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RESEARCH ARTICLE

Primo Vascular System of Murine Melanoma and Heterogeneity of Tissue Oxygenation of the Melanoma

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Abstract
Murine melanoma requires the complex development of lymphatic, vascular, and non-vascular structures. A possible relationship between the primo vascular system (PVS) and the melanoma metastasis has been proposed. In particular, the PVS may be involved in oxygen transport. Vasculogenic-like networks, similar to the PVS, have been found within melanoma tumors, but their functional relationship with the PVS and meridian structures are unclear. Herein, we report on the use of an electrochemical O_2 sensor to study oxygenation levels of melanoma tumors in mice. We consistently found higher tissue oxygenation in specific sites of tumors ($n = 5$). These sites were strongly associated with vascular structures or the PVS. Furthermore, the PVS on the tumor surface was associated with adipose tissue. Our findings suggest that the PVS is involved in the regulation of metastasis.

1. Introduction

A study by Soh et al (2009) [1] suggested that a primo vascular system (PVS) is well developed in lung cancer tumors and may serve as a pathway for cancer metastasis. A similar vasculogenic-like network composed of undifferentiated melanoma cells, known as vasculogenic mimicry [2], has been extensively studied. Although the relationship between the PVS and vascular mimicry is unclear, the importance of non-lymphatic and non-vascular systems in cancer development and treatment has been acknowledged. Soh et al [1] suggested that the PVS may play an important role in transporting materials within the body, possibly serving as a conduit for oxygen transport.

Higher tissue oxygenation has been associated with acupoints on the human hand [3], suggesting that acupuncture meridians have higher metabolic demands. Metabolic demands and hemodynamic signals are strongly correlated [4,5]. In particular, changes of neuronal activation during brain signal processing induce vasodilation, which increases in blood flow tissue oxygenation to the area (i.e., neurovascular coupling). A recent study provided evidence for the

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role nitric oxide release in regulating hemodynamics and tissue oxygenation of the activated brain area using a dual electrochemical sensor able to monitor real-time changes in hemodynamic signals *in vivo* [4].

Cancer involves uncontrolled cell division, which increases metabolic demands. Therefore, perfusion-based *in vivo* imaging techniques such as positron emission tomography and single photon emission tomography are used in cancer diagnosis and treatment. However, these conventional imaging techniques have low spatial and temporal resolution, which may result in a low rate of detection of early cancers. The ability to monitor the hemodynamic changes in cancer tissues may thus improve diagnosis and treatment.

In this study, we characterized the PVS associated with tumors in a mouse model of melanoma by immunocytochemistry. In addition, and tissue oxygenation in melanoma tissues was measured using an electrochemical oxygen sensor to assess the role of the PVS in oxygen transport.

2. Materials and Methods

2.1. Induction of murine melanoma cancer

To generate the mouse model of melanoma, B16BL6 murine melanoma cells (MD Anderson Cancer Center) were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin. Cells were incubated at 37°C in a humidified atmosphere containing 5% CO_2.

Male C57BL6 mice (4 weeks old, 15—20 g, $n = 5$) were used in this study (Orient Bio Inc). All procedures involving the animals, their care, and surgical procedures followed the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1996). The animals were acclimated at 25°C in a 12-hour light-dark cycle. After a 1-week adjustment period, the B16BL6 cells (1×10^6 cells/100 μl DMEM) were transplanted into the abdomen area.

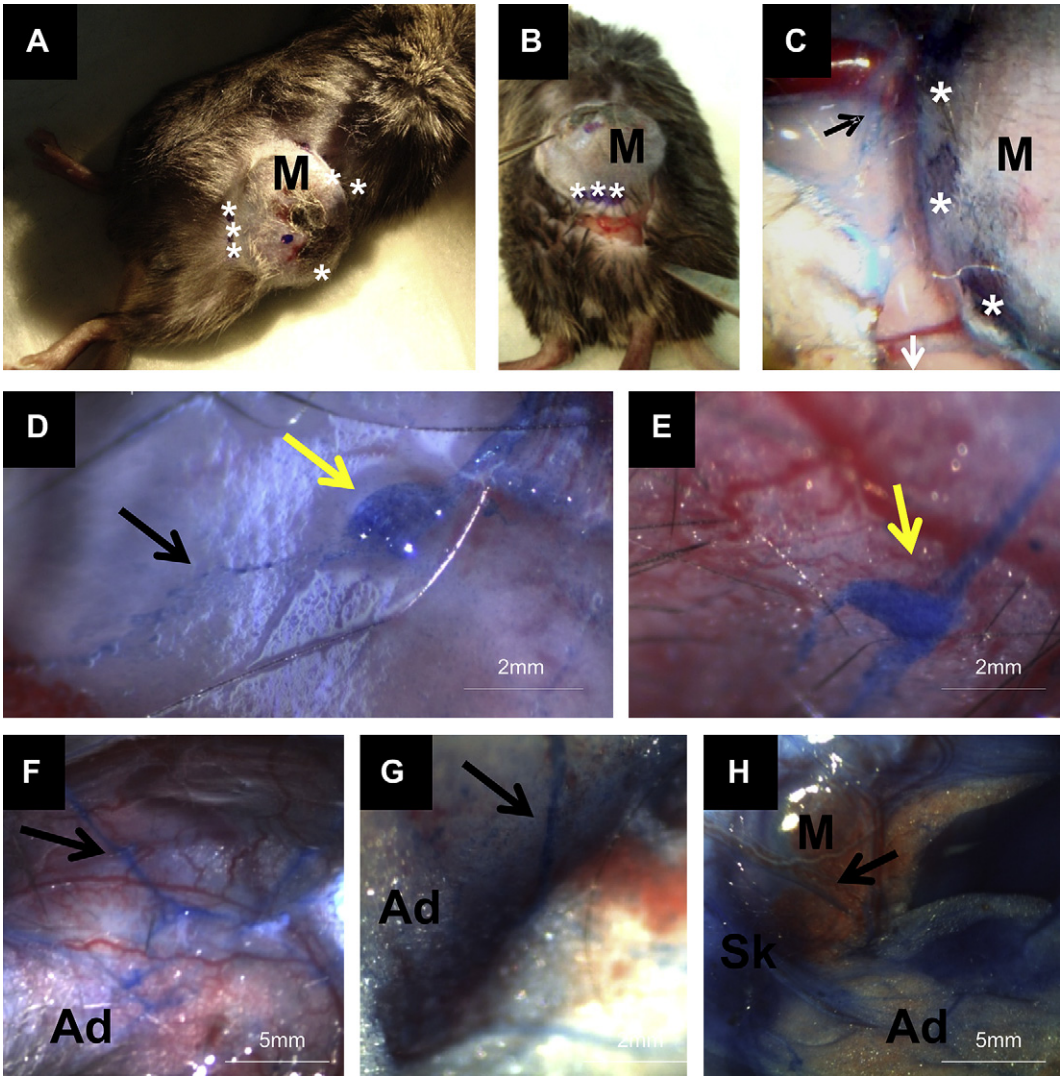

Figure 1 Primo vascular system of a melanoma tumor. (A, B) Tumors in a mouse model of melanoma. White asterisks indicate oxygen sensor measurement points. (C) The primo vascular system is associated with a blood vessel. (D, E) A primo node (yellow arrow) and primo vessel (black arrow) of the primo vascular system. (F, G) Adipose tissue is associated with the primo vascular system on the surface of the tumor. (H) Adipose tissue recruited to the injection site. Ad = adipose tissue, M = melanoma and Sk = skin.