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LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

Incorporation of endothelial progenitor cells into the neovasculature of malignant glioma xenograft

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Abstract Endothelial progenitor cells (EPCs) are important initiators of vasculogenesis in the process of tumor neovascularization. However, it is unclear how circulating EPCs contribute to the formation of tumor microvessels. In this study, we isolated $CD34^+/CD133^+$ cells from human umbilical cord blood (HUCB) and obtained EPCs with the capacities of forming colonies, uptaking acetylated low-density lipoprotein (ac-LDL), binding lectins and expressing vascular endothelial growth factor (VEGF) receptor 2 (VEGFR-2, KDR), CD31 and von Willebrand factor (vWF). These EPCs were actively proliferative and migratory, and could formed capillary-like tubules in response to VEGF. When injected into mice bearing subcutaneously implanted human malignant glioma, EPCs specifically accumulated at the sites of tumors and differentiated into mature endothelial cells (ECs), which accounted for 18% ECs of the tumor microvessels. The incorporation of circulating EPCs into tumor vessel walls significantly affected the morphology and structure of the vasculature. Our results suggest that circulating EPCs constitute important components of tumor microvessel network and contribute to tumor microvascular architecture phenotype heterogeneity.

Keywords Endothelial progenitor cells · Glioma · Angiogenesis · Vasculogenesis

Introduction

The growth and progression of solid tumors are dependent on newly-formed microvessels, where niches for tumor cells as well as cancer stem cells exist [1–4]. Both angiogenesis and vasculogenesis contribute to tumor neovascularization, which provides oxygen and nutrients for tumor cell survival and proliferation [5–7]. Angiogenesis is a process of new capillary formation from pre-existing host blood vessels, while vasculogenesis is conducted by circulating endothelial progenitor cells (EPCs). However, it remains unclear whether and how vasculogenesis by EPCs incorporates into angiogenesis by sprouting pre-existing endothelial cells (ECs) in the process of neovascularization.

Tumor microvessls are structurally diverse, which forms the basis for tumor microvascular architecture phenotype heterogeneity (T-MAPH) [8] and differential potential targets for anti-cancer therapy. Unfortunately, the existing antiangiogenic agents have not shown consistently effective tumor suppression in clinical trials [9–11]. This raises the possibility that the complexity of T-MAPH needs to be taken into consideration because T-MAPH may consist of ECs derived from different sources such as from existing host vessels and circulating precursors in the blood.

In this study, we examined the possible incorporation of EPCs in host circulation into glioma neovascularization.

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