Platelet-Derived Growth Factor-AB Limits the Extent of Myocardial Infarction in a Rat Model  
Feasibility of Restoring Impaired Angiogenic Capacity in the Aging Heart

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Background—Compared with younger patients, myocardial infarction in the elderly has been associated with less favorable clinical outcomes, which may be attributable to a decline in angiogenic capacity in the aging heart.

Methods and Results—To test the hypothesis that the functional phenotype of cardiac microvascular endothelial cells is maintained partly by a cardiac myocyte platelet-derived growth factor (PDGF)-B–induced paracrine pathway, we conducted in vitro studies with murine cardiac cells. These studies demonstrated that unlike young endothelial cells, endothelial cells of the aging heart do not express PDGF-B when cultured in the presence of cardiac myocytes. The functional significance of this endothelial dysregulation was assessed with an ex vivo pinnal cardiac allograft model to demonstrate that senescent cardiac angiogenic activity was depressed (2 of 17 allografts were viable in 18-month-old mice versus 19 of 20 in 3-month-old mice; \( P < 0.01 \)). PDGF-AB pretreatment specifically restored the viability of the cardiac allografts in the aging hosts (13 of 13 allografts were viable; \( P < 0.01 \) versus 18-month-old controls). Finally, in vivo studies in rat hearts demonstrated that pretreatment by intramyocardial delivery of PDGF-AB promotes angiogenesis and minimizes the extent of myocardial infarction in the aging hearts after coronary ligation (myocardial infarction size: 10.0\( \pm \)7.0\% of left ventricular area in PDGF pretreatment \( [n=7] \) versus 17.6\( \pm \)5.6\% in control \( [n=5] \) groups; \( P < 0.03 \)).

Conclusion—Aging hearts have impaired angiogenic function as a result of depressed PDGF-B production. Restoration of the dysregulated endothelial PDGF-mediated angiogenic pathway in the aging heart reverses the senescent impairment in cardioprotective angiogenic function and offers a foundation for developing novel therapies for cardiovascular disease in older individuals. (Circulation. 2002;105:608-613.)

Key Words: endothelium ■ heart ■ angiogenesis ■ aging

Ischemic heart disease is the most common cause of morbidity and mortality in the population over the age of 65.\(^1\)-\(^4\) In younger individuals, myocardial ischemia induces the development of a collateral supply that partially protects the cardiac tissue from subsequent coronary events.\(^5\)-\(^8\) However, angiogenesis is impaired in the cardiac\(^9\)-\(^13\) and peripheral vascular beds of older individuals,\(^14\)-\(^15\) and this defect may underlie the increased severity of cardiovascular disease in the geriatric population. Therefore, elucidation of the cellular and molecular pathways that are impaired with aging is critical for developing specific strategies to prevent and reduce the pathogenesis of cardiovascular disease associated with advancing age.

Despite recent progress in our understanding of the molecular pathways regulating angiogenesis during embryonic development, the mechanistic alterations in angiogenic function in the senescent vasculature are not well understood. Previously, we described\(^16\) a platelet-derived growth factor (PDGF)-AB–mediated communication between cardiac microvascular endothelial cells (CMECs) and the neighboring cardiac myocytes. Cardiac myocytes induce CMECs to express the PDGF-B isofrom, which combines with the constitutively expressed PDGF-A isofrom to form the PDGF-AB heterodimer. This results in the induction of a cascade of molecular events that maintain vascular integrity, including the endothelial expression of vascular endothelial growth
factor (VEGF) and VEGF receptor-2 (Flk-1, VEGFR-2), therefore, dysregulation of these angiogenic pathways, which occurs in aging through alterations in cardiac PDGF-

levels, may lead to angiogenic defects. On the basis of these previous observations, we hypothesized that interventions targeted at reestablishing the angiogenic potential in senescent cardiac endothelial function may attenuate the detrimental impact of obstructive vascular disease in the aging heart. Therefore, we focused on defining the aging-associated changes that regulate angiogenic pathways in the cardiac endothelium.

In the present report, we extend our previous findings, demonstrating that endothelial dysregulation in the PDGF communication pathway underlies the impairment in senescent cardiac angiogenic potential. Moreover, reestablishment of the PDGF pathways to facilitate cardiac angiogenesis protects both young and aging rodent hearts from myocardial infarction.

Methods

Molecular Studies

To determine the molecular defects leading to impaired cardiac angiogenic activity, samples of the ventricular myocardium were isolated from 3-month-old (n = 3) and 18-month-old C57B6/L mice (n = 5) (National Institute on Aging Colony; maintained by Harlan Sprague Dawley, Inc). Total DNA was isolated (RNaseasy and QIAshedder kits, Qiagen) and analyzed by reverse transcriptase-polymerase chain reaction (RT-PCR) (Hotstar Taq PCR, Qiagen) for expression of PDGF-A, PDGF-B, and β-actin. In order to dissect the physiological effects of aging on endothelial function, CMECs were isolated from 3- and 18-month-old wild-type mice. Moreover, transwell cocultures with fetal cardiac myocytes were used in order to control the myocyte contribution to the cardiac microvascular regulation of the different endothelial cells. CMECs were cultured from 3- and 18-month-old C57B6/L mice and cardiac myocytes from fetal murine hearts as previously described. The CMEC cultures were expanded for 2 passages, confirmed by Di-Ac-LDL uptake and platelet endothelial cell adhesion molecule (PECAM) staining, and plated into 12-well dishes (105 cells per well) (Costar). Cardiac myocytes (embryonic 15.5 days) were plated in 12-mm 0.4-μm pore transwells (105 cells per transwell), transferred into CMEC-seeded wells on days 0, 1, and 2, and cultured for 3 days as previously described. At the termination of the coculture, total RNA was isolated from the CMEC wells and RT-PCR was performed. The following sets of oligonucleotide primers were used:

**PDGF-A**

Forward: 5′TCAAGGTGGCCAAAGTGGAG3′

Reverse: 5′CTTCTCTGACAAAGGAGCT3′

**PDGF-B**

Forward: 5′ATCGCCGATGCAAGAGCGG3′

Reverse: 5′AAGCACCATTGGCGCTCCGA3′

**PDGF-α Receptor**

Forward: 5′ACAGAGACGTGAGGGCGTACA3′

Reverse: 5′TTCCAAGAAGGAGGGAGCA3′

**PDGF-β Receptor**

Forward: 5′TGAAGCTCACCTATCAAGTTGC3′

Reverse: 5′GTGCCACCGGATGGC3′

**VEGF**

Forward: 5′GGATCCAATGCACTTCTCTCAGTTTG3′

Reverse: 5′TTCTGGCCTTGTGTCTCTTGTGG3′

**Flk-1**

Forward: 5′CAGCTTGCTCTTCCTCATC3′

Reverse: 5′TCTGGAGAGCGAACAACCA3′

**PECAM**

Forward: 5′CAAGCGGCTGTAATGACAC3′

Reverse: 5′CCTGCTTGGACTGTTAAG3′

**β-actin**

Forward: 5′GTGGGCGCTCTAGACCA3′

Reverse: 5′CTTCTTGTGTACGACAGTT3′

Cellular and secreted protein samples were isolated from additional CMEC cocultures and were applied to Nunc maxisorb plates (Roskilde) as previously described. Polyclonal antibodies to PDGF-A (sc-128) and PDGF-B (sc-7878, Santa Cruz Biotechnology); VEGF (AF 493-NA), Flk-1 (AF 644), PDGF-α receptor (PDGFR-α) (AF322), and PDGFR-β (AF385, all R&D Systems); and PECAM (550274, BD Pharmigen) were then used. The plates were assayed as previously described to quantify the relevant cardiac myocyte-induced fold-changes in protein levels as a functional correlate to the senescent changes in endothelial gene expression dynamics. All studies were performed a minimum of 3 times.

Ex Vivo Cardiac Tissue Angiogenesis Studies

To test the physiological significance of the alterations in aging endothelial function, we used a cardiac allograft model, which allows the assessment of cardiac angiogenic potential in different age groups. In this model, allograft neovascularization is mediated by host endothelial cells recruited into the donor hearts, which recapitulate the cardiac myocyte–endothelial cell communication in vivo. Neonatal C57B6/L (24-hour-old) murine hearts were transplanted into the pinnae of both young adult and senescent C57B6/L mice as we have previously described (3-month-old mice, n = 20; 18-month-old mice, n = 17). As controls, senescent mice were transplanted with inert silicon (1 × 1 × 2 mm2) to test wound-healing response (n = 8) or neonatal pulmonary allografts to test cardiac-specific angiogenesis (n = 8) in place of the neonatal cardiac tissue.

In addition, to test the physiological effects of age on cardiac or pulmonary allograft transplantation, sets of young adult mice also were treated with single subcutaneous pinnal injections of antibodies to neutralize PDGF-AB (10 μg in 20 μL PBS, AB-20-NA, R&D Systems, n = 8 cardiac, 8 pulmonary allografts), PDGFR-α, PDGFR-β (10 μg in 20 μL PBS, AB-307-NA and AB385, R&D Systems, respectively; n = 7 cardiac allografts), or nonimmune rabbit immunoglobulin G (10 μg in 20 μL PBS, AB-105-C, R&D Systems; n = 8 cardiac, 8 pulmonary allografts). Sets of senescent hosts also were pretreated with subcutaneous pinnal injections of VEGF (R&D Systems, 100 ng per 20 μL PBS, n = 12), PDGF-AB (R&D Systems, 100 ng per 20 μL PBS, n = 13) or PBS alone (n = 8) 1 day before receiving cardiac allograft transplants. Allograft viability was scored by pinnal and transplant integrity. Pinnal electrocardiograms also were recorded to further document cardiac allograft viability.

In Vivo Rat Heart Model: PDGF-AB Enhancement of Angiogenic Function

**Intracardiac Injections of PDGF-AB**

Instead of using the murine heart, an in vivo rat model was chosen in order to allow a more comprehensive histological assessment of the role of PDGF-AB in promoting and restoring angiogenic activity in the endogenous heart. Sets of both young adult (4-month-old) and aging F344 (24-month-old) rats (National Institute on Aging Colony; maintained by Harlan Sprague Dawley, Inc) were anesthetized and underwent left intercostal thoracotomy. After identifying the left anterior descending artery (LAD), 100 ng of PDGF-AB in 50 μL
PBS solution was injected through a 30-gauge needle using a 250-μL Hamilton syringe. Two injections (25 μL per injection, 2 mm apart) were made at the mid-left ventricular anterior wall. Control rats received PBS pretreatment. The chest wall was then closed, the lungs inflated, the rat extubated, and the tracheotomy closed.

Cardiac Angiogenic Assessment
Rats receiving pretreatments alone (PDGF-AB or control, 4 and 24 months old, n=3 each group) were euthanized 24 hours after injection, and hearts were excised, fixed, and sectioned for vascular density analysis, as previously described. Blood vessels were highlighted by immunostaining for von Willebrand factor (vWF) (082, DAKO), visualized with diaminobenzidine (DAB). Vascular density was assessed by examining a single mid-papillary section (proximal to the injection site) from each heart and identifying all vWF-stained endothelial cell–lined structures in a total of 8 high-power fields (magnification ×40) per region per heart. Vascular counts were performed by 2 investigators in a blinded fashion.

Myocardial Infarction Model
The pro-angiogenic and cardioprotective effects of PDGF-AB pretreatments were studied in a myocardial infraction model. One day after PDGF-AB (4-month-old rats, n=15; 24-month-old rats, n=7) or control (4-month-old rats, n=12; 24-month-old rats, n=5) intramyocardial injections, the rats were anesthetized, the heart exposed, and the LAD ligated just below left atrial appendage with 8-0 nylon sutures. Additional sets of 4-month-old rats were treated with PDGF-AB (n=3) or control (n=3) at the time of LAD ligation. Pallor and regional wall motion abnormality of the left ventricle confirmed occlusion. The chest wall was closed, and after recovery, the rats were returned to the animal facility and kept for 14 days. The rats then were euthanized and the hearts harvested, fixed, and sectioned as described above. Myocardial infarction size measured at the level of the mid-papillary heart muscles was scored by Masson’s trichrome staining, as previously described, and the images were analyzed in a blinded fashion with ImageJ 1.22 software (NIH Image). Infarction size was expressed as a percentage of the total left ventricle myocardial area. An independent pathologist (Dr Feirt) who was blinded to the treatment received reviewed these measurements.

Statistics
Differences were tested for statistical significance by the Student’s t test. A value of P<0.05 was considered significant.

Results
Induction of PDGF-B Is Impaired in Senescent Endothelial Cells
RT-PCR analysis revealed that PDGF-A was expressed in ventricular myocardial samples from both the young adult and senescent hearts (Figure 1A). PDGF-B expression, however, was detected only in young adult murine cardiac samples, which is in agreement with previous findings in the rat heart. Furthermore, transwell cocultures confirmed that CMECs of both young and senescent hearts constitutively expressed PDGF-A (Figure 1B and 1C). However, only the young adult CMECs expressed PDGF-B in the presence of the fetal cardiac myocytes, resulting in a significant increase in protein levels of PDGF-B in the CMECs of the 3- but not the 18-month-old hearts. Furthermore, PDGFR-α was expressed in CMECs from both young adult and senescent hearts.

In addition to the dysregulation of PDGF-B, the expression pattern of other pro-angiogenic genes was also altered in the CMECs from aging mice (Figure 1B and 1C). Unlike the young adult CMECs, in which VEGF was induced in the coculture with the cardiac myocytes, the endothelial cells derived from aging hearts expressed the growth factor when cultured in isolation. However, senescent CMEC VEGF mRNA, but not protein, levels decreased in the presence of the cardiac myocytes. Furthermore, the expression of Flk-1, the principal mitogenic receptor for VEGF, was altered significantly in the senescent cells.

PDGF-AB Restores Angiogenesis of Exogenous Cardiac Tissue
The potential functional significance of the endothelial dysregulation in senescent mice then was examined. These studies used a syngeneic neonatal murine cardiac allotransplantation model that recapitulates PDGF-AB–PDGFR-α pathway in the organ bed–specific regulation of endothelial cells recruited from host peripheral vascular beds, and is specifically enhanced by PDGF-AB. Neutralization of PDGF-AB or PDGFR-α, but not PDGFR-β, in the young murine pinnae at the time of transplantation significantly reduced the viability of cardiac allografts, whereas pulmonary transplant engraftment was unaltered by neutralization of PDGF-AB (Table). Thus, the pinnal cardiac allotransplantation model could provide a direct in vivo comparison of the cardiac myocyte/myocardial–induced angiogenic potential of the endothelium in young adult and senescent mice.

Although wound healing was preserved in the older hosts, as demonstrated by the integrity of silicon implants, our
studies revealed that cardiac allograft survival was impaired markedly in the aging mice compared with the young adult mice (Figure 2). Moreover, the viability of the pulmonary allografts suggested that the aging-associated changes were the result of diminished senescent endothelial angiogenic function induced by the transplanted cardiac myocytes/myocardial tissue.

We also tested the potential of the various molecular mediators that are downregulated in the senescent endothelial cell–cardiac myocyte cocultures in an effort to restore cardiac angiogenic potential in the aging mice. The subcutaneous pinnal administration of VEGF at concentrations previously demonstrated to enhance auricular neovascularization failed to improve the success of cardiac transplantation in the aging mice. However, reconstitution of PDGF-AB restored the capacity of the senescent host to neovascularize the transplanted cardiac tissue. These data suggest that the angiogenic dysfunction in PDGF-AB generation in response to cardiac myocytes underlies the impaired function in senescent cardiac angiogenic potential observed in vivo, and that the level of PDGF-AB expressed in the cardiac endothelium endogenous to the transplanted tissue is insufficient to induce effective revascularization in the senescent hosts.

PDGF-AB Promotes Cardiac Angiogenesis in the Endogenous Heart

To assess whether restoration or augmentation of the endogenous cardiac PDGF-AB pathways would rapidly enhance angiogenesis in the adult heart and offer a novel means of improving cardiac function by the injured myocytes/myocardial infarction, we used the rat heart, which, on the basis of size, provides better histological quantification than does the murine heart. Our studies revealed that PDGF-AB significantly increased vascular density in both the young and the aging intact heart (Figure 3), demonstrating the functional integrity of the angiogenic pathway downstream of PDGF-B induction in the senescent cardiac microvasculature.

PDGF-AB Protects the Endogenous Heart From Myocardial Infarction

Our findings in the endogenous hearts suggested that PDGF-AB pretreatment could reduce the extent of myocardial infarction after LAD ligation significantly. Quantification of myocardial infarction size by Masson’s trichrome stain revealed that PDGF-AB reduced the size of myocardial infarction by approximately half in the young adults (Figure 4). Indeed, the infarction size in 24-month-old heart pretreated with PDGF-AB was approximately half the size of infarctions in control-injected hearts (Figure 5). Treatment at the time of coronary ligation, however, had no effect on myocardial infarction size (15.7 ± 3.1%; n = 3).

Discussion

The results of the present studies suggest the following: (1) Endothelial expression of PDGF-B may be downregulated in the senescent heart; (2) endothelial dysregulation in the communication with cardiac myocytes may be the primary defect in the impaired cardiac angiogenic function in the aging heart; and (3) therapies directed at impaired senescent cardiac angiogenic function may protect the aging heart from myocardial infarction. Moreover, targeting these pathways in the young heart may provide similar angiogenic enhancement and cardioprotective effect, suggesting that studies of the molecular basis of the aging-associated dysregulation in cardiac angiogenic activity may lay the foundation for the development of novel strategies for the treatment of ischemic cardiovascular disease in both young and older individuals.

Mechanism of Impaired Angiogenesis in the Aging Heart

Thus far, the precise molecular and cellular defects leading to impaired senescent cardiac angiogenic activity have been unknown. Our studies reveal that aging-associated alterations in endothelial cells result in the inhibition of the PDGF-AB–induced cardiac communication pathway that governs cardiac angiogenic function. Furthermore, the endothelial cells in the aging vasculature may develop a deficiency in as yet unrecognized constitutive or inducible receptor(s) required for the generation of a permissive environment for cardiac angiogenesis in the senescent heart; and (2) endothelial dysregulation in the communication with cardiac myocytes may be the primary defect in the impaired cardiac angiogenic function in the aging heart; and (3) therapies directed at impaired senescent cardiac angiogenic function may protect the aging heart from myocardial infarction. Moreover, targeting these pathways in the young heart may provide similar angiogenic enhancement and cardioprotective effect, suggesting that studies of the molecular basis of the aging-associated dysregulation in cardiac angiogenic activity may lay the foundation for the development of novel strategies for the treatment of ischemic cardiovascular disease in both young and older individuals.

PDGF in Pinnal Cardiac Allograft Vascularization

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*IgG indicates immunoglobulin G; ND, not determined.

*P < 0.05 vs IgG heart and anti–PDGF-AB lung trials; †P < 0.05 vs IgG and anti–PDGFR-β heart trials.

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angiogenic function. Alternatively, the senescent endothelium may have lost its paracrine mediators that sustain cardiac myocyte–dependent communication with the PDGFR-α-expressing CMECs.16 Restoration of Angiogenic Potential Our studies demonstrate that augmentation of the PDGF-AB–dependent pathways in the endogenous heart is sufficient to restore angiogenic potential and markedly reduces the extent of myocardial infarction in the aging heart. Because PDGF-AB restores angiogenic capacity in the intact hearts of all age groups, the critical downstream pathways in the endothelial cells from the senescent cardiac vasculature are likely to be intact. Such downstream components may include factors that act synergistically with VEGF and other proangiogenic factors to promote the formation of mature blood vessels to vascularize the cardiac allografts. Indeed, PDGF-AB may restore the expression patterns of genes that are dysregulated in the aging CMECs, such as VEGF, which is mediated by the PDGF-AB pathway in the young cardiac endothelial cells.16 Therefore, identification of the critical pro-angiogenic set of genes regulated by PDGF-AB pathways may provide a regimen tailored for the induction of angiogenic function specifically in the myocardium. Moreover, such a set of genes may provide a more potent approach for reversing senescent vascular impairment than the delivery of PDGF-AB alone, which may be limited by its actions on nonendothelial vascular cell types, such as smooth muscle cells, in which it promotes proliferation.29 Further studies integrating aging-associated changes in cardiac myocytes30–32 and smooth muscle cells33 may help define additional targets to augment the actions of the endogenous PDGF-AB pathways to reverse the senescent cardiac vascular phenotype.

The findings of our present studies provide a unique insight into the molecular and cellular alterations in endothelial function that may contribute to the worse clinical outcome after a cardiac event in older individuals.34,35 Augmentation or restoration of endothelial PDGF-AB–dependent proangiogenic pathways can reduce the size of infarct size after experimental coronary artery occlusion. The clinical translation of these findings will require future studies aimed at defining and potentially expanding the therapeutic window of this approach, testing under transient and chronic hypoxic conditions, and using relevant disease models that enhance the vascular pathology in the aging heart (eg, hypertension, diabetes, and hyperlipidemia). It is hoped that the integration of results of such studies with our present observations will provide further understanding of more precise pathways in myocardial angiogenesis and will facilitate the development of future therapeutic approaches for the treatment and possible prevention of ischemic heart disease.

Acknowledgments

This work was supported by National Institutes of Health P01 HL59312, the Ellison Medical Foundation, the American Federation for Aging Research, the Society for Geriatric Cardiology, and a Weill Cornell Center for Aging Research and Clinical Care grant (Dr Edelberg); the American Heart Association-Student Research Grant (Manmeen Kaur); and the Michael Wolk Foundation (Dr Hong).
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_Circulation_. 2002;105:608-613; originally published online December 31, 2001;
doi: 10.1161/01.HC0502.103672
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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