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## Stem Cells and Development

### Hematopoietic Stem Cell–Derived Pericytic Cells in Brain Tumor Angio-Architecture

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**Bone marrow-derived cells are recruited into tumor vasculature in response to angiogenic signals, and some of the cells within the newly forming tumor vessels are hematopoietic stem cells (HSCs) in origin. Previous studies suggest that bone marrow-derived pericytes are associated with newly formed vessels in tumors. In this study, we used an orthotopic rat glioma model (RT-2/RAG) to examine the contribution of long-term hematopoietic stem cell (LT-HSC)-derived pericytic cells to brain tumor angiogenesis. Mice (RAG-2/KO5.2) were lethally irradiated, and their hematopoietic cells were repopulated by transplantation of double fluorescence-activated cell-sorted LT-HSCs that express green fluorescent protein (GFP<sup>+</sup>). RT-2/RAG cells were then injected into the striatum of the chimeric mice 6 weeks post-transplantation. The animals were sacrificed 9 days after tumor implantation, and the**

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incorporation and lineage-specific marker expression profile of the GFP<sup>+</sup> cells within the growing tumor and tumor periphery were analyzed. LT-HSC-derived GFP<sup>+</sup> cells were noted to incorporate onto the surface of tumor vessels within the perivascular space. LT-HSC-derived GFP<sup>+</sup> cells express the pericyte progenitor marker, platelet-derived growth factor receptor- $\beta$  (PDGFR $\beta$ ), as well as mature pericyte markers such as nerve/glial antigen 2 proteoglycan (NG2),  $\alpha$ -smooth muscle actin ( $\alpha$ SMA), and desmin. These LT-HSC-derived cells may represent a population of progenitor or committed pericytes within the neovascular tree and may play a role in shaping the angio-architecture in the vascular niche of brain tumors.

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## Hematopoietic Stem Cell-Derived Pericytic Cells in Brain Tumor Angio-Architecture

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### ABSTRACT

Bone marrow-derived cells are recruited into tumor vasculature in response to angiogenic signals, and some of the cells within the newly forming tumor vessels are hematopoietic stem cells (HSCs) in origin. Previous studies suggest that bone marrow-derived pericytes are associated with newly formed vessels in tumors. In this study, we used an orthotopic rat glioma model (RT-2/RAG) to examine the contribution of long-term hematopoietic stem cell (LT-HSC)-derived pericytic cells to brain tumor angiogenesis. Mice (RAG-2/KO5.2) were lethally irradiated, and their hematopoietic cells were repopulated by transplantation of double fluorescence-activated cell-sorted LT-HSCs that express green fluorescent protein (GFP<sup>+</sup>). RT-2/RAG cells were then injected into the striatum of the chimeric mice 6 weeks post-transplantation. The animals were sacrificed 9 days after tumor implantation, and the incorporation and lineage-specific marker expression profile of the GFP<sup>+</sup> cells within the growing tumor and tumor periphery were analyzed. LT-HSC-derived GFP<sup>+</sup> cells were noted to incorporate onto the surface of tumor vessels within the perivascular space. LT-HSC-derived GFP<sup>+</sup> cells express the pericyte progenitor marker, platelet-derived growth factor receptor- $\beta$  (PDGFR $\beta$ ), as well as mature pericyte markers such as nerve/glial antigen 2 proteoglycan (NG2),  $\alpha$ -smooth muscle actin ( $\alpha$ SMA), and desmin. These LT-HSC-derived cells may represent a population of progenitor or committed pericytes within the neovascular tree and may play a role in shaping the angio-architecture in the vascular niche of brain tumors.

### INTRODUCTION

**A**NGIOGENESIS IS A NECESSARY PROCESS that allows for an increase in blood flow to oxygen-deprived tumor cells [1]. Emerging data suggest that both endothelial and perivascular progenitor cells from the bone marrow are recruited to constitute and stabilize blood vessels in response to proangiogenic stimulation [2]. These blood vessels are composed of two interacting cell types: endothelial cells, which form the inner lining of the vessel

wall, and pericytic cells, also referred to as pericytes, which wrap around the vascular tube [3–6]. Endothelial progenitors are recruited from the bone marrow to contribute to the inner lining of angiogenic tumor vessels [7,8], whereas pericytes are recruited by platelet-derived growth factor (PDGF)-expressing endothelial cells to support and stabilize the outer lining of new vessels [4,9,10].

During pathological angiogenesis in tumors, pericytes display morphological and structural abnormalities [11].

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