The impact of platelet glycoprotein IIIa and Ia polymorphisms in cardiovascular thrombotic disease

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Key words:
Acute coronary syndromes; Platelets; Thrombosis.

Platelet adhesion and aggregation play key roles in initiating coronary thrombosis and acute coronary syndromes. During the last decade platelet glycoprotein Ia and IIIa polymorphisms have been studied intensely in order to clarify their contribution to the thrombotic process and moreover their role in acute coronary syndromes. Studies examining these polymorphisms have been inconclusive and often controversial. Polymorphisms in the glycoprotein Ia seem to increase the risk for acute coronary events in younger persons and especially in the presence of other risk factors. The correlation of the Leu33Pro allele of platelet glycoprotein IIIa regarding platelet thrombogenicity is strong but it does not seem to alter the thrombotic risk of the general population. In conclusion, further studies need to elucidate their impact and the potential association with acute thrombotic events.

(Ital Heart J 2003; 4 (1): 17-22)

Received June 6, 2002; revision received October 21, 2002; accepted November 25, 2002.

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Cardiovascular disease remains the major cause of morbidity and mortality in western countries[1]. Atherosclerosis manifesting as myocardial infarction, angina pectoris, cerebral ischemia and peripheral artery disease is a multifactorial disease with the environment and genetics contributing to its pathogenesis[2-4]. During the last decade several genes involved in the atherosclerotic process – ranging from cholesterol metabolism to arterial thrombosis – and their polymorphisms have been alleged to increase the thrombotic predisposition and to influence the risk for acute coronary syndromes. Among these genes, platelet polymorphisms have been intensely studied[5]. Platelets play a significant role in thrombus formation and a number of genetic polymorphisms of platelet receptors may also induce gain or loss of platelet function and ultimately may predispose to thromboembolic events.

This review will consider the two platelet glycoprotein (GP) polymorphisms Ia and IIIa as risk factors for thrombosis.

Platelet receptors and their role in thrombosis

Most platelet receptors are protein complexes and two or more polypeptide subunits are non covalently associated within the platelet membrane[6]. These receptors interfere in the first step of platelet adhesion to the subendothelial matrix as well as in the subsequent steps of platelet activation and aggregation. In case of a vessel wall injury, platelets adhere to the surface bound von Willebrand factor (vWF) through the platelet GPIb/X/V under high shear stress conditions[7]. This interaction is rendered more stable and secure by subsequent multiple interactions between GPIa/IIa with collagen and GPIIb/IIIa and Ic/IIa with vWF and fibronectin respectively[8].

Given the importance of platelet GPs in primary hemostasis, it is reasonable to suggest that in certain circumstances, inherited differences in these platelet receptors may contribute to an increased risk of acute coronary events by altering their activity. A platelet polymorphism in a regulatory gene region, for instance, may alter the expression of the receptor on the platelet surface. Moreover, a nucleotide polymorphism that results in an amino acid substitution may change the tertiary structure of the receptor and subsequently alter the platelet adhesive function.

Glycoprotein IIb/IIIa structure and polymorphisms

GPIIb and GPIIIa are present in the platelet membrane as a heterodimeric complex the formation of which requires the

presence of divalent cations[9]. Two chains of GPIIb are associated non covalently with one chain of GPIIIa for the formation of the GPIIb/IIIa complex[10,11]. There are approximately 80 000 copies of the GPIIb/IIIa complex per platelet[9] and its major ligands are fibrinogen and the vWF either when they are immobilized or in solution after platelet activation[8].

The genes that encode GPIIb and GPIIIa are both in chromosome 17q21[11]. A number of point mutations have been described in the GPIIb/IIIa gene and there are now data to suggest their interference in the etiology of acute coronary syndromes. Polymorphisms of GPIIb as well as of GPIIIa have the ability to produce platelet specific alloantibodies. These antibodies are the main cause of several disorders such as post-transfusion purpura and neonatal alloimmune thrombocytopenia[10]. There are at least seven GPIIIa alleles[12] but the most common polymorphism in GPIIIa is described by the human alloantigen system HPA-1 (Pl^A)[13]. Due to the substitution of a cytosine for a thymidine at position 1565 in exon 2 of the GPIIIa gene, the platelet antigen Pl^{A2} variant displays a proline instead of a leucine at amino acid 33[13].

Leu33Pro dimorphism of glycoprotein IIIa and cardiovascular disease. The Pro33 allele was correlated with a 2.8-fold increase in the risk for myocardial infarction for the first time in 1996[14]. Since then the Pro33 allele has been investigated as a putative risk factor for coronary artery disease in several studies[15-28]. Several studies show a positive correlation[16,28] while others do not. A recent meta-analysis[27] investigated the association between the Pl^{A2} polymorphism and myocardial infarction in 23 studies performed mainly in Caucasian populations through October 1999. In this meta-analysis no association was observed between the Pro33 allele and the risk of myocardial infarction and this negative result persisted even after subgroup analyses. Moreover, a second meta-analysis[20] examined 34 studies published through June 2000 and included patients with myocardial infarction as well as those with a broader definition of symptomatic coronary artery disease. In this second overview the association of the Pl^{A2} allele with cardiovascular disease, despite being statistically significant, was weak and was influenced by publication bias and inadequate co-factor adjustment. The association appeared to be stronger when a less heterogeneous group of patients was considered, such as the younger cohorts and the restenosis subset with stents. These inconsistent findings between studies can be mostly attributed to differences in the design as well as to the choice of the control group and the endpoint of the studies. Subgroup analyses investigating the impact of the Pl^A polymorphism on patients with other known risk factors for coronary artery disease have been conflicting[20,27,29]. Few individual studies – including men with additional atherosclerotic risk factors[16,18], or documented coronary atherosclerosis[28] or including young men who had a fatal myocardial infarction[23] – have suggested that the Pro33 allele may increase the susceptibility to myocardial infarction at an early age. On the contrary, in two other studies no association was noticed between the Pro33 allele and the risk for an acute occlusive event among women < 45 years old[25,26].

There are also data in the literature regarding the role of the Pl^{A2} polymorphism in the outcomes after coronary revascularization[30,31], angiography[18,32,33] and autopsies[22]. Although these studies have yielded inconclusive results they tend to be more homogeneous in their design compared to the unstable coronary studies.

From all these conflicting data, what appears to consistently emerge is that the Pl^{A2} polymorphism is associated with coronary syndromes especially in young cohorts who have additional cardiovascular risk factors.

Leu33Pro dimorphism and functional consequences. All the observations suggesting that the Pl^{A2} allele is a risk factor for arterial thrombosis led to the concept that the Pro33 substitution in β_3 integrin may induce platelets into a hypercoagulable state.

The mechanisms of platelet activation and thrombus formation are generally well established; however, it is still unclear how a single gene polymorphism may affect platelet function. The Leu33Pro allele, although not in a functional gene area, has attracted great scientific interest as it seems to cause structural changes in the GPIIb/IIIa receptor. This structural change may lead to a different ligand binding of the active GPIIb/IIIa receptor or to post-receptor occupancy events. Several studies[34,35] have shown that Pl^{A2} subjects, both heterozygotes and homozygotes, have shortened bleeding times compared to carriers of the Pl^{A1A1} allele. In studies performed in Chinese hamster ovary cells[36] the Pl^{A2} receptor exhibits enhanced "outside in" signaling, detected as phosphorylation of the focal adhesion kinase. In addition, Pl^{A2} positive platelets show different responses *in vitro* when stimulated by various agonists (i.e. adenosine diphosphate and epinephrine) compared to the Pl^{A1A1} ones[37-39]. There are also conflicting reports[37,40,41] regarding the Pl^A genotype differences as they are related to platelet fibrinogen binding.

Further *in vitro* studies of the functional relevance of this polymorphism should be conducted to provide biological plausibility for the observed clinical findings.

Leu33Pro polymorphism and antiplatelet therapy. Genetic factors are postulated as modulators of the drug response either in determining the efficacy of the drug or the risk of adverse events. It has been hypothesized that the clinical efficacy of antiplatelet drugs (i.e. aspirin) might be related to the Pl^A polymorphism[9]. Aspirin inhibition of platelets varies according to the Pl^A genotype[34,35,42]. Pl^{A1A2} platelets show a greater sensitivity and Pl^{A2} individuals show blunted bleeding times in

response to aspirin[34]. In addition to a more specific antiplatelet therapy, GPIIb/IIIa antagonists have been suggested to cause different responses according to the Pl^A genotype[43,44]. GPIIb/IIIa antagonists bind to the receptor and prevent platelet aggregation to all known agonists but oral GPIIb/IIIa antagonists have been proven to be ineffective and even harmful when administered in patients with acute coronary syndromes[43,45]. Whether the Pl^{A2} variant of the GPIIb/IIIa antagonists is more susceptible to the partial agonist activity induced by smaller ligands such as GPIIb/IIIa antagonists and whether this hypothesis can explain the observed variability in the response to these drugs in humans has yet to be addressed.

Glycoprotein Ia/IIa structure and polymorphisms

GPIa/IIa (integrin $\alpha_2\beta_1$) mediates the divalent cation-dependent adhesion of platelets to fibrillar (type I and III) or non fibrillar (type IV and VI) collagen[46].

The expression of GPIa/IIa on the platelet surface differs among healthy subjects and this depends mostly on the inheritance of the four alleles of the α_2 gene[47,48]. The gene for the GPIa is located on chromosome 5[49]. Sequence analysis of this gene has revealed silent[50] and non silent polymorphisms[51] which are responsible for the structural and functional changes of this receptor and for the variability in the number of copies of the GPIa/IIa receptor on the platelet surface[52,53]. Three allelic differences in the α_2 (GPIa) gene are associated with the expression levels of the GPIa/IIa on the platelet surface[47]. Two linked silent GPIa polymorphisms – 807 C-T (Phe^{224}) and 873 G-A (Thr^{246}) – were correlated with a variable expression of the platelet surface receptor[48,52,54]. The genotype 807TT (873AA) was associated with a higher receptor density and the genotype 807CC (873 GG) with a lower density, whereas heterozygotes express intermediate receptor levels.

A third polymorphism is due to G to A substitution at position 1648. This causes the Glu/Lys substitution in position 505 (Br system) and is responsible for the human platelet alloantigen system HPA-5[47,51,55,56]. The A allele frequency among Caucasians is 79.45% while the G allele has a frequency of 20.55%[53]. It has been also noted that there is a genetic relationship between GPIa 807 C/T and Glu505Lys and that the Br polymorphism is linked to a rare polymorphism located at nucleotide 837 (C-T)[47]. Carriers of the allele 1 (807T/873T/873A/Br^b) express high levels of GPIa/IIa whereas individuals who carry alleles 2 (807C/837T/873G/Br^b) and 3 (807C/837C/873G/Br^a) exhibit a lower expression of the platelet integrin[47].

Platelet glycoprotein Ia polymorphisms and cardiovascular disease. Given the importance of the GPIa/IIa receptor in primary hemostasis, it is reasonable to suggest that inherited differences in this receptor may contribute to an increased risk for acute coronary and ischemic events. Some recent data regarding the association between these GPIa/IIa dimorphisms and the risk for coronary artery disease have provided conflicting results[57-70].

Several studies have suggested that the 807T variant may be associated with an increased risk for acute ischemic events especially among smokers and diabetics[62,65,67]. Subsequent reports also found the 807T allele to be a risk factor for myocardial infarction particularly in young patients[59,68]. In contrast, other studies[60,64] revealed no correlation between the 807T allele and the risk for acute thrombus formation. This negative result persisted even when the analysis was performed in a subgroup of patients with other cardiovascular risk factors (smoking, diabetes). Moreover, in two large German studies of patients undergoing coronary angioplasty, stent placement or directional atherectomy, the C807T polymorphism was not associated with the risk for post-procedural thrombotic complications[63,70]. Inconsistent are also the preliminary data regarding the role of the 1648 A/G polymorphism in acute ischemic events. This polymorphism is in complete linkage disequilibrium with the silent T837C sequence polymorphism of GPIa[51].

Several small case-control studies have studied the association between the Glu505Lys polymorphism and the risk for myocardial infarction. Among 88 patients with myocardial infarction and 100 control subjects matched for age and sex in a Japanese population, Hato et al.[61] found no correlation between this dimorphism and the risk for myocardial infarction. Moreover, no association has been observed between the Glu505Lys polymorphism and coronary artery disease in diabetics[69] and in women under age 45[66] with myocardial infarction and stroke. Finally, Kroll et al.[62] recently examined this dimorphism in 2163 men who underwent coronary angiography and found that the Glu505Lys dimorphism was neither related to myocardial infarction nor to coronary artery disease.

In summary, on the basis of the existing data, the 807T allele seems to be a risk factor in younger patients while there is not enough evidence to support the role of platelet GPIa Glu505Lys as an important determinant of the atherothrombotic risk.

Glycoprotein Ia polymorphisms and platelet function. GPIa polymorphisms have been related to an increased collagen receptor density[48,52,54]; this finding could represent a risk factor for thrombotic disease. *In vitro* studies revealed that platelets expressing the 807T allele show greater adhesive properties under shear forces[47]. In another study[54], although these findings were confirmed, no differences in the aggregation to 200 μg/ml collagen were observed.

These results highlight the need for further studies to define the biologic effects of GPIa polymorphisms more accurately.

Conclusions

Although inconclusive and often controversial, the preliminary data suggest that the Pl^{A2} and 807T polymorphisms of GPIIIa and GPIa respectively have a stronger impact on the incidence of cardiovascular events in the young. It is reasonable to believe that genetic factors are more likely to affect younger rather than older people and that they may contribute to many different mechanisms leading to atherosclerotic lesions. The existing data in the young are limited and are mostly derived from studies including small populations. This is probably due to the restricted number of young individuals who present with a cardiovascular event. Some risk factors such as smoking, dyslipidemia and a family history of cardiovascular disease are more prevalent in the young in comparison to diabetes and hypertension which generally manifest in older age groups. This contributes to the difficulty encountered in quantitatively estimating the independent contribution of genetic factors.

The discrepancy in the results of different studies may be explained partly by differences in the design of the studies but also by differences in the analysis. Many studies suffer from a limited sample size, which is frequently too small to confirm or rule out the presence of a relevant epidemiological association between specific polymorphisms and cardiovascular disease. Moreover, studies differ in the ethnicity, bias in the selection of patients and controls, the plurality in clinical endpoints and in the variation of environmental factors. Furthermore, as far as the correlations between genes and myocardial infarction are concerned, the true effect of genotype can be masked if mortality rates are the endpoint. We already know that atherosclerosis is a multifactorial disease; it would be too simplistic to suppose that genetic inheritance alone could explain the interindividual variations. Correlations between platelet polymorphisms and environmental risk factors reinforce this belief. Moreover, several genes are in linkage disequilibrium with other genes and simultaneous studies of several genes may reveal associations that at present seem to be weak.

Understanding the interaction of platelet GP polymorphisms with cardiovascular risk factors and endovascular procedures may also influence treatment strategies targeting a specific susceptibility gene implicated in coronary thrombosis. Further studies are needed to clarify the potential association between platelet polymorphisms, coronary heart disease and myocardial infarction. Only then will it be possible to select those patients who may benefit from a more intensive and extensive antithrombotic therapy.

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