Vascular precursor cells in tissue injury repair

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Vascular precursor cells include stem cells and progenitor cells giving rise to all mature cell types in the wall of blood vessels. When tissue injury occurs, local hypoxia and inflammation result in the generation of vasculogenic mediators which orchestrate migration of vascular precursor cells from their niche environment to the site of tissue injury. The intricate crosstalk among signaling pathways coordinates vascular precursor cell proliferation and differentiation during neovascularization. Establishment of normal blood perfusion plays an essential role in the effective repair of the injured tissue. In recent years, studies on molecular mechanisms underlying the regulation of vascular precursor cell function have achieved substantial progress, which promotes exploration of vascular precursor cell–based approaches to treat chronic wounds and ischemic diseases in vital organ systems. Verification of safety and establishment of specific guidelines for the clinical application of vascular precursor cell–based therapy remain major challenges in the field. (Translational Research 2017;184:77–100)

Abbreviations: 7AAD = 7-aminoactinomycin D; αSMA = alpha smooth muscle actin; AKT = protein kinase B; ALK = activin receptor-like kinase; Ang = angiopoietin; Ang II = angiotensin II; BCRP1 = breakpoint cluster region pseudogene; bFGF = basic fibroblast growth factor; C1P = ceramide-1-phosphate; CA12 = carbonic anhydrase 12; CAC = circulating angiogenic cell; CAR = SDF-1–abundant reticular; CCR = CC receptor; CD = clusters of differentiation; CEACAM1 = carcinoembryonic antigen-related cell adhesion molecule 1; CEP = circulating endothelial precursor; c-kit = stem cell growth factor receptor; CLF = chemokine-like function; CPM = carboxypeptidase M; CSPG4 = chondroitin sulfate proteoglycan 4; CXCL12 = CXC motif chemokine 12; CXCL16 = CXC motif chemokine 16; CXCR = CXC receptor; DAMP = damage-associated molecular pattern ligand; DR3 = death domain–containing receptor 3; ECFC = endothelial colony-forming cell; eGFP = enhanced green fluorescent protein; EnMT = endothelial-to-mesenchymal transdifferentiation; eNOS = nitric oxide synthase; EPC = endothelial progenitor cell; ERK1/2 = extracellular-signal-regulated kinases 1/2; ESC = embryonic stem cell; FGF = fibroblast growth factor; Flk1 = fms-like tyrosine kinase-1; Flt3L = Flt3 ligand; G-CSF = granulocyte colony-stimulating factor; GFP = green-fluorescent protein; GM-CSF = granulocyte-macrophage colony-stimulating factor; GRO = human growth-regulated oncogene; HAEC = human aortic endothelial cell; HIF = hypoxia-inducible transcription factor; HLA-DR = human leukocyte antigen-antigen D related; HRE = hypoxia-response element; HSC = hematopoietic stem cell; HUVEC = human umbilical vein endothelial cell; ICAM-1 = intercellular adhesion molecule-1; IFNγ = interferon-gamma; IGF-1 = insulin-like growth factor-1; IL-1α = interleukin-1 alpha; IL-1β = interleukin-1 beta; IL-1R = interleukin-1 receptor; IL-3

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= interleukin-3; IL-6 = interleukin-6; IL-6R = interleukin-6 receptor; IL-8 = interleukin-8; IL-10 = interleukin-10; IL-18 = interleukin-18; Jmjd6 = Jumonji domain–containing protein 6; KC = keratinocyte chemoattractant; KDR = kinase insert domain receptor; KGF = keratinocyte growth factor; kitL = kit ligand; LacZ = β-galactosidase; Lin = lineage; LRP1 = low-density lipoprotein receptor–related protein; MAPK = mitogen-activated protein kinase; MCP-1 = monocyte chemoattractant protein-1; M-CSF = macrophage colony-stimulating factor; MIF = macrophage migration inhibitory factor; MMP-2 = matrixmetalloproteinase-2; MMP-9 = matrixmetalloproteinase-9; MSC = mesenchymal stem cell; NAP-2 = neutrophil-activating peptide-2; NG2 = neural/glial antigen 2; Notch1 = Notch homolog 1; OCT4 = octamer-binding transcription factor 4; PAMP = pathogen-associated molecular pattern ligand; PBMC = peripheral blood mononuclear cell; PCG = polycaprolactone-gelatin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; PEDF = pigment epithelium–derived factor; PGE2 = prostaglandin E2; PGF = placenta growth factor; PI3K = phosphatidylinositol-3 kinase; PKC = protein kinase C; PKD = protein kinase D; PLC-γ = phospholipase C-gamma; PRR = pattern recognition receptors; RAMP1 = receptor activity-modifying protein 1; RGS5 = regulator G-protein signaling 5; S1P = sphingosine-1-phosphate; Sca1 = stem cell antigen-1; SCF = stem cell growth factor; SDF-1 = stromal cell-derived factor-1; SLE = systemic lupus erythematosus; SM = smooth muscle; SM-22α = smooth muscle-22α; SMC = smooth muscle cell; SMemb = embryonic form smooth muscle myosin heavy chain; SMPC = smooth muscle progenitor cell; SP = side population; SPC = stem/progenitor cell; STAT = signal transducer and activator of transcription; TβR = transforming growth factor beta receptor; TGF-β = transforming growth factor-beta; TIE2 = receptor for angiopoietin; TNF = tumor necrosis factor; TNFSF15 = Tumor necrosis factor superfamily 15; UEA1 = *Ulex europaeus* agglutinin-1; VCAM-1 = vascular cell adhesion molecule-1; VEGF = vascular endothelial growth factor; VEGFR-1 = vascular endothelial growth factor receptor-1; VEGFR-2 = vascular endothelial growth factor receptor-2; VEGI = vascular endothelial growth inhibitor; vWF = von Willebrand factor

INTRODUCTION

Re-establishment of blood circulation is essential for repair of tissue injury. Tissue vascularization commonly involves vasculogenesis, angiogenesis, and arteriogenesis. Vasculogenesis is the formation of new blood vessels from vascular precursor cells. Angiogenesis is the process of outgrowing vessels from the existing vasculature. Arteriogenesis involves remodeling of arteries where collateral arterial anastomoses undergo abluminal expansion. Cell composition in blood vessels is highly heterogeneous and dynamic. Endothelial cells assemble in a monolayer lining the inner surface of all blood vessels. Pericytes are cell components of the microvasculature, including capillaries, arterioles, and venules. In addition to these cells, large blood vessels have many other cell types such as smooth muscle cells (SMCs), fibroblasts, master cells, dendritic cells, and macrophages.

Since the discovery of unique cell subpopulations with the functional similarity to embryonic angioblasts in the peripheral blood of adults,[1,2] vascular precursor cells have drawn a broad attention for their role in repair of the blood vasculature. At the site of tissue injury, hypoxia and inflammation result in an increase in the local production of bioactive mediators which function as chemoattractants and/or activators. These mediators orchestrate the migration of vascular precursor cells from their niche environment to the site of tissue injury. Proliferation and differentiation of vascular precursor cells, particularly endothelial progenitor cells (EPCs), contribute to the formation of new blood vessel islets. The initially formed vascular cores via vasculogenesis are pruned and extended by angiogenesis. Maturation of the blood vasculature can be subsequently achieved through remodeling processes with the participation of different vascular precursor cell types, such as mesenchymal stem cells (MSCs) and smooth muscle progenitor cells (SMPCs) (Fig 1 sketches the involvement of vascular precursor cells in neovascularization during the process of tissue injury repair). This review discusses the recent progress in characterization of vascular precursor cells and highlights signaling mechanisms underlying the regulation of their function in promoting neovascularization during the process of tissue injury repair. Efforts in exploring the application of vascular precursor cells for the treatment of tissue injury are also addressed.

VASCULAR PRECURSOR CELLS

Vascular precursor cells denote stem and progenitor cells that give rise to mature cell types in the wall of blood vessels, including endothelial cells, SMCs, and fibroblasts. The existence of circulating EPCs in adults was initially reported by Asahara et al. in 1997.[1] In their