Role of Endogenous Platelet-Derived Growth Factor in Arterial Smooth Muscle Cell Migration After Balloon Catheter Injury

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The process of intimal thickening after de-endothelializing injury to the rat carotid artery is dependent on the migration of smooth muscle cells from the media. Recent reports have suggested that platelet-derived growth factor may be an important mediator of migration after injury. We have addressed this issue by directly determining smooth muscle cell migration in injured arteries of animals depleted of platelets and after administration of an antibody that blocks platelet-derived growth factor. Because there is a reported association between plasminogen activator synthesis and smooth muscle cell migration, we assayed the activity levels of plasminogen activators after arterial injury and also assessed the effect of a plasmin inhibitor on migration. The data suggest that platelet-derived growth factor, released by platelets at sites of arterial injury, is an endogenous mediator of smooth muscle cell migration; that plasmin generation, catalyzed by tissue-type plasminogen activator, is necessary for migration; and that one way in which platelet-derived growth factor may act is by stimulation of the synthesis of tissue-type plasminogen activator by smooth muscle cells. (Arteriosclerosis and Thrombosis 1993;13:1218-1226)

KEY WORDS • smooth muscle • platelet-derived growth factor • plasminogen activator • cell migration • vascular injury • thrombocytopenia • tranexamic acid

The intima of the normal rat carotid artery does not contain smooth muscle cells (SMCs), but within days after balloon catheter injury a neointima develops consisting predominantly of SMCs that have migrated across the internal elastic lamina from the media and have then replicated. SMC migration is therefore a key step in the development of intimal lesions, but until recently little was known of the factors that control migration or of its biochemical basis. We have previously shown that platelet depletion inhibits intimal thickening in balloon-injured rat arteries but does not affect SMC replication, suggesting that platelets stimulate migration. Administration of exogenous PDGF to rats causes a marked stimulation of intimal SMC accumulation but has little effect on the replication rate of these cells. Moreover, inhibition of the activity of endogenous PDGF with a blocking antibody causes a significant reduction in intimal thickening but has no effect on replication. Although the clear inference from these studies is that PDGF is an endogenous mediator of SMC migration, this issue has not been addressed directly. In the present study we used an anti-platelet antibody to induce a marked thrombocytopenia and then determined its effects on plasminogen activator activity and SMC migration. To determine if PDGF is the specific platelet component influencing SMC migration, we used an antibody that blocks the activity of this cytokine.

We and others have suggested that the generation of plasmin from plasminogen is associated with the migration of SMCs because the time of onset of migration after injury coincides with a marked increase in the expression of tissue-type plasminogen activator (t-PA) in the vessel wall. This hypothesis has now been further explored, first by measuring the activity and localization of plasminogen activators after injury, and second by determining the effect of a pharmacological inhibitor of plasmin, tranexamic acid, on SMC migration. We also investigated the effects of antibody neutralization of PDGF on arterial plasminogen activator activity because PDGF has been reported to influence the synthesis of proteolytic enzymes by smooth muscle and other cell types.

Methods

Balloon Catheter Injury

Male Sprague-Dawley rats were obtained from Tyler Laboratories (Bellevue, Wash.) and were surgically anesthetized by intraperitoneal injection under ether anesthesia of ketamine hydrochloride, 71.7 mg/kg (Ketaset, Aveco Co, Fort Dodge, Iowa) and xylazine, 4.6 mg/kg (AnaSed, Lloyd Laboratories, Shenandoah, Iowa). The common carotid arteries were injured by three rotating passes with a size 2F arterial embolectomy catheter (American Edwards Laboratories, Añasco, Puerto Rico) inflated with saline.
Measurement of SMC Migration

Rats were killed 4 days after arterial injury by intravenous injection of sodium pentobarbital (Anthony Products Co, Arcadia, Calif) and were exsanguinated by perfusion with lactated Ringer's injection USP (Baxter Healthcare Corp, Deerfield, Ill) at a pressure of 120 mm Hg. The animals were fixed by perfusion with 2% glutaraldehyde and 1% paraformaldehyde in phosphate buffer (0.15 mol/L). The common carotid arteries were removed and postfixed overnight at 4°C. The vessels were opened longitudinally and pinned to Teflon cards. They were dehydrated in ethanol before being dried in a critical-point drier (Tousimis Research Corp, Rockville, Md). The dried specimens were mounted on aluminum stubs with colloidal silver paste. After sputter coating with gold/palladium, the specimens were examined in a JEOL 35C scanning electron microscope at an accelerating voltage of 15 kV and at a magnification of $\times86$. An acetate sheet with a ruled grid was placed over the electron microscope screen. Each square of the grid was 81 mm$^2$, which corresponded to 4133 $\mu m^2$ on the specimen. The total area of the specimen and the area occupied by intimal SMCs were determined by counting squares. Intimal SMCs were distinguishable from adjacent platelets by the criteria of size, morphology, and orientation. SMCs were generally arranged in a longitudinal orientation parallel to the direction of blood flow. The long axis was approximately 20 $\mu m$ to 40 $\mu m$, and the short axis was approximately 5 $\mu m$ to 15 $\mu m$, giving an average surface area of about 270 $\mu m^2$. Platelets were spheres of approximately 3-$\mu m$ diameter before spreading, after which they took on astellate appearance, with an approximate diameter of 6 $\mu m$. Leukocytes were occasionally seen adhering to the intimal surface. They were, in contrast to SMCs, highly electron reflective. They were spherical, with a diameter of approximately 10 $\mu m$.

Assay of Arterial Plasminogen Activator Activity

Rats were killed by intravenous injection of sodium pentobarbital and were exsanguinated by perfusion with lactated Ringer's injection USP at a pressure of 120 mm Hg. The left common carotid artery was dissected and removed. Adventitial fat and connective tissue were removed, and each artery was homogenized in 50 mmol/L ice-cold tris(hydroxymethyl)aminomethane (Tris)-HCl buffer, pH 9.0. Insoluble matter was removed by centrifugation at 14 000g. Parallel aliquots of the supernatant were incubated with plasin-free human plasminogen, 0.3 U/mL (Sigma Chemical Co, St Louis, Mo), des-AA-fibrinogen, 100 $\mu g$/mL (Desafib, American Diagnostica Inc, Greenwich, Conn), amiloride dihydrate, 1 mmol/L (Sigma), and a chromogenic substrate for plasmin, 0.5 mmol/L (Spectrozyme-PL, American Diagnostica). Standard curves were prepared by using human high-molecular-weight urokinase-type plasminogen activator (u-PA; Calbiochem Corp, La Jolla, Calif) and human single-chain t-PA (American Diagnostica). The absorbances of the reaction mixtures were determined at the signal wavelength of 405 nm and at a reference wavelength of 630 nm by using a microplate reader (Bio-Tek Instruments Inc, Winookski, Vt). Absorbances were measured again after incubation of the reaction mixtures for 1 hour at 37°C. The change in the absorbance differences between the signal and reference wavelengths was calculated. The protein concentrations of the tissue samples were determined by the bicinchoninic acid method using a kit (Pierce Chemical Co, Rockford, Ill). The calibration curve was constructed with bovine serum albumin (Sigma). The total plasmin-generating activity of each tissue sample was expressed in terms of the activity of human u-PA and was normalized in terms of the protein content. The relative contributions of u-PA and t-PA to the total plasmin-generating activity were determined by comparing parallel aliquots incubated with and without amiloride, which specifically quenches u-PA. Amiloride inhibited 87% of the activity of human high-molecular-weight u-PA but had no effect on the activity of human single-chain t-PA. In samples of rat arterial tissue obtained 6 days after balloon catheter injury, the total plasmin-generating activity that was not blocked by amiloride was blocked by a goat polyclonal antibody that neutralizes human melanoma t-PA (American Diagnostica). This shows that all of the plasmin-generating activity of injured rat arterial tissue is accounted for by u-PA and t-PA and that amiloride may be used to discriminate between them.

Immunocytochemical Localization of t-PA

Animals were killed by intravenous overdose of sodium pentobarbital and were perfused fixed with 0.1 mol/L phosphate-buffered 4% paraformaldehyde at 120 mm Hg. The common carotid arteries were removed and embedded in OCT compound (Miles Inc, Elkhart, Ind) and were frozen in an ethanol/solid carbon dioxide bath. Frozen sections were washed in phosphate-buffered saline (PBS) with 0.1 mol/L glycine and then were incubated in PBS with 0.3% H$_2$O$_2$ to block endogenous peroxidase. Nonspecific protein binding was blocked with 2% normal goat serum/1% bovine serum albumin in PBS for 30 minutes. After incubation with affinity-purified rabbit anti-human t-PA immunoglobulin G (IgG) for 30 minutes, the sections were incubated with biotinylated rabbit anti-goat IgG for 30 minutes. Peroxidase labeling was performed using an avidin-biotin complex (Elite ABC, Vector Laboratories, Burlingame, Calif) and was visualized by using 0.05% 3'-diaminobenzidine (Sigma) in 50 mmol/L Tris-HCl, pH 7.6, with 50 $\mu L$ of 30% H$_2$O$_2$. All sections were exposed to the diaminobenzidine solution for 5 minutes. A second set of sections was stained identically, with the exception that nonimmune rabbit IgG was substituted for anti-t-PA IgG. All steps were followed by three rinses in PBS.

RNA Isolation and Blot Hybridization

Animals were killed by intravenous overdose of sodium pentobarbital, and the carotid arteries were quickly removed and frozen in liquid nitrogen. The tissue was ground to a fine powder under liquid nitrogen, and the total cellular RNA was prepared by guanidinium isothiocyanate and phenol-chloroform extraction. Equal amounts of total cellular RNA, as determined by absorption of the extracts at 260 nm, were loaded on a 1.2% agarose gel. Agarose gel electrophoresis and RNA transfer to nylon membranes were performed as previously described. After transfer, RNA was cross-linked to the membrane by baking...
at 80°C for 2 hours. Blots were exposed to UV light to visualize the ribosomal bands to verify equal loading and transfer in each lane. The RNA was hybridized with cDNA probes labeled by the random-primer extension method (Amersham Corp, Arlington Heights, Ill) with [32P]dCTP. Blots were then washed at 60°C in two changes of 45 mmol/L NaCl/4.5 mmol/L sodium citrate/0.1% sodium dodecyl sulfate. Signals were detected by exposure to Hyperfilm-MP (Amersham) at −80°C.

Administration of Anti-PDGF Antibody

A polyclonal antibody was raised by immunizing a goat with purified human platelet PDGF. IgG was dialedyzed against PBS and concentrated by ultrafiltration to a final protein concentration of 64.3 mg/mL. Nonimmune goat IgG was prepared by the same techniques from commercially available goat plasma. Before use, the IgG was sterilized by filtration through a 0.22-μm filter and then stored at 4°C. IgG was administered by intraperitoneal injection at a dose of 600 mg/kg given 24 hours before balloon injury, immediately after balloon injury, and then every 24 hours. The last dose was given 24 hours before the animals were killed.

Administration of Anti-Platelet Antibody

A polyclonal antibody was raised by immunizing a goat with rat platelets. The IgG was dialyzed against PBS and used at a final concentration of 27.6 mg/mL. A single intraperitoneal injection of 100 mg/kg was administered approximately 12 hours before balloon catheter injury. A 20-μL blood sample was taken from the tail vein into ammonium oxalate immediately before balloon catheter injury, and platelets were counted in a hemocytometer. The platelet count in normal rats was 1.09±0.05×10⁸/μL (mean±SEM). Animals with platelet counts below 2×10⁶/μL were considered to be thrombocytopenic, and animals injected with anti-platelet antibody but with platelet counts above this value were excluded from these studies.

Administration of Tranexamic Acid

Tranexamic acid (trans-4-[aminomethyl]cyclohexane-carboxylic acid; Sigma) was administered simultaneously in the drinking water at a concentration of 15 mg/mL and by gavage. For gavage, the drug was suspended in 2% sodium carboxymethyl cellulose (Sigma) at a concentration of 200 mg/mL and administered once daily in a volume of 5 mL/kg. The precise dose therefore depended on the rate of water consumption, which was measured daily. The mean dose was 2.73 g/kg per day (range, 2.36 to 3.00 g/kg per day).

The serum concentration of tranexamic acid was determined in rats that had received the drug for 4 days at an average daily dose of 2.98 g/kg of body weight. Blood was drawn from the abdominal aorta under anesthesia with sodium pentobarbital. After clotting, it was centrifuged at 1300g for 20 minutes at 4°C. The serum was diluted with an equal volume of 50 mmol/L Tris-HCl, pH 9.0, and then heated at 75°C for 30 minutes. After further centrifugation at 14 000g for 5 minutes at room temperature, the denatured serum samples were passed through microconcentrators (10⁴ molecular-weight cutoff; Amicon, Beverley, Mass) by centrifugation at 7000g for 60 minutes at 4°C. The filtrate was assayed for its ability to inhibit the generation of plasmin from human plasminogen by human single-chain t-PA by using methods similar to those described above for the assay of rat arterial t-PA activity. The inhibitory activities of the test sera were compared with a standard curve obtained by extracting control serum that had been spiked with known concentrations of tranexamic acid.

Statistical Analysis

The significances of differences between group mean values were determined using Student's t test. Two-tailed probability values of less than .05 were considered significant.

Results

SMC Migration After Balloon Injury

SMCs were first detectable in the intima of rat carotid arteries 3 days after balloon injury, when a few scattered cells were observed covering 0.2% of the intimal surface (Fig 1). After an additional 24 hours, the proportion of the intima covered by SMCs rose to 11.0%, a 52-fold increase. This increase over a 24-hour period is too great to be caused by the proliferation of intimal cells, because if all of the cells present on the intimal surface 3 days after arterial injury then went on to divide during the next 24 hours, they would double their intimal surface coverage to 0.4% at day 4. The dominant factor, contributing at least 96% of the accumulation of SMCs
In the intima 4 days after balloon catheter injury, is therefore their migration from the underlying media. In normal rat carotid arteries u-PA activity was not detectable and the t-PA activity was minimal (0.27±0.14 IU u-PA/mg protein). Sham operation of the carotid artery caused a significant increase in u-PA activity (0.61±0.17 IU u-PA/mg protein), but there was no significant effect on t-PA activity. Levels in balloon-injured vessels did not differ from those in sham arteries until the fourth day after injury (Fig 2). At this time point there was a 4.5-fold increase in t-PA activity, but no change in u-PA activity was observed. The t-PA activity reached a peak 6 days after injury and then gradually decreased, until by 28 days after injury it had returned to the level found in sham-treated animals. The activity of u-PA rose above that of sham animals at 5, 7, 8, and 9 days after injury but at other time points was not significantly different. The peak value was observed on day 5 (Fig 2).

Immunocytochemical analysis of t-PA localization showed that in uninjured arteries t-PA was associated mainly with the endothelium, with light staining in the adventitia (Fig 3, B). Two days after balloon injury, staining was visible in the occasional SMC close to the internal elastic lamina (Fig 3, C). By the fourth day after injury, most of the medial SMCs adjacent to the internal elastic lamina stained positively for t-PA (Fig 3, D). Those SMCs that had migrated to the intima at this time were also strongly stained for t-PA.

The time course of plasminogen activator gene expression was also investigated in balloon-injured rat arteries (Fig 4). Low levels of t-PA and u-PA mRNA were detectable in normal carotid arteries. A marked increase in the levels of both plasminogen activators was observed 4 days after balloon catheter injury, which was sustained until 7 days after injury.

**Inhibition of Plasmin**

A plasmin inhibitor, tranexamic acid, was administered orally to rats to assess the contribution of plasmin to SMC migration after balloon injury. As shown in Fig 5, tranexamic acid reduced the proportion of the intimal surface covered by SMCs 4 days after balloon injury by 73.1%, suggesting that plasmin is necessary for SMC migration. The plasmin inhibitory activity caused by tranexamic acid could not be directly measured in the tissue because of its high aqueous solubility and subsequent loss from the artery during ex vivo processing. Therefore, to verify that the injured vessels in vivo were exposed to concentrations of tranexamic acid that would inhibit plasmin, we determined the plasma concentrations in those animals given the drug. The measured plasma tranexamic acid concentration was 86±20 μmol/L, which was sufficient to significantly inhibit the activities of rat arterial t-PA and u-PA by 41±4% in an ex vivo assay. This dose had no significant effect on circulating platelet count (control, 1.03±0.05×10^6/L; tranexamic acid, 1.30±0.18×10^6/L).

**Thrombocytopenia**

The circulating platelet count in animals selected as thrombocytopenic was 7700±1000/L (mean±SEM), which represents less than 1% of the platelet count in normal animals. As shown in Fig 6, thrombocytopenia inhibited SMC migration when measured 4 days after balloon injury by 77.0%. The nonimmune goat IgG had no effect on SMC migration.

The level of t-PA activity was also significantly reduced at this time point by the induction of thrombocytopenia (Table 1). The mean activity was reduced by 57.1% in animals treated with the anti-platelet antibody. No change in u-PA activity was observed (data not shown). Neither the anti-platelet antibody nor the nonimmune IgG had any direct effect on the assay for plasminogen activator activity at concentrations up to 1 mg/mL.

**Inhibition of Endogenous PDGF**

The migration of SMCs to the intima was measured 4 days after balloon catheter injury in animals that had
FIG 3. Immunocytochemical localization of tissue-type plasminogen activator (t-PA) in rat carotid arteries after balloon catheter injury. Thin sections of rat carotid artery were obtained at intervals after balloon catheter injury, and a rabbit anti-human recombinant t-PA antibody was used to detect t-PA. The presence of brown peroxidase reaction product indicates sites of antigen recognition. Methyl green was used as a nuclear counterstain. Arrowheads mark location of internal elastic lamina. A, Staining with nonimmune rabbit immunoglobulin G; B, uninjured vessel; C, 2 days after injury; and D, 4 days after injury.

been treated 24 hours before injury with PBS, nonimmune goat IgG, or neutralizing anti-PDGF goat IgG. The anti-PDGF IgG significantly reduced migration by 79.0% as measured by the proportion of the intimal surface covered with SMCs (Fig 7). The nonimmune IgG had no effect on migration.

One puzzling feature of this study was the low rate of SMC migration seen in all groups. Only 4.2% of the

FIG 4. Expression of plasminogen activators in rat carotid arteries after balloon catheter injury. RNA was extracted at intervals after balloon injury and hybridized with probes for urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA). I, intima; M, media; 18S and 28S designate positions of 18S and 28S subunits, respectively, of rRNA.
Smooth Muscle Cell Migration (\% of Intimal Area)

**FIG 5.** Bar graph showing effect of inhibition of plasmin on smooth muscle cell migration 4 days after balloon catheter injury to the rat carotid artery. Tranexamic acid, a plasmin inhibitor, was administered orally to rats and migration was quantified by electron microscopic survey of the intimal surface. Results are expressed as mean values with associated standard error bars for groups of 6 rats.

The intimal surface was occupied by SMCs in the PBS-treated control animals, compared with 10.5% seen in previous control groups. The t-PA activity in these animals, however, was similar to that in previous control groups (present study, 3.07±0.47 IU u-PA/mg protein; historical control animals, 3.41±0.33 IU u-PA/mg protein). We cannot explain the low rate of migration in this study, although perhaps it could be related to the stress of receiving daily intraperitoneal injections. However, we think that the level of t-PA activity, the absence of any difference in migration between the PBS and nonimmune IgG groups, and the magnitude of the effect of the neutralizing antibody allow us to conclude that blocking endogenous PDGF results in significant reductions in SMC migration and t-PA activity.

The administration of the PDGF antibody also inhibited t-PA activity in balloon-injured carotid arteries (Table 2). t-PA activity was significantly inhibited by 42% in rats given the anti-PDGF antibody, whereas the nonimmune IgG had no effect. Neither the nonimmune nor the blocking antibody had any direct effect on the assays for rat u-PA and t-PA activity (data not shown).

**Discussion**

There are no SMCs in the intima of the normal rat carotid artery. Balloon catheter injury to this vessel results in the rapid development of a new tissue, the neointima, which is composed almost exclusively of SMCs. These cells originate in the media and migrate across the internal elastic lamina to populate the intima. Therefore, SMC migration is an obligatory step in the formation of a neointima in the rat carotid artery.

**SMC Migration After Arterial Injury**

There is limited information concerning the process of SMC migration into the intima, even though it is a

**TABLE 1. Reduction of t-PA Activity by Thrombocytopenia**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
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</thead>
<tbody>
<tr>
<td>PBS</td>
<td>6</td>
<td>3.72</td>
<td>0.39</td>
</tr>
<tr>
<td>Nonimmune IgG</td>
<td>12</td>
<td>5.27</td>
<td>0.62</td>
</tr>
<tr>
<td>Anti-platelet IgG</td>
<td>8</td>
<td>2.26*</td>
<td>0.43</td>
</tr>
</tbody>
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*P<.01 compared with nonimmune goat IgG.
PDGF as a Chemoattractant In Vivo

PDGF is a potent chemoattractant for SMCs in vitro, raising the possibility that it may have the same activity in injured arteries. It is likely that the most important source of PDGF in the injured vessel wall is the platelet. The predominant PDGF isoform in rat platelets is PDGF-BB, which is a high-affinity ligand for the β-subunit and which has been shown to stimulate rat SMC migration in vivo. Exposure of subendothelial collagen by balloon catheter injury causes platelets to adhere and to release α-granule contents, including PDGF. Therefore, in the acutely denuded artery there should be a high concentration of PDGF-BB at the luminal surface. Diffusion into the media creates a concentration gradient that is stabilized and maintained by binding of PDGF to proteoglycans in the extracellular matrix. This binding also prevents the clearance of PDGF. The presence of such a concentration gradient could be important for the directed migration of medial SMCs into the intima.

The concept that PDGF is important for SMC migration is supported by our finding that the presence of intimal SMCs is markedly inhibited in balloon-injured arteries of thrombocytopenic rats. Interestingly, this procedure does not influence SMC replication. However, platelets contain a number of other substances that are potent chemoattractants for SMCs and which...
would also be removed by platelet depletion. Our data on the PDGF antibody, which blocked SMC migration after balloon injury to the same degree, strongly suggest that PDGF is the major platelet component important for the migration of SMCs.

**PDGF and Plasminogen Activator Activity**

There are a number of reports that PDGF can influence the synthesis of proteolytic enzymes by cells in culture. It has been shown to stimulate the expression of collagenases by SMCs, and also stimulate plasminogen activator activity in osteoblasts. PDGF stimulates the production of plasminogen activator inhibitor-1 by SMCs, but it has been reported not to influence their overall fibrinolytic activity. In the present study we show that t-PA activity in injured arteries is significantly reduced by thrombocytopenia and with a blocking antibody to PDGF. These data strongly suggest that PDGF stimulates plasminogen activator expression in SMCs in vivo. It is possible that this is an indirect effect mediated by basic fibroblast growth factor (bFGF), as has been suggested for the effect of PDGF on SMC migration in vitro. In this regard, we have recently found that an antibody that blocks endogenous bFGF also markedly inhibits SMC migration after injury but without any significant reduction in plasminogen activator activity (C.L. Jackson, PhD, unpublished results). This suggests that bFGF and PDGF have different effects on SMCs in injured arteries and that both factors are necessary for stimulation of t-PA expression and the migration of cells to the intima. The ways in which PDGF, bFGF, and other factors interact to control SMC migration are not yet understood and will form a focus of future investigation.

Another unresolved issue concerns the timing of the migratory response to growth factors. Platelets adhere to the de-endothelialized vessel wall within seconds, but as is shown by our data, t-PA activity and SMC migration are not detectable until 3 to 4 days after injury. Although SMCs are not detectable in the intima until 3 to 4 days, their journey through the medial tissue could begin shortly after injury and not be detected. The expression and synthesis of t-PA may represent a final stage in the migratory process, facilitating movement across the internal elastic lamina. This could suggest that t-PA is necessary but not sufficient for migration, a hypothesis reinforced by the finding that some agents can inhibit SMC migration without affecting t-PA activity.

In summary, we have shown that inhibition of endogenous PDGF with a blocking antibody markedly reduces the migration of SMCs from the media to the intima after balloon injury to the rat carotid artery. We have also found that induction of thrombocytopenia inhibits the subsequent migration of SMCs, suggesting that platelets are an important source of promigratory PDGF. The generation of plasmin within the vessel wall is necessary for SMC migration, shown by the marked antimigratory effect of the plasmin inhibitor tranexamic acid. Both thrombocytopenia and inhibition of PDGF result in significant reductions in arterial t-PA activity, supporting the argument that plasmin is necessary for migration and suggesting that one way in which PDGF acts is to stimulate the expression and synthesis of t-PA by SMCs.
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