Aging and plasminogen activator inhibitor-1 (PAI-1) regulation: implication in the pathogenesis of thrombotic disorders in the elderly

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Received 27 August 2004; received in revised form 19 October 2004; accepted 10 November 2004
Available online 8 December 2004

Time for primary review 27 days

Abstract

Thrombotic cardiovascular diseases increase in incidence in the elderly, a tendency dependent on the age-related changes in vascular and hemostatic systems that include platelets, coagulation, and fibrinolytic factors as well as in the endothelium. The hypercoagulability of and advanced sclerotic changes in the vascular wall may contribute to the increased incidence of thrombosis in the elderly. One of the important key genes for aging-associated thrombosis is plasminogen activator inhibitor-1 (PAI-1), a principal inhibitor of fibrinolysis. The expression of PAI-1 is not only elevated in the elderly but also significantly induced in a variety of pathologies associated with the process of aging. These conditions include obesity, insulin resistance, emotional stress, immune responses, and vascular sclerosis/remodeling. Several cytokines and hormones, including tumor necrosis factor-α, transforming growth factor-β, angiotensin II, and insulin, positively regulate the gene expression of PAI-1. The recent epidemic in obesity with aging in the industrialized society may heighten the risk for thrombotic cardiovascular disease because adipose tissue is a primary source of PAI-1 and cytokines. Emotional or psychosocial stress and inflammation also cause the elevated expression of PAI-1 in an age-specific pattern. Thus, PAI-1 could play a key role in the progression of cardiovascular aging by promoting thrombosis and vascular (athero)sclerosis. Further studies on the genetic mechanism of aging-associated PAI-1 induction will be necessary to define the basis for cardiovascular aging in relation to thrombosis.

Keywords: PAI-1; Obesity; Stress; Immune response; Vascular remodeling

1. Introduction

The incidence of thrombotic cardiovascular disease increases with age [1], and recent studies have begun to address the important clinical problem of “aging and thrombosis” [2]. Age-related changes may occur in the vascular and hemostatic systems, which include platelets, coagulation, and fibrinolytic factors as well as in the endothelium. Aging-associated sclerotic changes in the vascular wall may also contribute to the increased incidence of thrombosis in the elderly [3]. The hypercoagulability of the blood in the elderly may be yet another cause of the increased thrombotic tendency. For example, platelet activity is enhanced with advancing age, and aging is associated with increased plasma levels of several blood coagulation factors (e.g., factor VII, factor VIII, and fibrinogen) [4], all of which have been shown to be risk factors for thrombotic diseases [5]. On the other hand, a proportional increase in natural anticoagulant factors (e.g., protein C, protein S, antithrombin, tissue factor pathway inhibitor, etc.) has not been observed in the elderly [6]. The fibrinolytic system is impaired by aging since a progressive prolongation of the euglobulin lysis time [7] and an increase in plasminogen activator inhibitor-1 (PAI-1), a principal
regulator of fibrinolysis [8], have been observed with aging [9]. Thus, the inappropriate expression of procoagulant/antifibrinolytic genes may underlie the occurrence of thrombotic events, which are frequently observed in the elderly. However, the molecular link between aging and prothrombotic states due to aberrant expressions of procoagulant/antifibrinolytic genes remains to be elucidated. One aim of this review is to describe the pathological significance of PAI-1 in cardiovascular aging in relation to thrombosis based upon clinical observations and animal studies.

2. PAI-1 and its regulation in various clinical states associated with aging

PAI-1 is a rapid and specific inhibitor of both tissue-type and urokinase-type plasminogen activators (t-PA and u-PA) and may be the primary regulator of plasminogen activation in vivo [8]. The synthesis of PAI-1 is increased in activated or injured endothelial cells and smooth muscle cells, and abundant PAI-1 is also secreted by activated platelets. The increased expression of this potent inhibitor in vivo will suppress the normal fibrinolytic system and create a prothrombotic state, resulting in pathological fibrin deposition followed by tissue damage. Increased expression of PAI-1 in vivo is related to the development of tissue pathologies [10] such as thrombosis, fibrosis, and cardiovascular disease [11]. Factors inducing PAI-1 expression in vitro and pathologies associated with elevated PAI-1 in vivo are listed in Table 1.

2.1. Myocardial infarction

A rise in the circulating level of PAI-1 has been shown to precede the occurrence of myocardial infarction [12]. Survivors of myocardial infarction had impaired fibrinolytic activity due to elevated levels of plasma PAI-1 [13], which is also associated with early recurrence of myocardial infarction [14]. Acute increases in plasma PAI-1 levels in patients with acute ST-elevated myocardial infarction are strongly associated with the risk of mortality during a 1-month period [15]. Thus, PAI-1 seems to be a risk factor for the development and recurrence of thrombotic cardiovascular diseases. It is also known that the renin–angiotensin system is activated after acute myocardial infarction [16]. A strong relationship has been shown between the activation of the renin–angiotensin system and plasma PAI-1 [17], and it is known that angiotensin II can induce the expression of PAI-1 [18]. The plasma level of another fibrinolytic inhibitor, thrombin-activatable fibrinolysis inhibitor (TAFI), is also associated with increased risk for cardiovascular diseases [19,20]. The activity of TAFI in young patients with myocardial infarction was found to be significantly higher and has been correlated positively with the PAI-1 level [21], suggesting that a hypofibrinolytic state largely contributes to the occurrence of cardiovascular events.

2.2. Obesity and insulin resistance

Clinically, thrombotic cardiovascular diseases occurring in aged subjects are often associated with obesity. Obesity is an independent risk factor for the development of thrombotic cardiovascular disease [22]. In a large community-based sample, an increased body-mass index has been associated with increased risk of heart failure [23]. The increased incidence of cardiovascular disease may be associated with impaired fibrinolysis, which has been shown to be present in obese patients [24]. For example, increased plasma PAI-1 levels have been correlated with the amount of visceral fat in obese humans [25], and PAI-1 is commonly and predictably elevated in individuals with insulin resistance and type II diabetes [26]. Vascular dysfunction caused by insulin resistance is associated with the activation of the renin–angiotensin system [27]. Taken together, obesity, insulin resistance, and hypertension are closely related in terms of PAI-1 induction, resulting in the development of thrombotic cardiovascular disease. In this context, we have speculated on the potential benefit of therapies that might prevent an acute increase in plasma PAI-1. These potentially include angiotensin-converting enzyme inhibitors [28], insulin-synthesizing [29] or-sensitizing agents [30], and other agents that improve endothelial function and nitric oxide production systematically.

2.3. Atherosclerosis

By limiting extracellular proteolysis in developing atherosclerotic lesions, PAI-1 may play a significant role not only in the organization of mural thrombi within the plaque but also in the neointimal proliferation of smooth muscle cells and in the neovascularization of the plaque. High plasma levels of PAI-1 may be associated with the development of atherosclerosis. Investigations of PAI-1 expression in the arteries of atherosclerotic subjects have
revealed significantly increased levels of PAI-1 mRNA in severely atherosclerotic vessels, including the abdominal aorta, iliac artery, and femoral artery, as compared with those in normal or mildly affected arteries [31]. In situ hybridization analysis revealed an abundance of cells (e.g., endothelial cells, smooth muscle cells, and macrophages) positive for PAI-1 mRNA within the thickened intima of atherosclerotic arteries, mainly around the base of the plaque [31,32]. Fibrin, which is a consistent component of atherosclerotic plaques, may contribute to plaque growth through the stimulation of smooth muscle cell proliferation [33,34] and through the binding and accumulating of low-density lipoprotein [35]. Intravascular or mural thrombosis [33,34] and through the binding and accumulating of low-density lipoprotein [35]. Intravascular or mural thrombosis is a frequent histological feature of atherosclerotic lesions and appears to play a role in the intimal thickening and fibrotic characteristic of advanced lesions. Thus, localized alterations in fibrinolytic activity due to the increased expression of PAI-1 in blood vessels may contribute to the progression of atherosclerotic process by promoting fibrin deposition and extracellular matrix accumulation in the lesions [36].

2.4. Stress

Hypercoagulability and thrombotic diseases appear to be induced also by mental [37] and psychosocial stress [38]. Because aged subjects may have lower tolerance to stress, they are susceptible to thrombosis caused by a variety of stress factors [39]. Chronic stress, defined as feelings of fatigue, lack of energy, increased irritability, and demoralization, has also been associated with elevated plasma PAI-1 antigen in middle-aged men [40]. The stress-mediated activation of the sympathetic nervous system, whose activity is heightened in older subjects [41], may contribute to the induction of PAI-1 [42]. Oxidative stress, one of the characteristics of diabetes, boosts PAI-1 expression by activating the PAI-1 promoter through an AP-1 response element [43]. Thus, the stress-induced PAI-1 may be responsible for the onset of thrombotic disease associated with a variety of stress factors, especially in the elderly.

2.5. Endotoxemia

PAI-1 is an acute-phase reactant linked to inflammatory and prothrombotic markers because it is induced by a variety of cytokines [e.g., tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-1 and -6], but most strongly by the endotoxin of Gram-negative bacteria [44,45]. Endotoxin (lipopolysaccharide, LPS) profoundly alters the fibrinolytic system [46], frequently leading to prothrombotic states. Recently, PAI-1 has been regarded as a prognostic marker of sepsis caused by Gram-negative bacteria [47], which is often observed in hospitalized elderly patients. Septic patients with high plasma PAI-1 levels have a poor prognosis because of progressive multiple organ failure due to microvascular fibrin deposition and subsequent cell damage [48,49]. After endotoxin administration, elderly individuals are more susceptible to endotoxin-induced effects than the young, showing severe abnormalities in the cardiorespiratory system, such as hypotension, increased heart rate, and increased respiratory rate [50]. Overall, PAI-1 is regarded as a key molecule in the development of septic organ damage because this protein is strongly induced by inflammatory mediators and promotes microvascular and extravascular fibrin deposition.

2.6. Malignancy

A couple of reports have stated that basal plasma PAI-1 levels were found to be significantly elevated in patients with malignant conditions [51], which are sometimes observed in elderly subjects. Deep-vein thrombosis is sometimes observed in patients with malignancy due, not only to the increased activation of coagulation, but also to impaired fibrinolysis. An increasing number of studies demonstrate that high PAI-1 levels indicate a poor prognosis for the survival of patients with a variety of cancers, including breast [52], lung [53], and gastric [54] cancer. PAI-1 may play a critical role in tumor-cell invasion, and the possible mechanism is that PAI-1 blocks the interaction of integrins with vitronectin, thereby loosening the cells from their substratum and promoting cell migration [55].

2.7. Genomics on the PAI-1 up-regulation in relation to thrombosis

The genomics of PAI-1 is relevant to the PAI-1 regulation in association with thrombotic/bleeding phenotype as follows. There have been several reports describing elevated plasma PAI-1 levels in familial or sporadic venous thrombophilia [56]. On the other hand, several individuals have been identified with little or no detectable functional PAI-1 in their plasma due to the mutation in the PAI-1 gene [57], and all have had lifelong bleeding problems [58]. Moreover, disruption of the PAI-1 gene in mice was associated with a mild hyperfibrinolytic state and increased resistance to thrombosis [59]. Transgenic mice overexpressing the human PAI-1 gene developed thrombotic problems in the extremities [60], and an excess of PAI-1 can promote coronary arterial thrombosis in these mice [61]. The coronary thrombi developed in an age-dependent manner in the transgenic mice, and 90% of the mice older than 6 months had spontaneous thrombotic occlusions of the coronary arteries [61].

An association between one of the DNA sequence variations of the human PAI-1 gene, the 4G/5G polymorphism, and plasma PAI-1 levels has been suggested, with the 4G homozygotes having the highest PAI-1 levels and the 5G homozygotes having the lowest [62]. For example, in young myocardial infarction patients, the prevalence of the unfavorable 4G allele was higher than in healthy controls [62]. Furthermore, the 4G/4G genotype has
been shown to be significantly associated with a history of coronary artery disease in patients diagnosed by coronary angiography [63] and also in patients with noninsulin-dependent diabetes mellitus [64,65]. However, it is still controversial whether the 4G/5G polymorphism increases the risk for myocardial infarction and thromboembolism [66].

3. PAI-1 induction in animal models of aging and prothrombotic states

Experimental studies on animals have also demonstrated a link between increased expression of PAI-1 and thrombotic events. In the following, we describe the induction of the PAI-1 gene in a variety of mouse models of aging and prothrombotic states.

3.1. PAI-1 expression in a mouse model of premature aging, "klotho"

A mouse model of premature aging, named the “klotho (kl/kl) mouse”, was generated through the insertional mutation of a transgene disrupting a newly found gene locus named “klotho” [67]. The kl/kl mouse exhibits a syndrome resembling human aging, including a short life span, growth retardation, osteoporosis, arteriosclerosis, obstructive pulmonary disease, and atrophy of the skin. Higher levels of renal PAI-1 mRNA expression and active PAI-1 antigen in the plasma were found in kl/kl mice in comparison with wild-type mice [68], suggesting impaired fibrinolysis in this mouse model of aging. The kidneys of kl/kl mice showed severe sclerotic changes, with calcification and spontaneous glomerular fibrin deposition. These observations suggest that the aging-associated induction of PAI-1 contributes to the development of renal sclerotic changes and thrombosis. Interestingly, in the heart of kl/kl mice, the cardiomyocytes and the cells in the myxomatous-degenerated mitral valve with calcification also expressed abundant PAI-1 mRNA [68]. The induction of PAI-1 gene expression in cardiomyocytes may contribute to microvascular injury and cardiac muscle degeneration in the hearts of kl/kl mice.

3.2. PAI-1 induction in an experimental model of vascular remodeling

One candidate for the paracrine factor involved in vascular remodeling would be the metalloproteinases (MMPs), of which activity is increased in the arteries of aged animals [69]. The plasminogen activator/plasmin system is an important regulatory system in the onset of cardiac wound healing and arterial remodeling [70] because plasmin can modulate the activity of MMPs by activating proMMPs to MMPs [71]. Age-dependent induction of PAI-1 would enhance the accumulation of ECM components in a variety of tissues, including cardiac and vascular tissues. It has been reported that adenoviral PAI-1 overexpression resulted in the prevention of cardiac rupture after myocardial infarction through the inhibition of local proteolysis [72]. Moreover, PAI-1-deficient mice were found to be resistant to the progression of coronary perivascular fibrous change in a model of long-term nitric oxide (NO) synthase inhibition [73]. Mice deficient in PAI-1 showed less development of cardiac fibrosis after infarction than wild-type mice [74], suggesting that PAI-1 deficiency may prevent the increase of collagen deposition by accelerating matrix degradation. Thus, PAI-1 could regulate the activation of MMPs and has indeed been implicated as an important modulator during the process of cardiac repair and vascular remodeling.

3.3. PAI-1 induction in a mouse model of obesity

High expression levels of PAI-1 mRNA have been detected in murine adipose tissue [75]. This observation suggests that adipose tissue is the primary source of PAI-1 in the obese condition. Adipose-derived PAI-1 expression is dramatically up-regulated and significantly increased as a function of age in genetically obese mice, whose adipocytes express PAI-1 mRNA abundantly [76]. PAI-1 expression in cultured adipocytes has been strongly induced by insulin [76] and glucose [77], suggesting that PAI-1 expression in adipocytes may be strongly associated with insulin resistance [78]. Interestingly, insulin-resistant adipocytes can still respond to insulin stimuli in terms of the induction of the PAI-1 gene [79], suggesting that the expression of PAI-1 is up-regulated by insulin signal independently of insulin sensitivity.

3.4. Stress-induced PAI-1 and thrombosis in association with aging

A dramatic induction of PAI-1 gene has been observed in a mouse restraint-stress model [80], indicating that PAI-1 is a major stress-induced gene. The specific localization of the increased PAI-1 mRNA in epithelial cells, vascular smooth muscle cells, cardiovascular endothelial cells, adrenomedullary chromaffin cells, and neural cells of the para-aortic sympathetic ganglion has been demonstrated in restraint-stressed aged mice [80]. Restraint stress activates the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, leading to the increased secretion of glucocorticoid hormone and adrenaline, both of which induce PAI-1 expression in vivo [42,81]. The magnitude of PAI-1 mRNA induction due to restraint stress is the highest in the adipose tissue among the tissues examined, and the adipocytes are responsible for this induction [80]. Thus, adipose tissue/adipocytes may be one of the principal sources of PAI-1 expression in response to stress.

More importantly, stress-induced PAI-1 expression has been dramatically enhanced in aged mice [80], indicating an increased ability of aged animals to mount a PAI-1 response to stress. The mRNA induction of a procoagulant gene,
tissue factor (TF), in several tissues due to restraint stress is also higher in aged mice than in young mice [82]. These responses may elevate the procoagulant/antifibrinolytic potential, contributing to the increased incidence of stress-associated thrombotic events in the elderly. Indeed, stress-induced renal glomerular thrombosis is more pronounced in aged mice compared with young mice [80]. This difference in the thrombosis phenotype between young and aged mice may result from a much greater induction of the PAI-1 gene at the systemic and regional levels in aged mice. Thus, an age-related increase in the PAI-1 response to stress may exacerbate vascular injury and subsequent tissue damage as aging progresses.

3.5. Increased microthrombosis with PAI-1 induction in LPS-treated aged animals

Aged rats have shown increased susceptibility to hemorrhaging and intravascular hypercoagulation following endotoxin administration, resulting in a higher mortality of aged rats as compared to young rats [83]. In these studies, a greater increase in PAI-1 activity and a more significant decrease in total PA activity have been demonstrated in the plasma of aged rats treated with endotoxin in comparison with young rats [84]. Interestingly, renal glomerular fibrin deposition and renal PAI-1 gene expression were markedly induced and sustained in LPS-treated aged mice, as compared with young mice [85]. This increased response of the aged mice to LPS in PAI-1 induction, together with the observation that little fibrin was detected in LPS-treated PAI-1 deficient mice, suggests that PAI-1 contributes to an enhanced thrombotic tendency in aged mice suffering from endotoxemia. Thus, aged animals may tend to develop thrombosis due to the high antifibrinolytic potential in endotoxemia and inflammatory processes.

3.6. Enhanced immune response with cytokine induction in aged animals

The expression of CD14, which is a major receptor for LPS on the cell surface triggering a signaling cascade leading to cytokine production [86], has been induced by LPS in a variety of tissues [87]. The expression of CD14 in rat cardiac tissues was found to be more increased in aged animals after LPS treatment, suggesting that innate immune response is augmented with aging [88]. The magnitude of the induction in tissues of CD14 and Toll-like receptor 4 (TLR4), which is identified as another signaling receptor for LPS [89], was found to be greater in LPS-treated aged mice than in young mice [85], suggesting that LPS binding and signaling inside cells is augmented in aged mice. Indeed, higher levels of TNF-α have been detected in the plasma of LPS-treated aged mice in comparison with those of young mice [85], and this response of TNF-α may result in the dramatic induction of PAI-1 in aged mice. Overall, the greater magnitude of the induction of CD14 and TLR4 gene in LPS-treated aged mice may cause a larger increase in PAI-1 expression, leading to enhanced tissue microthrombosis.

Obesity could be considered a low-grade inflammatory state [90]. Several observations indicate that interleukin-6 and TNF-α are elevated in obesity [91], the latter contributing to the insulin-resistant state [92]. Interleukin-6 probably plays an important pathogenic role in a variety of disorders associated with chronic stress and physiological aging [93], such as the induction of PAI-1 [94]. Obese mice treated with neutralizing antibodies to TNF-α not only acquire increased insulin sensitivity but also significantly reduced levels of plasma PAI-1 antigen and adipose-tissue PAI-1 and TGF-β mRNAs [95]. These observations provide direct evidence that TNF-α is a common link between obesity, insulin resistance/hyperinsulinemia, PAI-1, and TGF-β, the last of which is also elevated in obese mice [96]. This establishes a central role for TNF-α in a number of the metabolic disorders associated with obesity. Similar striking elevation of TNF-α was observed in restraint-stressed aged mice [80], suggesting that the induction of cytokines in response to stress is augmented in aged individuals.

4. Procoagulant proteins/molecular markers and platelet function in the elderly

The levels of fibrinogen and factor VIII, both of which are acute-phase reactants, are significantly increased in the elderly [97]. Elevated levels of fibrinogen and factor VIII have been correlated with increased risk of venous thrombosis and cardiovascular events [98,99]. In contrast, factor VII is not an acute-phase reactant and has been identified as an independent risk factor for cardiovascular events [100]. Importantly, factor VIIa is also increased in centenarians [101], suggesting that the coagulation response, initiated by the binding of factor VIIa to TF, is accelerated in the elderly.

Molecular markers of thrombin generation also increase with age [102]. For example, elevated levels of the prothrombin fragment 1+2 (F1+2) have been observed in the elderly, suggesting the presence of excessive plasma factor Xa activity [103]. Other molecules of prothrombotic markers (e.g., fibrinopeptide A and B, factor X-activation peptide, factor IX-activation peptide, and the thrombin–antithrombin complex) have been observed to increase with age [101]. Centenarians have been found to have higher levels of the plasmin–antiplasmin complex and D-dimer compared with younger controls, suggesting a hypercoagulable state with reactive hyperfibrinolysis [101].

Although the proximate cause of elevated coagulation factor levels with aging may be multifactorial, recent studies have demonstrated that certain genomic elements regulate the age dependency of expression. Two genetic elements, AE5’ and AE3’, which contribute to the age-related increase
in factor IX levels, have been discovered in the human factor IX gene [104]. AE5', which is present in the 5' untranslated region and a consensus motif for the transcriptional factor, is necessary for the liver-specific expression of the human factor IX gene and for its stable transcription as the individual ages. AE3', which is an element in the 3' untranslated region, would increase human factor IX mRNA stability with age. The elements that control age-related gene expression were also discovered in the gene of anticoagulant protein C [105]. However, in general, it appears that the elevation in the anticoagulant proteins levels with aging does not keep pace with that of coagulant protein levels, thus contributing to a prothrombotic state in the elderly [106].

Platelet function is a critical determinant of the propensity to thrombosis, because activated platelets greatly accelerate thrombin generation. Markers of platelet activation, β-thromboglobulin and platelet factor 4, are significantly elevated with age [107]. Platelets from elderly patients may be less susceptible to inhibition by prostacyclin because the density of both high- and low-affinity receptors for prostacyclin decreases with aging [108]. The increase platelet activity with aging is correlated with a larger content of platelet phospholipids, suggesting an age-related increase in platelet transmembrane signaling or second messenger accumulation [109]. Von Willebrand factor, which enhances platelet interaction with the damaged endothelium or subendothelium and which is associated with atherosclerosis, also increases with age [110].

5. Alterations in the vascular wall with aging

Structural changes in the vascular wall at the level of the extracellular matrix, vascular smooth muscle, and endothelium could contribute to the increased risk for thrombosis in the elderly. Advanced age is accompanied by stiffness and dilation of the arteries due to the degeneration of elastic fibers and the increase in collagen content [111]. Gene polymorphisms of elastin and angiotensin II type-I receptor may predispose the elderly to a highly significant age-dependent stiffening and loss of vessel distensibility [112,113]. Aging is also associated with reduced endothelium-dependent dilation [114]. The aged blood vessels express less endothelial nitric oxide (NO) synthase [115], resulting in less NO production [116]. Decreased NO production may contribute to increased platelet activation and arterial thrombosis [117] as well as enhanced atherogenesis [118]. Also, the angiotensin II pathways may play a role in age-related endothelial dysfunction. The expression of angiotensin II is increased in the arterial intima with advancing age [119], and the cardiac expression of receptors for angiotensin II is significantly increased [120]. These observations suggest that age-associated arterial remodeling and the development of atherosclerosis are partially mediated by the increased angiotensin II signaling.

6. Summary

Hypercoagulability and advanced vascular sclerotic changes may contribute to the increased incidence of thrombosis in the elderly. One of the important key genes for the age-associated prothrombotic state is PAI-1 (Fig. 1). The expression of PAI-1 is not only elevated in the elderly but also significantly induced in a variety of pathologies associated with the process of aging. These conditions include obesity, insulin resistance, psychosocial stress, immune responses, and vascular sclerosis/remodeling, all of which accompany aging. Indeed, the expression level of
PAI-1 has been regarded as an important marker for cardiovascular risk. Several cytokines and hormones, including TNF-α, TGF-β, angiotensin II, and insulin, positively regulate the gene expression of PAI-1. These components are primarily synthesized or affected by adipocytes/adipose tissue, which is highlighted because of its relevance to the increased risk for atherosclerosis and cardiovascular events. Thus, PAI-1 could play a key role in the progression of cardiovascular aging and must be considered the most crucial gene for thrombosis and vascular (athero)sclerosis in current developed societies, where the elderly, the obese, and individuals exposed to stress are increasing in number. Further studies on the mechanism of age-regulated expression of PAI-1 are necessary in order to define the basis for cardiovascular aging in relation to thrombosis. It is also important for future clinical research to establish the most promising strategies for controlling PAI-1 expression so that cardiovascular diseases associated with aging can be prevented.

Acknowledgements

This work was supported by grants-in-aid from the Ministry of Education, Science, Sports and Culture, from the Ministry of Health and Welfare, Japan.

References


