Endoglin Has a Crucial Role in Blood Cell–Mediated Vascular Repair

Linda W. van Laake, MD*; Sander van den Driesche, PhD*; Simone Post, MD; Alie Feijen, MS; Maurits A. Jansen, PhD; Mariette H. Driessens, PhD; Johannes J. Mager, MD; Repke J. Snijder, MD; Cornelius J.J. Westermann, MD, PhD; Pieter A. Doevendans, MD, PhD; Cees J.A. van Echteld, PhD; Peter ten Dijke, PhD; Helen M. Arthur, PhD; Marie-José Goumans, PhD; Franck Lebrin, PhD†; Christine L. Mummery, PhD†

Background—Endoglin, an accessory receptor for transforming growth factor-β in vascular endothelial cells, is essential for angiogenesis during mouse development. Mutations in the human gene cause hereditary hemorrhagic telangiectasia type 1 (HHT1), a disease characterized by vascular malformations that increase with age. Although haploinsufficiency is the underlying cause of the disease, HHT1 individuals show great heterogeneity in age of onset, clinical manifestations, and severity.

Methods and Results—In situ hybridization and immunohistochemical analysis of mouse and human hearts revealed that endoglin is upregulated in neoangiogenic vessels formed after myocardial infarction. Microvasculature within the infarct zone was strikingly lower in mice with reduced levels of endoglin (Eng<sup>−/−</sup>) compared with wild-type mice, which resulted in a greater deterioration in cardiac function as measured by magnetic resonance imaging. This did not appear to be because of defects in host inflammatory cell numbers in the infarct zone, which accumulated to a similar extent in wild-type and heterozygous mice. However, defects in vessels formation and heart function in Eng<sup>−/−</sup> mice were rescued by injection of mononuclear cells from healthy human donors but not by mononuclear cells from HHT1 patients.

Conclusions—These results establish defective vascular repair as a significant component of the origin of HHT1. Because vascular damage or inflammation occurs randomly, it may also explain disease heterogeneity. More generally, the efficiency of vascular repair may vary between individuals because of intrinsic differences in their mononuclear cells.

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Key Words: angiogenesis  ■ genetics  ■ magnetic resonance imaging  ■ myocardial infarction  ■ vessels

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evascularization of injured, ischemic and regenerating organs is essential to restore organ function. Neovascularization resulting from the proliferation, migration, and remodeling of terminally differentiated endothelial cells (ECs) from preexisting blood vessels is called angiogenesis. Evidence suggests that mononuclear cells (MNCs), which include endothelial progenitor cells, circulating ECs, and bone marrow mononuclear lineages, home to sites of ischemic damage and contribute to new blood vessel formation through vasculogenesis, transdifferentiation into ECs, and secretion of cytokines that stimulate neoangiogenesis.

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Hereditary hemorrhagic telangiectasia (HHT; or Rendu-Osler-Weber syndrome) is an autosomal-dominant disorder with low prevalence, estimated to be 1 in 10 000. It is characterized by epistaxis, telangiectases, and multiorgan vascular dysplasia. Two variants of HHT, HHT1 and HHT2, have been linked to mutations in the ENG (endoglin) and ACVRL1 (activin receptor-like kinase 1 or ALK1) genes, respectively, although recently, 2 more genes have been implicated. Endoglin is highly expressed by active ECs...
from most blood vessels. Deletion of endoglin in mice revealed its critical role during cardiovascular development. Mutant endoglin (Eng<sup>−/−</sup>) mice die at embryonic day 10.5 as a result of defects in vessel and heart development. Vasculogenesis in the Eng<sup>−/−</sup> mice is normal but angiogenesis is impaired, along with the remodeling of the primary vascular plexus. Endoglin is an accessory receptor for transforming growth factor-β (TGF-β), a cytokine controlling proliferation, migration, adhesion, and apoptosis of many cell types. The activated form of TGF-β binds to type II receptors (TβRⅡs), which recruit TGF-β type I serine/threonine kinase receptors to the complex and propagate signals to the nucleus by phosphorylating intracellular effectors called Smads. Two type I receptors mediate TGF-β signaling: ALK1, expressed mainly in endothelium, and ALK5, expressed widely in most cell types. In ECs, TGF-β/ALK5 signaling via Smad2/3 leads to inhibition of cell signaling: ALK1, expressed mainly in endothelium, and ALK5, expressed widely in most cell types. In ECs, TGF-β/ALK5 signaling via Smad2/3 leads to inhibition of cell migration and proliferation, whereas TGF-β/ALK1 signaling via Smad1/5/8 promotes cell migration and proliferation.

Several studies have implied haploinsufficiency as the mechanism responsible for HHT and indicated that disease heterogeneity is not related to the position or type of mutation; all mutations in the ENG gene result in reduced functional cell surface protein and deregulation of TGF-β signaling pathways. Individuals with HHT1 show great variability in age of disease onset, clinical manifestations, and severity, however, both within and between families with the same mutation. In addition, epigenetic factors, including exposure to ultraviolet light and local inflammation, have been implied as contributing to its diversity, suggesting that HHT is a complex genetic disorder.

Here, we used experimental myocardial infarction (MI) in wild-type and endoglin-heterozygous mice to investigate the effects of the HHT1 mutation on angiogenesis and vasculogenesis that are integral components of the remodeling after MI. Thus, experimental MI represents a useful model for studying these processes in normal and mutant adult mice. In addition, because cardiac biopsies are available from adult humans after MI, there are opportunities to translate the findings in mice to human disease.

**Methods**

**Mice and Coronary Artery Ligation**

Endoglin mice contain a β-galactosidase reporter cassette in the disrupted locus. Analyses were carried out on wild-type (Eng<sup>−/−</sup>) and endoglin-heterozygous transgenic mice (Eng<sup>+/−</sup> ) from a C57Bl/6J genetic background. Balb/c mice also were used for injection of human MNCs via the tail vein. MI was induced as described. Briefly, adult mice bred in our laboratory (Hubrecht Laboratorium, Utrecht, The Netherlands; 20 to 35 g) were intubated and ventilated with 2% isoflurane/98% oxygen. The left coronary artery was exposed via a left thoracotomy and opening of the pericardium and occluded just below the inferior border of the left auricle with a 7-0 prolene ligature. Sham-operated mice underwent similar operations without coronary artery ligation. Animal experiments were approved by the Animal Care Committee.

**Isolation, Culture, and Injection of Human MNCs**

Blood samples from healthy human volunteers or HHT1 patients were collected in potassium/ethylenediaminetetraacetic acid tubes (Monovette, Sarstedt, Nümbrecht, Germany). MNCs were isolated by density gradient centrifugation with histopaque-1077 (Sigma-Aldrich, St Louis, Mo) following the manufacturer’s protocol and washed twice with phosphate-buffered saline (PBS) containing 2 mmol/L ethylenediaminetetraacetic acid. Cells (10×10<sup>6</sup>) were plated in fibronectin-coated plates and cultured in EGM2 (Clonetics, Cambrex, East Rutherford, NJ) with 20% fetal calf serum and incubated in 5% CO<sub>2</sub> at 37°C. Patient procedures were approved by the Medical Ethics Committee at St Antonius Hospital. The investigation conformed to principles in the Declaration of Helsinki.

For MNC injection, mice underwent MI as above, received 5×10<sup>6</sup> human MNCs in 40 μL PBS via a tail vein injection 1 to 3 hours later, and were immunosuppressed with tacrolimus (5 mg · kg<sup>−1</sup>· d<sup>−1</sup>) subcutaneously. Mice were divided randomly into groups for follow-up at 4, 7, 14, or 30 days to assess homing of human MNCs to the infarct area, angiogenesis, and cardiac function.

**Analyses of Myocardial Function by Magnetic Resonance Imaging**

Cardiac- and respiratory-triggered cine magnetic resonance images were acquired on a 9.4-T scanner (Bruker Biospin GmbH, Rheinstetten, Germany) using a birdcage radiofrequency coil. A gradient-echo pulse sequence was used to acquire data with a repetition time of 9.8 ms, an echo time of 1.9 ms, a matrix of 256×256, a field of view of 3.0×3.0 cm, a slice thickness of 1 mm, a flip angle 18°, and 4 signal averages. The number of phases was 11 to 13, depending on heart rate. Seven to 8 short-axis slices were needed to image the entire left ventricle. Images were processed with dedicated imaging software (CAAS-MRV, Pie Medical Imaging BV, Maastricht, the Netherlands).

**Isolation and Processing of Hearts**

The hearts were dissected from euthanized mice 7, 14, or 30 days after MI, fixed overnight in 4% paraformaldehyde in PBS, washed twice in 0.83% NaCl, and washed once each in 0.42% NaCl, 50% ethanol, and 70% ethanol, all overnight at 4°C. After paraffin embedding, hearts were sectioned (6 μm) onto coated slides (Klinipath, Duiven, the Netherlands) and stored at 4°C. For MNC homing experiments, hearts were isolated 4 days after MI and processed for cryosections as described. Human fetal hearts were collected after elective abortion and with informed consent as previously. Biopsies from adult human cardiac tissue were obtained from the Pathology Department after autopsy. Formalin-fixed samples were embedded in paraffin, and 6-μm sections were used for immunohistochemical analysis.

**RNA Isolation and Real-Time Reverse-Transcription Polymerase Chain Reaction**

Total RNA from dissected atria and ventricles was isolated using TRIzol Reagent (Invitrogen, Carlsbad, Calif) following manufacturer’s instructions. Samples were treated with DNase I to eliminate genomic DNA, and 1 μg RNA was reversed transcribed. Real-time polymerase chain reaction (PCR) was performed in an MxP single-color real-time detection system (Bio-Rad Laboratories, Hercules, Calif). Samples were normalized with glyceraldehyde phosphate dehydrogenase.

**Immunohistochemistry and Immunofluorescence on Sections**

Paraffin sections were stained with the tyramide signal amplification biotin system (Perkin Elmer, Life Science, Wellesley, Mass). Briefly, sections were treated with 0.25% trypsin in 9 mol/L CaCl<sub>2</sub>/50 mmol/L Tris-HCl, pH 7.8, for 30 minutes at room temperature for antigen retrieval. Primary antibodies were rat anti-mouse platelet endothelial cell adhesion molecule (PECAM) (Clone MEC13.3, dilution 1:100, BD Biosciences, San Jose, Calif), rat...
anti-mouse endoglin (Clone 2Q1707, dilution 1:100, USBiological, Swampcott, Mass), rat anti-mouse CD68/macrosialin (Clone FA-11, dilution 1:100, Serotec Ltd, Kidlington, Oxfordshire, UK), rat anti-mouse Mac-3 (Clone M3/40, dilution 1:100, BD Pharmingen, San Diego, Calif), and rat anti-CD45 (Clone 30F11.1, dilution 1:100, BD Pharmingen) incubated overnight at 4°C. Biotin-conjugated goat anti-rat IgG (1:250, Dako, Glostrup, Denmark) was used as a secondary antibody incubated for 1 hour at room temperature. Peroxidase activity was detected with 3,3′-diaminobenzidine tablet set (Fast DAB, Sigma) following manufacturer’s instructions.

Paraffin sections used for K67 immunohistochemistry were treated as described previously. Primary antibody was mouse anti-Ki67 (Clone MM1, dilution 1:500, Monosan, Uden, the Netherlands) incubated overnight at 4°C. Secondary antibody was goat anti-mouse PowerVision Poly-HRP-Conjugates (Immunovision Technologies, Springfield, Ark) incubated for 30 minutes at room temperature. Peroxidase activity was detected with 3,3′-diaminobenzidine tablet set (Fast DAB, Sigma) following manufacturer’s instructions. Sections were counterstained with hematoxylin, dehydrated, and mounted in Depex.

Cryosections of hearts containing human MNC-derived ECs were fixed in acetone for 10 minutes at 4°C, dried for 30 minutes at room temperature, permeabilized for 5 minutes with 0.2% Triton X-100 in PBS, and blocked with 2% bovine serum albumin in PBS at room temperature for 1 hour. Slides were then incubated with rat anti-mouse PECAM antibody (Clone MEC 13.3, dilution 1:100, BD Biosciences) overnight at 4°C, washed 4 times in PBS, and incubated 1 hour simultaneously with goat anti-rat Cy3 (Jackson ImmunoResearch Laboratories, West Grove, Pa) and Ulex europaeus agglutinin I (UEA-1) lectin coupled to fluorescein isothiocyanate (1:100 dilution from 1 mg/mL stock, Sigma) diluted in 2% bovine serum albumin in PBS. Cryosections of human fetal hearts were incubated with UEA-1 and with goat anti-human PECAM antibody (Clone M2-20, 1:100 dilution, Santa Cruz Biotechnology, Inc, Santa Cruz, Calif). The slides were then washed 4 times in PBS and mounted in Mowiol before confocal laser microscope analysis.

**In Situ Hybridization**

The endoglin probe was generated from a BamHI fragment (266 to 1039 bp) from full-length mouse endoglin (clone pCDNA1-7/18) cloned into Bluescript and linearized with Xmal. The antisense RNA probe was generated by transcription of the T7 RNA polymerase in the presence of [α-35S]-UTP (Amersham, Uppsala, Sweden). Autoradiography was performed with Ilford photo emulsion. The slides were exposed for 1 to 2 weeks at 4°C. Photography consisted of combining bright-field (blue filter) and dark-field (red filter) images.

**Statistical Analysis**

Statistical significance was evaluated with the Mann-Whitney U test for comparison between two groups and the median test for multiple group comparisons using SPSS version 11.5 for Windows. Results are expressed as median±interquartile range. A value of P<0.05 or P<0.01 denoted statistical significance.

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

We examined endoglin expression by in situ hybridization and immunohistochemistry in hearts of normal adult mice (Figure 1A through 1E) and 1 week after coronary artery ligation–induced MI (Figure 1F through 1I). Endoglin mRNA was expressed predominantly in the atria but was detectable at low levels in the ventricles of normal hearts (Figure 1B and 1C). One week after MI, expression was strongly increased in the infarcted area compared with healthy tissue in sham-operated hearts (Figure 1D and 1H). Staining of comparable sections from sham-operated and MI hearts with anti-PECAM and anti-endoglin antibodies 1 week postoperatively revealed overlapping protein expression, indicating that endoglin is expressed only in ECs in the infarct zone and not in myofibroblasts (Figure 1I), as previously described, or in vessels in the noninfarcted zone (Figure 1E). Neangiogenesis within the scar is an integral component of the remodeling process occurring after MI. To compare the prevalence of activated blood vessels in hearts from sham-operated mice, sections from healthy noninfarcted zones and corresponding infarcted zones of adult mice 1 week after MI were stained with antibodies against Ki67, a marker for cycling cells, PECAM, and endoglin. In both the sham-operated hearts and the noninfarcted zone 1 week after MI, 5% to 8% of blood vessels were Ki67+. In contrast, ~50% of blood vessels were Ki67+ in the infarct zone (Figure 2A). Staining of sections from biopsies of human hearts with MI taken from within and outside the infarct zone showed similar differences in the prevalence of activated vessels (Figure 2B).

Because our data indicated that endoglin expression was highly associated with sites of active neangiogenesis in both mice and humans, we used endoglin-heterozygous (Eng+/−) mice to investigate its function in adult neovascularization. Eng+/− mice survive into adulthood but have reduced endoglin levels and can develop HHT symptoms. Hearts from Eng+/− and Eng−/− mice were stained for endoglin after MI. This staining revealed that expression was increased in both groups in the infarct zone but more in Eng−/− mice as previously reported (Figure 3A). We also characterized the inflammatory cell accumulation in the infarct zones 1 week after MI by staining with antibodies against CD68 and Mac-3 for macrophages or with anti-CD45 for polymorphonuclear leukocytes (Figure 3B). This revealed no significant differences in the number of immunoreactive cells in the infarct zones of Eng−/− mice compared with Eng+/− mice (Figure 3C through 3E). In contrast, although we found a slight increase in the basal number of vessels in Eng+/− mice (online Data Supplement, Figure IA), the number of vessels in the infarct zone of Eng−/− mice was significantly lower than in Eng+/− mice 1 week after MI (657±39 versus 1138±86 vessels per 1 mm2; Figure 3F), suggesting that defects in angiogenesis occur during cardiac remodeling as a result of reduced endoglin levels.

We next analyzed heart function in these mice by magnetic resonance imaging (MRI). There were no differences between Eng+/− and Eng−/− mice before MI or 1 week after MI (Figure 4B, supplementary Figure IB and IC). The survival curves of the Eng+/− and Eng−/− mice also were identical (65% versus 67%, respectively; P=0.979; supplementary Figure IIA). However, MRI analysis 1 month after MI showed that stroke volume index, cardiac index, and ejection fraction were significantly lower in Eng−/− mice compared with Eng+/− littermates (0.914±0.286 versus 1.348±0.556 mL/kg, P=0.001; 0.426±0.097 versus 0.7±0.219 L·min−1·kg−1, P=0.001; 16.7±14.6% versus 35.3±16.0%, P=0.001, respectively; Figure 4A through 4E). The number of vessels also was lower in Eng−/− compared with Eng+/− mice (260153 versus 476.7±75.2 vessels per 1 mm2, P=0.004; Figure 4F), indicating that neangiogenesis defects in Eng−/−
mice were associated with markedly greater deterioration in cardiac function after MI.

In the light of evidence that MNCs contribute to the formation of new blood vessels, we investigated whether MNCs might contribute to these angiogenesis defects by injecting MNCs from healthy human donors and MNCs from HHT1 patients into the tail veins of Eng−/− mice after MI. For ENG mutations of the patients, see supplementary Tables I and II. Previous analysis of endoglin protein levels in affected patients strongly supported haploinsufficiency and associated reduced levels of functional protein as the underlying cause of HHT1.4 This suggested that disease heterogeneity cannot be explained by the position and type of mutations.21,22 The survival curves of the injected and noninjected groups were identical (supplementary Figure IIA). MRI analysis 1 month later revealed that MNCs from healthy human donors significantly improved heart function of Eng−/− mice (ejection fraction, 16.7±14.6% versus 34.9±3.4%; P=0.004; Figure 4B and 4E) and stimulated neoangiogenesis (260±153 versus 460±89.5 vessels per 1 mm²; P=0.003; Figure 4F), whereas MNCs from HHT1 patients had no effect (ejection fraction, 16.7±14.6% versus 18.8±10.8%; P=0.749; Figure 4B and 4E; and 260±153 versus 305.8±55.0 vessels/mm²; P=0.317, respectively; Figure 4F). To confirm the difference in the ability of MNCs from healthy donors and HHT1 patients to contribute to vascular repair, we injected MNCs intravenously into wild-type mice 1 to 3 hours after MI. We found that 75% of mice receiving PBS vehicle alone, 89% receiving healthy donor MNCs, and 81% receiving HHT1 MNCs recovered normally from the procedure (supplementary Figure IIB). The number of vessels in the infarct zone was determined 14 days after MI. Vessel formation was efficiently stimulated by intravenous injection of MNCs from healthy donors (271.8±106.5 versus 418±265.8 vessels per 1 mm²; P=0.028; Figure 5A). However, MNCs from HHT1 patients showed consistently impaired ability to stimulate neoangiogenesis (269.8±181.2 versus 271.8±106.5 vessels per 1 mm²; P=0.884; Figure 5A), even though fluorescent-activated cell sorter analysis of blood from the patients and control subjects used for injection into the mice indicated no
difference in the number of CD34⁺ cells or the number of CD34⁺/KDR⁺ cells. In this respect, the composition of control and patient blood samples was identical. In addition, there was no difference in cell numbers in MNC cultures from patients versus controls after 8 days. Because endoglin is expressed in vascular and various hematopoietic lineages, MNC-derived ECs homing to the infarct zone were traced by costaining with mouse-specific anti-PECAM antibody and human UEA-1 lectin, a marker commonly used for human cells with endothelial characteristics (Figure 5B). The number of UEA-1⁺ cells that accumulated in the infarct zone of mice receiving cells from HHT1 patients was significantly lower than in mice receiving cells from healthy donors (4.01 ± 12.33 versus 32.4 ± 26.7 MNC-derived ECs per 1 mm²; \( P = 0.003 \); Figure 5D). These MNC defects did not seem to depend on obvious differences in their ability to attach (Figure 5E), survive, or proliferate (S. Post, M.J. Goumans, unpublished observations), at least as determined in vitro on fibronectin-plated wells. In addition, we found no changes in expression of any major components of the TGF-β signaling pathway (Figure 5E).

Figure 2. Endoglin is upregulated in active endothelium. A, Upregulation of endoglin associated with neoangiogenesis after MI. PECAM in all vessels (top); endoglin specifically in the infarct zone (right). Ki67⁺ ECs associated with endoglin-positive vessels of the infarct zone (bottom). B, Endoglin and Ki67 immunohistochemistry of infarcted human hearts shows upregulation of endoglin associated with neoangiogenesis. Black arrows show Ki67⁺ cells.
Discussion

Neovascularization is a normal component of remodeling that occurs after MI. Its promotion has been proposed as an important target for therapeutic improvement of heart function. However, the mechanisms underlying neovascularization after MI are still not fully understood, although signaling pathways activated by TGF-β, vascular endothelial growth factor, and insulin-like growth factor are thought to be involved. Here, we examined the function of endoglin, a TGF-β receptor involved in angiogenesis during development. We demonstrated that endoglin has a crucial role in normal remodeling after MI that coincides with upregulation of its major ligand, TGF-β, in myofibroblasts in the infarct zone. Specifically, upregulation of endoglin in ECs, possibly stimulated by local TGF-β, correlates with neangiogenesis. Furthermore, Eng<sup>−/−</sup> mice showed impaired angiogenesis after MI, which resulted in enhanced deterioration of cardiac function; this confirmed recent findings using an ischemic hind-limb injury model. Our results are consistent with reports demonstrating that endoglin is a marker of angiogenesis, that endoglin activates TGF-β/ALK1 signaling and inhibits TGF-β/ALK5 signaling to promote EC proliferation, and that downregulation of endoglin expression induces EC apoptosis. More generally, impaired angiogenesis in Eng<sup>−/−</sup> mice may be mediated at least in part by EC defects.

Compelling evidence indicates that recruitment of circulating vascular and hematopoietic cells contributes to the revascularization of ischemic tissues. Because endoglin is expressed in various cell lineages making up the MNC fraction, we investigated the effects of reduced endoglin expression in these circulating cells using experimental MI in mice as a model system. With respect to the disease HHT1, the present study provides the first evidence that MNCs derived from patients are impaired in their capacity to stimulate vessel formation. Moreover, injection of healthy MNCs into Eng<sup>−/−</sup> mice was sufficient to restore vessel formation and to improve heart function defects associated with reduced levels of endoglin, but MNCs from HHT1 patients were not, demonstrating that the origin of HHT1 is possibly associated with defective ability of MNCs to repair local vessel damage.

It is unclear which cell populations are affected by decreased endoglin expression. Previous studies have shown
Figure 4. Injection of healthy donor but not HHT1 MNCs into Eng−/− mice with acute MI rescues neoangiogenesis and deterioration in cardiac function associated with reduced endoglin. A, MRI analysis of Eng−/− and Eng−/− mice 4 weeks after MI. B, Analysis of heart function of Eng−/− and Eng−/− mice without and 1 month after MI. C–E, Cardiac functions of Eng−/− mice are reduced vs Eng−/− mice. E, F, After healthy donor but not HHT1 MNC injection, ejection fraction is improved (E) and neoangiogenesis is rescued (F) in Eng−/− mice. HR indicates heart rate; EDV, end-diastolic volume; ESV, end-systolic volume; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SV, stroke volume; SVI, stroke volume index; CO, cardiac output; CI, cardiac index; MM, myocardial mass; and EF, ejection fraction.
Figure 5. MNCs from HHT1 patients fail to stimulate neoangiogenesis. A, Number of vessels in the infarcted zone of hearts of Balb/c mice 14 days after MI was determined by counting PECAM \(^{+} \) vessels after immunohistochemical staining. B, UEA-1 lectin–coupled fluorescein isothiocyanate stains ECs of human fetal heart and not other cell types. C, MNC-derived ECs were only in the infarcted zone. D, MNCs from HHT1 patients show impaired homing to infarcted mouse hearts. The number of MNC-derived ECs per 1 mm\(^2\) in hearts of Balb/c mice 4 days after MI was determined by counting UEA-1 \(^{+} \) cells. E, MNCs from healthy donors and HHT1 patients showed no differences in the number of UEA-1 \(^{+} \) and Ac Dil-LDL \(^{+} \) cells attached to fibronectin-coated plates after 8 days. Expression of TGF\(-\beta\) signaling pathway components in HHT1 MNCs were comparable to those in healthy donor MNCs.
that blood outgrowth ECs from HHT have abnormalities that would be compatible with a role in vascular lesions,43 that endoglin functions to support lineage-specific hematopoietic development from Flk-1 precursors44 and defines long-term repopulating hematopoietic populations,45,46 and that endoglin is expressed in activated monocytes.47,48 We demonstrated that MNC-derived ECs from HHT1 patients have a reduced ability to accumulate in the infarct zone in vivo and stimulate that MNC-derived ECs from HHT1 patients have a reduced ability to form endothelial progenitors may derive greater benefit from transplantation with matched heterologous bone marrow.

Conclusions

Because vessel damage may occur randomly in HHT patients as a result of trauma, ultraviolet light exposure, inflammation, or multiple individual pathological or physiological differences, this defect in normal repair may contribute to explanations of why families or even individual family members with the same mutation present with highly variable symptoms of the disease. Second, and more generally, in light of ongoing trials investigating the use of autologous bone marrow in vascular repair after MI, the results suggest that HHT1 patients and others with intrinsic defects in their capacity to form endothelial progenitors may derive greater benefit from transplantation with matched heterologous bone marrow.

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Disclosures

None.

References


Hereditary hemorrhagic telangiectasia is a rare disease characterized by weak-walled vessels and caused by mutation in cell surface receptors for the cytokine transforming growth factor-β. Here, we show that mononuclear cells from peripheral blood of patients with 1 type of mutation are defective in their ability to home to the infarct zone in the heart of mice that had undergone experimental myocardial infarction. In contrast to healthy individuals, the mononuclear cells of hereditary hemorrhagic telangiectasia patients are unable to restore cardiac function in the experimental mice. This indicates for the first time that defective vascular repair may contribute to the origin of hereditary hemorrhagic telangiectasia. More generally, in the context of using autologous bone marrow in cardiovascular repair, patients with intrinsic defects in the ability of their mononuclear cells to form endothelial progenitors may benefit less than from expected bone marrow infusion into the heart.
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