatic niche: cancer cells travel independently from nearest lymph nodes

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Abstract

The potential role of midkine, a growth factor, which is secreted by melanomas, was explored by Olmeda et al. They found this growth factor can promote lymphangiogenesis at distant site and related to metastatic cancer spread.

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Cancer cells usually spread from the primary site to specific organs through lymph nodes (lymphatic metastasis), especially for carcinoma. Lymphangionogenesis is the process of lymphatic vessels growth, which plays a critical role in metastasis. However, it is not clear whether the first lymph node dissection will decrease the motility of patients [1], leading to the doubt about the role of lymphangionogenesis in metastatic cancer spread. Olmeda [2] and his colleges revealed that the lymphangiogenesis in melanomas and their nearest lymph nodes is not indispensable for primary cancer cell spreads. In one type of skin cancer called melanomas, tumor cells can undergo metastatic spread through a previously undiscovered route to distant lymph nodes and organs. And midkine acts as a systemic inducer of neo-lymphangiogenesis due to the activation of mTOR pathway (Fig. 1). The authors used Flt4tm1.lSgo mice to engineer animal models for whole body imaging of neolymphangiogenesis in melanoma progression. Since the VEGFR3 is a lymphoreporter and closely tied to inflammation, cancer and lymphangiogenesis [3], Researchers were able to track the generation of lymphatic vessels with the help of luciferase, a protein which is encoded by the gene VEGFR3 in established animal model. Using this strategy, four different patterns of lymphangiogenesis related to tumor metastasis were revealed. After they exploited the melanoma metastasis induced by VEGFR3, researchers focused on the relationship between primary tumors and lymphangiogenesis at distant sites. Further studies identified the lymphangiogenesis around the primary tumors uncoupled from their colonization. Besides, tumoral VEGFC was neither sufficient nor essential for the activation of distal V3-Luc. It indicated the VEGFC protein production in primary tumors was not related to the distant metastases. Is the lymphangiogenesis at distant site related to metastases? Increasing studies have shown the pre, metastatic niches is critical for the tumor growth in distant tissues or organs [4]. The authors' data support the idea that the V3-Luc positive sites represent pre- metastatic niches. Furthermore, excision of primary tumors led to a marked reduction in VA-Luc expression. These data indicate the correlation between pre-metastatic niche formation and lymphangiogenesis. To identify factors that might drive distant lymphangiogenesis and metastasis, proteomic analyses were conducted, and the heparin-binding factor midkine (MDK) became the top candidate. This soluble protein is secreted by other cancers, involving in inflammation, cell proliferation and angiogenic functions [5]. It is encouraging that the function in lymphangiogenesis has been uncovered.

The levels of MDK were manipulated by loss and gain of function tests, and the authors demonstrated the downregulation of MDK resulted in marked inhibition of bioluminescence, lymphangiogenesis, metastasis to lymph nodes and visceral organs, such as the lungs or liver before tumor cells colonization (Fig. 2).

Olmeda and colleagues then focused on possible downstream effectors of MDK. Although mTOR pathway could modulate lymphangiogenesis, no previous report showed its role in MDK-associated signaling cascades. The researchers showed that MDK stimulated lymphangiogenesis by activating the mTOR signaling. In short, the authors' work has uncovered a pathway in melanomas metastasis through MDK-mediated lymphangiogenesis, which promotes pre-metastatic niches as well as tumor growth in distant tissues or organs. As a result, the role midkine played in metastasis was identified.
It is possible the MDK will cooperate with other tumor-secreted factors to determine the metastasis, and it will be interesting to determine these factors. And since the VEGFR3 gene can report pre-metastatic niches, its potential role in tumor-induced lymphangiogenesis regulation and drug testing of malignant disease remains to be defined.
With the growing understanding in early tumor metastasis, it's critical to predict metastatic risk precisely. Olmeda et al. showed high MDK expression in people with malignant melanoma, and it may provide an ideal biomarker for metastatic risk valuation. Developing advances in real-time lymphovascular imaging [6] will make their discoveries possible for cancer metastases prevention, diagnosis and treatment.

REFERENCES


