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Platelet Polymorphisms: Still a Long Way to Go

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Introduction

Platelets play a key role in primary hemostasis but show a great inter-individual functional heterogeneity with genetic factors probably involved, although the underlying mechanisms are not yet completely understood. Platelets contain many receptors and proteins involved in primary hemostasis that allow them to change the shape and secrete numerous substances from their granules. For many of these proteins, platelets are highly polymorphic. Thus, the study of platelet genetic polymorphisms can give an important contribution in a functional context, in the study of interactions genotype-environment or to better understanding the individual susceptibility in certain multifactorial diseases.

Platelet Polymorphisms

Considering that genetic differences that can change the expression, or the structure of platelet proteins, can also influence their function, a Single Nucleotide Polymorphism (SNP) that results in an amino acid substitution may change the structure of a receptor and subsequently platelet adhesive function. One example is the rs6065 polymorphism, where a threonine is substituted by a methionine at amino acid 161 of the Glycoprotein (GP) Ib-IX-V that was originally associated with platelet transfusion refractoriness when it was described [1]. It was also implicated in neonatal alloimmune thrombocytopenic purpura and post transfusion purpura [2]. In patients that lack the PLA1 allele, that implies the presence of a threonine and is present in approximately 90% of the population, the contact with blood containing platelets that bear PLA1 allele will lead to an immune reaction against that platelets. On the other hand, a platelet polymorphism in a regulatory gene region may influence the transcriptional activity of a receptor on the platelet surface, as in the case of polymorphism rs2243093, where an increased expression of the GP Ib-IX-V was reported [3]. This polymorphism lies in 5'UTR of GP1BA gene, where a T or a C may be present in position -5 from ATG start codon. Allele C was associated with increased expression of the receptor on the cell membrane [4], what might increase platelet adhesiveness. But not always a polymorphism lead to changes in protein structure or expression, and silent polymorphisms were also described as being involved in altered platelet function, as does rs938043469 polymorphism [5]. This polymorphism consists in a substitution of a cytosine by a thymine in position 807 (C807T) within the coding region of subunit alpha 2 of integrin α2β1 (GPIa-IIa). Despite being a silent polymorphism, rs938043469 is believed to influence the density of integrin GP Ia-IIa in platelet membrane, being allele T responsible for the highest expression of the glycoprotein [6,7].

Platelet Polymorphisms and Their Role in Disease

Given the importance of platelet receptors in primary hemostasis, it is reasonable to suggest that, in certain circumstances, inherited differences in these proteins may contribute to an increased risk of diseases where platelets are involved and play a crucial role. Most of the candidate gene association studies have focused on platelet receptors. Polymorphisms in major platelet receptors were associated with different cardiovascular diseases, although the results remain controversial, mainly due to differences in studied populations and diseases [8-11]. The conflicting results may also reflect the difficulty in establishing a pivotal role for a single polymorphism in such complex and multifactorial diseases. Nevertheless, it is well documented the importance of some SNP's in platelet physiopathology. For example, a single change of a thymine by a cytosine in position 1565 of exon 2 of ITGB3 gene, that change the codon of residue 59 from a leucine to a proline, is documented as the most common cause of Fetal-Maternal alloimmune Thrombocytopenia (FMAIT) [12]. As time passes, a growing list of evidence showing the relationship between polymorphisms of the major platelet receptors and increased risk for cardiovascular diseases accumulates. Only some examples, as the list is vast, are the augmented risk found of ischemic stroke in polymorphisms of P2Y12 receptor (H1 and H2 haplotypes) [13] and in C807T polymorphism of GPIa-IIa receptor [14]). In myocardial infarction, the stratification of patients according to their polymorphisms and other physiological variables were already been described [15], showing the relevance of knowing the genetic background to tune the therapeutic choice. Silent polymorphisms were also described as being able to increase the risk of cardiovascular diseases, namely myocardial infarction, as we found for rs938043469 polymorphism of the platelet GP Ia-IIa [16]. As previously explained, this polymorphism may influence the density of integrin GP Ia-IIa in the platelet membrane. This variation in the receptor density may account for higher platelet responsiveness to collagen in T/T genotype, enhancing the thrombotic potential of platelets in pathological states [16].

In a different perspective, polymorphisms in proteins that can lead to an altered platelet function can confer an increased risk in some cardiovascular disorders. A common example is the rs4244285 polymorphism in CYP2C19 gene that encodes a variant of the cytochrome P450 2C19 [17]. Patients that harbor this cytochrome variant are poor metabolizers of the antiplatelet drug clopidogrel that inhibits P2Y12 ADP receptors, thus leading to an increased risk of a cardiovascular event [18]. Other examples are the polymorphisms found in the enzyme endothelial nitric oxide synthase (eNOS) that is expressed both in endothelial cells and in a subpopulation (about

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80%) of circulating platelets [19]. Some eNOS polymorphisms can reduce the promoter activity of eNOS gene (NOS3) leading to a diminished production of Nitric Oxide (NO) [20]. This can cause several vascular and hemostatic disfunctions as increased vasospasm, fail to limit the oxidation of atherogenic Low-Density Lipoprotein (LDL) and a diminished platelet modulation either at rest or during platelet aggregation [19,21,22]. These alterations can lead to a state of higher risk, and these polymorphisms were already associated with increased risk of myocardial infarction, notably in young patients [23].

Interaction between Platelet Polymorphisms and the Environment

Another interesting point is the interaction between platelet proteins and the environment that can be influenced by external factors, such as virus. Polymorphism rs5918 leads to a change of a leucine to a proline in position 33 of subunit β3 from integrin α2bβ3, also known as GP IIb-IIIa [24]. One interesting aspect of this polymorphism is that the Andes virus, responsible for hantavirus pulmonary syndrome in humans and Syrian hamsters, recognize this site to infect endothelial cells that express the subunit β3 in integrin αVβ3 [25] and platelets that express the subunit β3 in integrin α2bβ3 [26], leading to the thrombocytopenia usually found in this type of virus infections. So, the ability of Andes virus to infect these cells vary according to the residue found in this position [25].

The study of positive selection of specific residues belonging to the structure of the major functional platelet glycoproteins is another aspect that deserves our utmost attention. Understand why some residues suffer alterations between species and why some residues change between the same species, giving rise to new polymorphic forms of the protein, will increase our knowledge about several aspects related to the protein function and how it interacts with the environment. In a previous study, we found that some residues of GP IIb-IIIa were under positive selection between ten mammal species [27]. Besides, some of them were polymorphic in humans [27]. This information may enhance the focus on the functional importance that these residues have in the glycoprotein structure and how they relate with the surrounding milieu.

Conclusion

Whether in basic research or clinical field, the study of platelet polymorphisms will contribute to elucidate several aspects related to the physiology and the development of diseases where platelets are implicated. In the same way, the newly pharmacogenetic approaches make use of this knowledge to deliver custom treatments when they are needed. Tools like Next Generation Sequencing (NGS) are increasing our knowledge about genetic variations, like SNP's, as never happened before [28]. This amount of information opens new perspectives, but also requires new approaches, making this topic a current field with still a long way to go.

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