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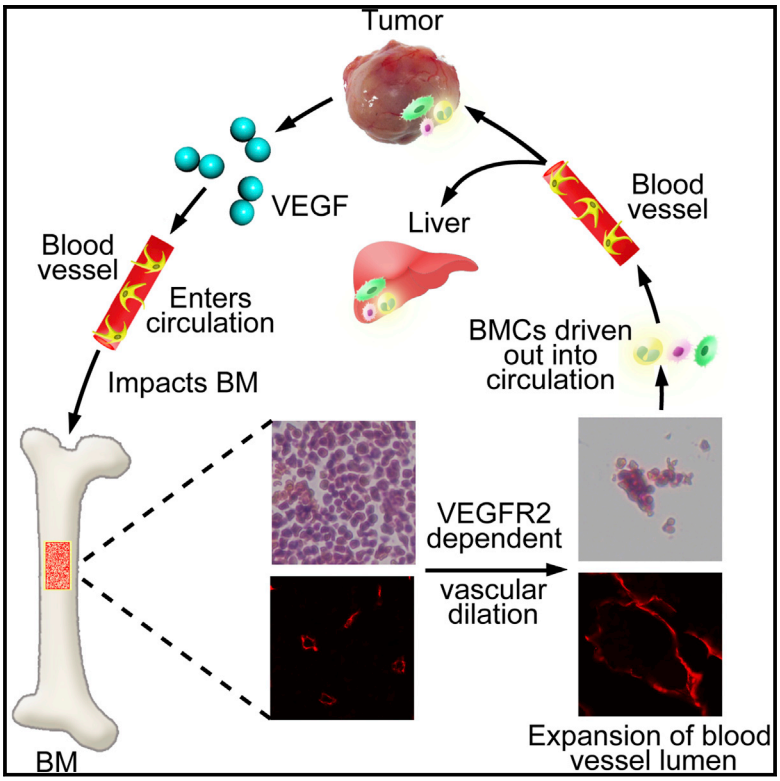
VEGFR2-Mediated Vascular Dilation as a Mechanism of VEGF-Induced Anemia and Bone Marrow Cell Mobilization

Graphical Abstract



Highlights

Tumor-derived VEGF induces BMC mobilization and vascular dilation

BMC mobilization and vessel dilation is VEGFR2 dependent

Genetic inactivation of VEGFR1 does not affect VEGF-induced BMC mobilization

Endothelial deletion of *Vegfr2* abrogates VEGF-induced BMC mobilization

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In Brief

Cancer patients often suffer from cancer cachexia and paraneoplastic syndrome, which significantly impair survival and the quality of life. Here, Lim et al. report that tumor-derived VEGF induces anemia in mice through the mechanism of vessel dilation in bone marrow. The VEGF-VEGFR2-triggered vascular dilation in bone marrow leads to mobilization of bone marrow cells to peripheral tissues and organs. These findings suggest a therapeutic option for treatment of cancer anemia by targeting VEGF-VEGFR2 signaling.

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VEGFR2-Mediated Vascular Dilation as a Mechanism of VEGF-Induced Anemia and Bone Marrow Cell Mobilization

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SUMMARY

Molecular mechanisms underlying tumor VEGF-induced host anemia and bone marrow cell (BMC) mobilization remain unknown. Here, we report that tumor VEGF markedly induced sinusoidal vasculature dilation in bone marrow (BM) and BMC mobilization to tumors and peripheral tissues in mouse and human tumor models. Unexpectedly, anti-VEGFR2, but not anti-VEGFR1, treatment completely blocked VEGF-induced anemia and BMC mobilization. Genetic deletion of *Vegfr2* in endothelial cells markedly ablated VEGF-stimulated BMC mobilization. Conversely, deletion of the tyrosine kinase domain from *Vegfr1* gene ($Vegfr1^{TK-/-}$) did not affect VEGF-induced BMC mobilization. Analysis of $VEGFR1^{+}$/$VEGFR2^{+}$ populations in peripheral blood and BM showed no significant ratio difference between VEGF- and control tumor-bearing animals. These findings demonstrate that vascular dilation through the VEGFR2 signaling is the mechanism underlying VEGF-induced BM mobilization and anemia. Thus, our data provide mechanistic insights on VEGF-induced BMC mobilization in tumors and have therapeutic implications by targeting VEGFR2 for cancer therapy.

INTRODUCTION

In the tumor microenvironment, tumor cells together with other host cellular components including inflammatory cells, stromal fibroblasts, and vascular cells collectively contribute to tumor development, progression, invasion, and metastasis (Hanahan and Weinberg, 2011). Malignant cells and the tumor-infiltrated host cells reciprocally interact with each other. This complex and intimate crosstalk is accomplished through various growth factors, cytokines, and cell-cell interactions. Genetic and epigenetic alterations, as well as microenvironmental changes, often lead to production of various growth factors and cytokines at high levels. Vascular endothelial growth factor (VEGF) is one of the most frequently highly expressed angiogenic factors found in various tumor tissues (Jubb et al., 2004), and its expression level can be further elevated by tissue hypoxia that often exists in solid tumor (Makino et al., 2001). Although VEGF is described as one of the relatively specific endothelial growth factors, it displays broad biological functions by targeting other cell types, including tumor, perivascular, hematopoietic, inflammatory, and neuronal cells (Cao, 2014; Ferrara et al., 2003). These broad tissue effects are determined by the specific distribution of VEGFRs on particular cell types.

VEGF displays its biological functions by activation of its receptors, and it is generally believed that VEGFR2, a cell-surface tyrosine kinase receptor, is the functional receptor that mediates VEGF-induced angiogenesis, vascular permeability, and vascular remodeling (Ferrara et al., 2003; Senger et al., 1983). Conversely, biological functions of VEGFR1-mediated signals remain largely unknown, and it has been suggested that VEGFR1 mediates negative signals that counteract VEGF-induced angiogenesis (Cao, 2009). Based on its relatively broad distribution in various cell types, some of the VEGF-induced non-endothelial activity has been associated with the VEGFR1-signaling system. For example, VEGFR1 is expressed in macrophages and hematopoietic progenitor cells and has been reported to be involved in recruiting these cells to the tumor microenvironment (Cao, 2009). Once these hematopoietic progenitor and inflammatory cells are recruited to the tumor microenvironment, they significantly contribute to tumor

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