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Platelets, platelet-derived growth factor and arteriosclerosis

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Summary. Platelets participate in the pathogenesis of arteriosclerosis and in the progression of atherosclerosis by adhering to the damaged arteries and subsequently forming mural thrombi which are either swept away and embolize or are endothelialized and thus become part of the vessel wall. Rheologic considerations predict and blood perfusion experiments using flow chambers with exposed vessel wall components demonstrate that platelet participation increases with the wall shear rate and is thus particularly important in stenosed arteries (acute thrombosis) and the microvasculature (hemostasis). In addition to their involvement in thrombosis, activated platelets release growth factors, most notably a platelet-derived growth factor (PDGF) which may be the principal mediator of smooth muscle cell migration from the media into the intima and of smooth muscle cell proliferation in the intima as well as of vasoconstriction. The recent discovery that PDGF can be produced by additional cells involved in the pathogenesis of arteriosclerosis (endothelial cells, monocytes/macrophages, smooth muscle cells themselves) and that they may play a role in tumorigenesis has tremendously increased the interest in this growth factor and in potential antagonists.
Key words. Thrombosis; blood flow; wall shear rate; platelet adhesion; platelet thrombus growth; fibrin; endothelium; smooth muscle cell migration and proliferation.

The platelet is the key participant in thrombosis and hemostasis, particularly at high shear conditions. Furthermore, it has received a lot of attention from investigators whose primary interest was not related to platelet function in health and disease. These investigators probably chose the platelet as their research tool because it is an easily accessible human cell fragment which has numerous features in common with more complex nucleated cells, such as smooth muscle cells and neurons.

This contribution does not look at the platelet as a model for pathophysiological research but rather tries to elucidate its role in the pathogenesis of thrombosis and arteriosclerosis. These growing fields of research have benefitted a great deal from the work of biochemists and pharmacologists who used the platelet as a research tool. In addition, the study of platelet interactions with vessel wall components in flow systems, the molecular characterization of congential defects of platelet function, the successful culture of vascular endothelial and smooth muscle cells, as well as connective tissue research have contributed to the substantial progress made during the past decade in our understanding of the role of platelets in arterial thrombosis and arteriosclerosis. This progress is summarized below and was highlighted by the identification, isolation and cloning of the platelet receptors and adhesive proteins involved in platelet adhesion and aggregation and last but not least by the discovery, isolation and cloning of platelet-derived growth factor (PDGF) and other growth factors which may be involved in the pathogenesis of arteriosclerosis.

Arteriosclerosis, atherosclerosis and platelets

The term *arteriosclerosis* encompasses all forms of arterial disease which lead to a thickening of the intima and thus to a narrowing of the lumen of an artery [10].

Atherosclerosis, the most common form of arteriosclerosis, is usually associated with hypercholesterolemia. The main feature of a fully developed atherosclerotic lesion is the atheroma which consists of a nucleus containing cholesterolester, cellular debris and fat laden foam cells surrounded by a fibrous cap made of connective tissue and a few smooth muscle cells [28]. The fatty streak consists of an accumulation of subendothelial foam cells and is believed to be the precursor of an atheromatous lesion. Most foam cells of fatty streaks are derived from monocytes which migrated from the blood through the endothelial lining into the subendothelial space where they accumulate cholesterolester by the scavenger pathway [26, 32]. It is very unlikely that platelets play a role in this initial process. However, once large numbers of subendothelial foam cells have accumulated, occasional disruptions of the endothelial lining occur and accumulation of platelets is observed at such sites [26]. These observations in non-human primates and rabbits are corroborated by the fact that human atherosclerotic lesions contain substantial amounts of platelet-specific material [24]. Thus platelets contribute to the progression of atherosclerotic lesions by forming mural thrombi. Such thrombi release factors, most notably PDGF (see below) which stimulate smooth muscle cell migration and proliferation. Thrombi may not only be swept away by the blood stream, but also be endothelialized and thus become part of the vessel wall.

Other forms of arteriosclerosis such as those observed in *homocystinuria* or induced by *iatrogenic arterial damage* (angioplasty, bypass surgery) are primarily proliferative in nature. Homocystinuric patients develop severe fibromuscular intimal thickening of arteries at an early age and often die of severe arteriosclerosis with thromboembolic complications before age 20 [7, 19]. Harker et al. [19] were able to induce homocystinuria-like vascular lesions by infusion of homocystein into baboons. They observed desquamation of endothelial cells followed by platelet adhesion, thrombus formation, smooth muscle cell migration from the media into the intima, smooth muscle cell proliferation and connective tissue synthesis leading to intimal thickening. Antiplatelet therapy

inhibited this process [19]. Injury to the artery wall such as that produced by balloon catheter [5] is followed by a sequence of events similar to that described above for homocystinuria [6, 27]. Platelet accumulation on subendothelium is transient, peaks at about 10 min after endothelial denudation in rabbits [3] and is associated with the release of platelet α-granule contents into the media [15]. Thus growth factors derived from platelets may reach the smooth muscle cells of the media and contribute to their stimulation (see below). Severe medial damage associated with smooth muscle cell necrosis is followed by less neointima formation than moderate balloon injury which causes only endothelial denudation and little morphologic alteration of medial smooth muscle cells [6] probably because the smooth muscle cells have to migrate longer distances to repair the damaged area. Interestingly, gentle abrasion of a few endothelial cells is followed by adhesion of a few platelets to subendothelium only and by rapid reendothelialization without any migration or proliferation of smooth muscle cells [25]. It remains to be established whether a critical number of platelets must accumulate on subendothelium in order to release sufficient amounts of growth factors which then induce smooth muscle migration and proliferation or whether moderate balloon injury stimulates smooth muscle cells directly. The fact that intimal thickening induced by moderate balloon injury is significantly inhibited in severely thrombocytopenic rabbits [13] lends additional support to the notion that platelet-derived growth factor(s) may indeed play a role in the induction of the proliferative response after vascular injury [28].

More recently, it became evident that PDGF-like growth factors can be produced by a number of additional cells which participate in the pathogenesis of atherosclerosis – including endothelial cells, smooth muscle cells themselves and monocyte/macrophages [26]. These cells do synthesize PDGF in vitro upon stimulation by a number of agents. Non-denuding endothelial injuries can be envisaged to induce endothelial synthesis of PDGF and its release into the underlying vessel wall. Among the conditions responsible for these forms of injury may be smoking (with carbon monoxide and/or hypoxia as the noci) and chronic hypercholesterolemia, the leading risk factor for atherosclerosis.

Furthermore, chronic hypercholesterolemia has been shown to promote attachment of monocytes to the endothelium, the entry of these cells into the subendothelium and their conversion into macrophages [26]. These macrophages, alone or in concert with endothelial cells and perhaps injured or activated smooth muscle cells, could then also become potential sources of PDGF and other growth factors.

The above considerations suggest that arterial thrombosis and platelet derived growth factor(s) play essential roles in the progression of atherosclerosis and in the proliferative response of the vessel wall to injury, respectively. They are therefore discussed in some greater detail in the following chapters.

Arterial thrombosis

Blood flow and thrombogenesis

Thrombogenesis induced by vascular subendothelium can be investigated in annular perfusion chambers at various blood flow conditions [3]. Recent perfusion studies using non-anticoagulated blood from rabbits and human volunteers, respectively, demonstrated that fibrin formation and platelet adhesion on subendothelium, as well as platelet thrombus growth are highly shear rate dependent [4, 37]. At low (venous) wall shear rates fibrin deposition on subendothelium predominates whereas at high (arterial) wall shear rates little fibrin forms initially and the thrombotic masses mainly consist of platelets. Rheologic considerations explain this difference: fibrin formation is the result of a cascade of time consuming enzymatic processes; procoagulant factors and fibrin-monomers are swept away at high shear before the latter can aggregate to form fibrin. By contrast, more platelets are present close to the vessel wall at high shear rate and they possess membrane glycoproteins which react immediately with components of the subendothelium to adhere irreversibly [34]. Platelet thrombus growth also increases with the shear rate. In addition, platelet thrombi which grow rapidly appear to be more stable than those which grow at intermediate shear rates [4]. Thus rapid occlusion of an injured blood vessel is the more likely to occur the higher the shear rate, i.e. particularly in stenosed arteries (acute arterial thrombosis) and the microvasculature (hemostatic plug formation).

Platelet adhesion

The rate of platelet adhesion increases with the shear rate [4, 34]. The mechanism of platelet adhesion is not yet fully understood. Based on perfusion studies using the combination of various substrates (subendothelium, defined connective tissue components) with various perfusates (blood from patients with defined platelet and/or plasmatic defects; poly- and monoclonal antibodies against certain epitopes of von Willebrand factor and/or against platelet glycoprotein Ib and IIb/IIIa; reconstituted blood lacking certain plasma components) the following simplified picture can be drawn at present [23]: The initial attachment of a platelet to a surface, particularly at high wall shear rates, requires von Willebrand factor (vWF) bound to collagen or possibly other connective tissue components on the surface and the presence of glycoprotein Ib (GPIb) on the platelet membrane. The binding of conformationally changed vWF to GPIb triggers the expression of the membrane glycoprotein IIb/IIIa (GPIIb/IIIa). This receptor for the adhesive proteins fibrinogen, fibronectin and vWF is involved in platelet-spreading, a second step in the adhesion process, and in platelet–platelet cohesion (thrombus growth). In addition GPIa, the putative receptor for collagen, appears to play a role in spreading [34].

Platelet thrombus growth and stability

Platelet thrombus growth may rapidly lead to vascular occlusion, i.e. acute thrombosis with all its consequences and hemostasis, respectively. Whether or not occlusion occurs depends on growth and stability of the platelet masses attached to the vessel wall. Particularly the regulation of platelet thrombus stability is still very poorly understood; thrombospondin and the activation of the coagulation system (but at least initially not actual fibrin formation) play important roles [4, 34, 36]. However, as shown by perfusion studies, the effects of a severe defect in the coagulation cascade on platelet thrombus growth and/or stability are also shear rate dependent and much more pronounced at low than at high shear [34, 36] (unpublished results). As for platelet thrombus growth, the expression of a functional GP IIb/IIIa receptor is essential. A defect in this receptor either hereditarily (thrombasthenia) or induced by antibodies abolishes platelet thrombus growth at all shear rates [23, 34, 36]. It is thus an attractive target for pharmacologic intervention.

Platelet-derived growth factor (PDGF)

Discovery and structure of PDGF

The discovery of PDGF in 1974 when it was observed that material released from platelets is the principal source of mitogen present in whole blood serum for a number of cultivated cells of mesenchymal origin, including smooth muscle cells and fibroblasts, but not endothelial cells (for early review see Ross and Glomset [28]).

Subsequently, PDGF was purified from platelets by a number of groups [29] and found to be a highly basic glycoprotein of Mr approximately 30,000. Reduction and alkylation de-

stroys the mitogenic activity of PDGF and produces several proteins of Mr 14,000 to 17,000, suggesting that it is a disulfide-linked dimer. Amino acid sequence analysis showed the presence of two distinct but homologous sequences, termed A and B [22]. The finding that in human platelets both chains are present in comparable amounts was initially taken to suggest that human platelet PDGF is an A–B heterodimer. This is now less clear, however, as it was found that porcine PDGF contains mitogenically active B–B homodimers [33] and PDGF produced by osteosarcoma cells consists of active A–A homodimers [9, 21]. Thus, it remains to be seen whether human platelet PDGF consists of A–B heterodimers or of a mixture of A–A and B–B homodimers or whether all three species can be present.

Sources of PDGF

In addition to the platelet/megakaryocyte a number of other cells have recently been found to synthesize and release PDGF or PDGF-like activity in vitro [29]. Among these are mononuclear phagocytes (monocytes/macrophages), endothelial cells and vascular smooth muscle cells. In addition a number of transformed cells also produce PDGF-like activity [29]. The latter will not be discussed in the framework of this essay.

Mononuclear phagocytes (monocytes/macrophages). Upon stimulation by agents such as lipopolysaccharides or immune complexes mononuclear phagocytes in vitro express the PDGF-B gene and release significant amounts of mitogenic material attributable to PDGF into the medium [31]. The ability of macrophages to synthesize PDGF may be of particular importance in the formation of the proliferative lesions of atherosclerosis.

Endothelial cells. Cultured vascular endothelial cells release PDGF-like activity into their culture medium and express the PDGF–B gene in particular if they are kept in culture for longer periods of time [29]. PDGF production or release by cultivated endothelial cells can be stimulated further by exposure to endotoxin and phorbol esters at toxic concentrations [12] as well as to thrombin [20] and factor X [14]. This may be taken to suggest that PDGF can be produced and/or released in vivo by endothelial cells that are stimulated e.g., when the coagulation cascade is activated by a vascular damage.

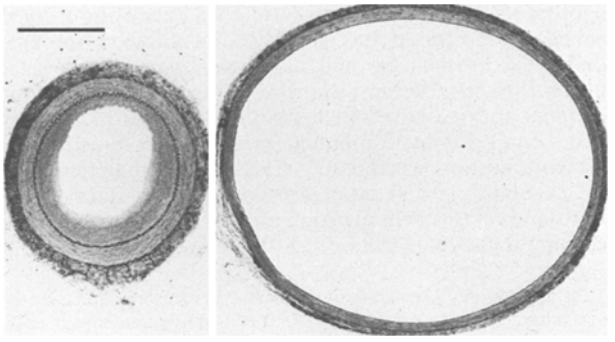
Vascular smooth muscle cells. Rat pup arterial smooth muscle cells (SMC) can synthesize PDGF-like activity [30]. In contrast to vascular endothelial cells which do not possess PDGF receptors, cultivated SMC do bind and respond to PDGF (see also below). These observations are consistent with the hypothesis that PDGF may, in an autocrine fashion, stimulate SMC proliferation and activity in the growing rat aorta [11]. The finding that rat carotid SMC cultivated from balloon catheter-induced neointimal proliferates produce more PDGF and express fewer PDGF receptors than do SMC from an uninjured artery [35], further suggests that PDGF production by adult rat SMC can be reactivated if these cells have been stimulated to proliferate in vivo. It remains to be seen whether SMC from other species can also produce PDGF or whether this is a rat-specific phenomenon.

Effects of PDGF

Proliferation. The major ultimate result of PDGF binding to responsive cells is cell doubling (proliferation) which requires 30–40 h to occur. However, prior to this event a number of cellular responses occur within seconds, to minutes, to hours following binding of PDGF to its receptor [29]. Among the rapidly occurring processes triggered by PDGF are: the autophosphorylation of the PDGF receptor on tyrosine, increased phosphorylation of cytoplasmic proteins and an increased metabolism of membrane phosphoinositides, giving rise to increased levels of the putative second messengers inositol trisphosphate and diacylglycerol. These second messengers, then, appear to lead to increased levels of cytoplasmic free Ca^{++} and activation of protein kinase C, respectively. Arachidonic acid formed from intracellular diglycerides can be transformed rapidly to prostaglandins, including PGI_2 and PGE [18]. Also within minutes to hours PDGF induces the protooncogenes c-fos [16] and c-myc [1], the products of which seem to play an important role in DNA synthesis. Over periods of hours PDGF increases the receptors for low density lipoproteins and somatomedin [26, 29]. Furthermore, PDGF leads to increased protein and RNA synthesis and increased connective tissue synthesis [29]. The accumulation of connective tissue around proliferating cells may play an important role in a variety of diseases including liver cirrhosis and rheumatoid arthritis and in the proliferative lesions of arteriosclerosis.

Of importance is the observation that PDGF is the only mitogen for mesenchymal cells that can also induce a chemotactic response in its target cells [17]. This property of PDGF may be of particular importance in arteriosclerosis, where PDGF would induce medial muscle cells to migrate into the subintimal space prior to stimulating them to proliferate. It is not known presently whether the structural features of PDGF responsible for mitogenic and chemoattractant activity are the same.

Vasoconstriction. PDGF has recently been shown to be a potent vasoconstrictor, inducing concentration-dependent contraction of rat aorta strips in subnanomolar concentrations [8]. This activity of PDGF could be of importance in vivo, as it may lead to a further reduction of the lumen at sites of an artery that is already narrowed by smooth muscle proliferative lesions. Indeed when rabbit iliac arteries were injured by balloon catheter to produce proliferative lesions [6] we consistently observed a marked vasoconstriction concomitant to intimal thickening (fig.). The observed reduction in lumen amounted to almost 70% and was mainly due to vasoconstriction (89%) and only to a minor part (11%) to neointima formation [2]. Experiments with PDGF neutralizing agents or a PDGF antagonist should help to find out whether PDGF is indeed responsible for the observed proliferative and vasoconstrictive responses.



Cross sections of the left and the right external iliac artery of a rabbit. The artery on the left was damaged by balloon catheter [5, 6] 4 weeks before fixation by perfusion of 2% glutaraldehyde at constant pressure of 80 mmHg. Removal of the endothelium and vascular damage resulted in the formation of a neointima (smooth muscle cells + connective tissue) and massive vasoconstriction. Bar indicates 1 mm.

Conclusion

Several mechanisms involved in the pathogenesis of arterial thrombosis and arteriosclerosis have been elucidated recently and are discussed above. Most of the ligands and receptors

involved in these mechanisms have been or are about to be cloned and expressed and should be accessible in amounts needed for biochemical and biophysical work in the near future. Precise structural knowledge together with epitope mapping and inhibitory peptides should help to rationally design and optimize compounds which interfere with these mechanisms and therefore might be useful in the prevention of thrombosis and arteriosclerosis. However, since the ligands and receptors in question are all fairly large proteins, reaching these goals will be a difficult task.

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