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ESDN Expression in the Tumor Microenvironment Coordinates Melanoma Progression

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Abstract : Malignant melanoma is currently the fifth most common cancer in the white population and it is fatal in its metastatic stage. Several research studies in recent years have provided evidence that cancer initiation and progression are driven by genetic alterations of the tumor and paracrine interactions between tumor and microenvironment. Scattered data show that the Endothelial and Smooth muscle cell-Derived Neuropilin-like molecule (ESDN) controls cell proliferation and movement of stroma and tumor cells. To investigate the role of ESDN in the tumor microenvironment during melanoma progression, murine melanoma cells (B16 or B16-F10) were injected in ESDN knockout mice in order to evaluate how the absence of ESDN in stromal cells could influence melanoma progression. While no effect was found on primary tumor growth, increased cell extravasation and lung metastasis formation was observed in ESDN knockout mice compared to wild type controls. In order to understand how cancer cells cross the endothelial barrier during metastatic dissemination in an ESDN-null microenvironment, structure, and permeability of lung blood vessels were analyzed. Interestingly, ESDN knockout mice showed structurally altered and more permeable vessels compared to wild type animals. Since cell surface molecules mediate the process of tumor cell extravasation, the expression of a panel of extravasation-related ligands and receptors was analyzed. Importantly, modulations of N-cadherin, E-selectin, ICAM-1 and VAP-1 were observed in ESDN knockout endothelial cells, suggesting the presence of a favorable tumor microenvironment which facilitates melanoma cell extravasation and metastasis formation in the absence of ESDN. Furthermore, a potential contribution of immune cells in tumor dissemination was investigated. An increased recruitment of macrophages in the lungs of ESDN knockout mice carrying subcutaneous B16-F10 tumors was found. In conclusion, our data suggest a functional role of ESDN in the tumor microenvironment during melanoma progression and the identification of the mechanisms that regulate tumor cell extravasation could lead to the development of new therapies to reduce metastasis formation.

Keywords : melanoma, tumor microenvironment, extravasation, cell surface molecules
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