A growing body of evidence suggests that circulating progenitors participate in vascular healing and remodeling under physiological and pathological conditions (Figure). It is believed that the majority of vascular progenitor cells originate from the bone marrow. Stem cells within the bone marrow usually exist in a quiescent state. Specific signals stimulate the stem cells to differentiate and move to systemic circulation (Mobilization). Progenitors are recruited and stay at the site of vascular repair or neovascularization (Homing), where they differentiate into endothelial-like cells or smooth muscle–like cells (Differentiation) and proliferate (Proliferation). The molecular processes leading to their mobilization from the bone marrow and homing to the sites of vascular remodeling or neovascularization are not fully understood.

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CXCR4, a Key Modulator of Vascular Progenitor Cells

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CXCR4+ cells in the neointima layer. M-CSF treatment significantly increased the number of CXCR4+ cells among peripheral blood mononuclear cells (MNCs) in vivo. Although M-CSF increased the number of CXCR4+ cells, incubation of isolated peripheral blood MNCs with M-CSF in vitro did not enhance CXCR4 expression. These results suggest other factors are required to activate and mobilize CXCR4+ BM-derived cells in vivo. Of interest, M-CSF incubation induced a significant increase of Mac-1 expression on isolated peripheral blood MNCs in vitro. Peripheral CXCR4+ cells which were increased by M-CSF treatment in vivo contained Mac-1+ cells, suggesting that Mac-1–mediated signaling is involved in activation and/or mobilization of CXCR4+ cells by M-CSF.

Moreover, Shiba et al report that AMD3100, a CXCR4 antagonist, significantly attenuated neointima formation by diminishing CXCR4+ cell incorporation, suggesting that CXCR4 plays an important role in M-CSF–stimulated BM-derived cell engraftment into the injured vascular wall. Hence CXCR4+ BM-derived cells could have detrimental effects in particular settings of vascular injury by incorporating into neointima and enhancing hyperplasia. The authors propose that inhibition of SDF-1–CXCR4 system may have therapeutic potential for the treatment of cardiovascular diseases.

In contrast to the proposal by Shiba et al, Walter et al suggest that stimulation and/or sensitization of CXCR4–mediated signaling may be applied for patients with cardiovascular diseases. Numerous reports suggest that BM-derived endothelial progenitor cells (EPCs) participate in angiogenesis either by incorporating into the neovascularure or by secreting proangiogenic factors. Walter et al demonstrated that pre-treatment of patient-derived endothelial progenitor cells (EPCs) with sphingosine-1-phosphate (SIP) activated CXCR4 and enhanced neovascularization when transplanted into ischemic hindlimb of nude mice. It was suggested that CXCR4 activation on EPCs could play a beneficial role in ischemic tissues by improving the function of EPCs from patients. Consistent with this notion, blockade of CXCR4 by either monoclonal antibody or AMD3100 partially inhibited blood flow recovery of ischemic hindlimb or VEGF-mediated incremental revascularization.

As a strategy to activate CXCR4, the authors targeted a G protein–coupled 7-transmembrane receptor, S1P3 receptor. S1P3 receptor was previously described to be expressed on hematopoietic progenitor/stem cell surface. Its ligand S1P is a bioactive lipid known to enhance SDF-1–stimulated hematopoietic progenitor homing, as well as endothelial cell migration and proliferation.

Moreover, activation of S1P receptors by FTY720, a synthetic analog of S1P, increased CXCR4 function in
hematopoietic progenitor cells both in vitro and in vivo, supporting thereby their homing and proliferation.\(^\text{24}\)\(^\text{24}\) Walter et al herein show that incubation of patient-derived EPCs with S1P or FTY720 induced CXCR4 phosphorylation and improved their function. The activation of the CXCR4 signaling by S1P was mediated via the S1P3 receptor with phosphorylation of Src and JAK2. Interestingly, other G protein–coupled receptors, such as PAR-1, the main thrombin receptor on vascular cells, have been reported to activate CXCR4. Specific activation of PAR-1 on EPCs by a peptide SFLLRN conferred proangiogenic properties to EPCs via SDF-1/CXCR-4 pathway.\(^\text{25}\)\(^\text{25}\) These results indicate that stimulation or sensitization of CXCR4 on EPCs or BM cells has therapeutic effect to improve collateral formation in patients with coronary artery diseases.

In summary, works by Shiba et al\(^\text{6}\) and Walter et al\(^\text{7}\) underline the pivotal role of CXCR4 in regulating BM-derived cell engraftment and function in vascular remodeling and neovascularization. Both studies provide evidence that new strategies other than direct stimulation by its natural ligand SDF-1 could be used to stimulate CXCR4 and to promote activation/mobilization of BM-derived cells. However, it should be kept in mind that CXCR4 is also expressed by non-hematopoietic stem cells and epithelial cancer cells,\(^\text{26}\)\(^\text{26}\) before proceeding to systemic administration of such factors and/or drugs targeting CXCR4. Therefore, understanding the molecular mechanisms regulating CXCR4 expression and activation in various CXCR4-positive cells would be necessary to develop therapeutic strategies targeting CXCR4 to treat patients with cardiovascular diseases.

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Disclosures
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