Platelet Collagen Receptors and Risk Prediction in Stroke and Coronary Artery Disease

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The importance of thrombosis as a health hazard cannot be overstated. Ischemic heart disease and cerebrovascular disease are the leading causes of morbidity and mortality among both adult men and adult women in the developed western world. Recent evidence indicates that the incidence of this disease is steadily increasing among Asian populations, and cardiovascular disease is now the leading cause of death among native American Indians. Epidemiological studies indicate that these diseases result from complex interactions between genetic susceptibility factors, long-term environmental influences (for example, hormonal imbalance, smoking, or obesity), and established, intercurrent disorders (such as diabetes, hypertension, dyslipidemia, or hyperhomocysteinemia).

A devastating complication of these disorders is acute myocardial infarction, which results from the formation of an occlusive thrombus at the site of a ruptured atherosclerotic plaque. The critical role of platelets in this process is now well accepted. Plaque rupture and/or endothelial damage lead to the exposure of von Willebrand factor and collagen, among other platelet-reactive substrates, which facilitate the adhesion of circulating platelets to the damaged vessel wall. Several receptors, each with distinct functions, are involved in this process, including the glycoprotein (GP) IIb-IX-V complex, the integrins α6β3 and α5β1, and platelet GP VI. As a result of these initial interactions, the platelet is activated, leading to a conformational change in another integrin, αmβ2, which contributes in a fundamental way to the homotypic aggregation of platelets into a thrombus. Thrombin generated at the blood-plaque interface converts fibrinogen to fibrin, which stabilizes thrombus growth.

At the same time, efficient platelet cohesion is necessary for the life-saving process of hemostasis, which is a normal response to vascular injury, typically at the site of a wound, to limit blood loss. The rate of platelet activation is one important variable that contributes to either beneficial or adverse outcomes, and collagens are important modulators of platelet activation through their stimulation of key platelet receptors.

In view of their key role in hemostasis and thrombosis, it is natural to wonder whether polymorphisms in platelet adhesion receptors might influence the risk for cardiovascular disease.

Genetic differences that might alter the surface expression or activity of these receptors could influence risk for adverse outcomes as a result of platelet responses to hemostatic challenges. In the last 5 years, there has been a rapid accumulation of literature concerning the relationship between genetic variations in platelet glycoproteins and risk for coronary artery disease.

The first receptor to be scrutinized was the integrin α6β3, the most abundant receptor on the platelet membrane surface; it has ≈80,000 copies per platelet and is recognized as the receptor for fibrinogen or von Willebrand factor that mediates platelet cohesion (ie, thrombus formation). The 2 most common and clinical important β3 alleles encode Leu145 (PIA1 or HPA-1a) and Pro3 (PIA2 or HPA-1b), with gene frequencies of 0.85 and 0.15, respectively, in a typical white population. Weiss et al were the first to report that the gene frequency of the PI A2 allele was 3.6 times higher among younger patients (<60 years of age) with myocardial infarction or unstable angina than in age-matched controls (odds ratio, 6.2). The impact of the PI A2 polymorphism as a genetic risk factor of ischemic vascular disease or myocardial infarction in younger individuals has been confirmed by many, but not all subsequent studies (for a recent review, see Reference 8). Likewise, the biological relevance for this dimorphism has been documented by some and not by others.

Additional studies have focused on the receptor for von Willebrand factor, GP Iba. An association has been found between the inheritance of the allele coding for Met145 (instead of the more common Thr145) and the risk for coronary artery disease or stroke in younger individuals, but there has not been a universal confirmation of this finding. Another dimorphism in the GP Iba gene, on the basis of the presence of either thymine (T) or cytosine (C) at position −5 from the initiator ATG codon, has also attracted scrutiny because it influences an adjacent Kozak site and modulates the expression of the protein. Initial clinical studies failed to show an association between the less common −5C and the risk for acute coronary artery disease. More recent reports, however, document an association with the severity of negative outcomes after acute myocardial infarction in younger individuals (≤62 years old) and a synergistic effect of −5C and Met145 on risk for stroke in younger individuals.

Because collagens are abundant in the extracellular matrix, collagen receptors are likely candidates for exerting an influence on the risk for cardiovascular disease.
Platelets have 2 major primary receptors for collagens, the integrin \( \alpha_2\beta_1 \) and the platelet-specific receptor GP VI. A third receptor that figures prominently at the very onset of adhesion, the GP Ib-IX-V complex, does not bind directly to collagen, but rather to von Willebrand factor that has become immobilized onto collagen. The GP Ib/von Willebrand factor interaction promotes the initial tethering of platelets to the surface, even when blood flow is very rapid but cannot, by itself, mediate irreversible adhesion.\(^6\) It is at this point that the 2 direct collagen receptors become involved, and signal transduction seems to be coupled with the engagement of both GP VI and, to a lesser extent, \( \alpha_2\beta_1 \). A number of factors, most notably the extent of collagen polymerization, will determine the relative contribution of these 2 receptors toward the formation of a stable monolayer of activated platelets that serves as a nidus for prothrombin conversion and thrombus formation.

The integrin \( \alpha_2\beta_1 \) was the first to be considered as a potential risk factor for thrombosis. A C\(_{807}\)T dimorphism of the integrin \( \alpha_2\) gene (ITGA2) is one single nucleotide polymorphism that can be used to distinguish donors with high platelet \( \alpha_2\beta_1 \) density (T\(_{807}\)) from those with low density (C\(_{807}\)). A correlation between T\(_{807}\) and risk for myocardial infarction has been established.\(^{15,16}\) Moreover, Roest et al\(^{17}\) reported increased vascular mortality associated with T\(_{807}\) among women who are heavy, long-term smokers. In addition, a significant association was also found in younger patients with stroke\(^{18}\) and in patients with diabetic retinopathy\(^{19}\), however, other studies have not confirmed the association in myocardial infarction (reviewed in Reference \(^9\)).

**What About the Second and Platelet-Specific Collagen Receptor, GP VI?**

The importance of GP VI in platelet responses to collagens has only been appreciated within the past few years, and it was only a matter of time before it too was evaluated as a potential contributor to risk for cardiovascular disease.

In this issue of *Circulation*, Croft et al\(^{20}\) describe, for the first time, the association of a GP VI dimorphism (T13254C) with risk for myocardial infarction. In a case-control study, the frequency of 13254C was significantly elevated among older individuals with myocardial infarction. This dimorphism encodes the substitution of Ser\(_{219}\) with Pro, a nonconservative amino acid difference that might be expected to modify the structure and/or function of GP VI, but the biological basis for the clinical correlation remains to be established.

In a related study, it was recently determined that there is a 5-fold variation in the platelet content of GP VI among normal donors.\(^{21}\) Prothrombinase activity induced by GP VI-specific agonists such as the snake protein, convulxin, or the collagen related peptide is directly proportional to the platelet content of GP VI. In view of the well-documented association of GP VI with platelet procoagulant activity, variation in GP VI content would contribute to risk for hemorrhagic or thromboembolic disorders. At this time, no correlation between platelet GP VI content and T13254C has yet been established.

**Which of the Collagen Receptors Is Then the Most Relevant With Regard to Risk for Thrombotic Disease?**

This question is more complex than one might suspect in view of the recent observation that, among normal donors, the content of GP VI seems to parallel the density of \( \alpha_2\beta_1 \).\(^{21}\) This intriguing and statistically significant correlation remains unexplained at this time. It is possible that these 2 receptors are physically associated at the platelet surface and that the expression of one is dependent on the presence of the other, in which case the genetic control on the density of one receptor would also affect the other. However, there is no evidence yet that this is the case. In contrast, it is also possible that the expression of both receptors is regulated during megakaryocyte development by an independent gene product, perhaps a transcriptional regulator common to both genes. The level of this third gene product might be genetically controlled. Consistent with this possibility, Lagrue-Lak-Hal et al\(^{22}\) recently observed that the appearance of GP VI and \( \alpha_2\beta_1 \) is coordinated during human megakaryocyte maturation, and both are expressed only on CD41+ cells. Because the levels of these receptors vary in parallel between individuals, it remains to be determined which of these receptors, if not both, is responsible for genetically controlled differences in platelet responses to collagens and risk for cardiovascular disease.

**References**


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