

Abstract of Presentation

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Tumor lymphangiogenesis: Impact on cancer metastasis

Abstract :

Tumor metastasis to regional (sentinel) lymph nodes represents the first step of dissemination in most human cancers and serves as a major prognostic indicator for disease progression. However, little is known about the mechanisms how tumor cells gain entry into the lymphatic system. In this respect, we have previously shown that tumors can actively induce the formation of lymphatic vessels (leading to the new concept of tumor lymphangiogenesis), thereby enhancing lymph node metastasis. Recently, we found that the extent of lymphatic vessel growth in primary human cutaneous melanomas was the most sensitive parameter for predicting whether these tumors had already metastasized to the sentinel lymph node at the time of surgery.

Moreover, we have recently found - for the first time - that metastatic tumor cells can induce lymphangiogenesis within lymph nodes. This has led to the new concept of lymph node lymphangiogenesis. Surprisingly, tumor cells can induce lymph node lymphangiogenesis already before they metastasize, giving a new twist to the seed-and-soil hypothesis and suggesting that tumors can prepare lymph nodes for their future arrival. Using a skin carcinogenesis model in VEGF-C transgenic mice, we have demonstrated that tumor-induced sentinel lymph node lymphangiogenesis even promotes cancer metastasis to distant lymph nodes and beyond. Using transcriptomic, proteomic and chemical genetics screening approaches, as well as stem cell differentiation assays and laser capture microdissection, we have identified a number of novel pathways involved in lymphatic formation and function. Several of these targets are currently evaluated for the therapeutic/diagnostic potential. Importantly, we found that distinct polymorphisms of the VEGFR3 gene - resulting in enhanced production of this lymphangiogenic receptor - lead to increased genetic susceptibility towards metastasis in human melanoma patients. Taken together, tumor lymphangiogenesis has not only emerged as a novel prognostic parameter for the metastatic risk of human cancers, but inhibition of tumor-associated lymphangiogenesis appears to represent a potential new strategy to inhibit tumor progression.