The HPA-1 polymorphism impacts the platelet-specific integrin $\alpha_{IIb}\beta_3$ by a ripple effect

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The human platelet antigen (HPA)-1 alloimmune system is a biallelic system carried by the megakariocyte/platelet specific integrin $\alpha_{IIb}\beta_3$, which mediates platelet adhesion and aggregation; it is essential for hemostasis but can also foster thrombus formation. The HPA1 polymorphism of $\alpha_{IIb}\beta_3$ arises from a leucine-to-proline exchange at residue 33 of the mature β_3 subunit resulting in HPA-1a (Leu33) or HPA-1b (Pro33) platelets [1]. Genotyping revealed that patients with coronary artery disease who carry the HPA-1b allele experience their myocardial infarction 5.2 years earlier than HPA-1a/1a patients [2]. It has been postulated that integrin exists in two main and mutually exclusive conformations; the bent, closed form, and the unbent, open structure. Local and global structural rearrangements are required in going from the closed to the open form, thereby leading to integrin activation. While the experimental observations have shown that HPA-1b (Pro33) is a prothrombotic variant of $\alpha_{IIb}\beta_3$, it has remained elusive so far how the mutation, located more than 90 Å away from any of the binding sites of the integrin, contributes to the heightened activatability of the integrin.

In the present study, the ectodomains of the two $\alpha_{IIb}\beta_3$ variants in the closed conformation were used as model systems, and the consequences of the Leu33Pro substitution on the structure and dynamics of the integrin were analyzed through molecular dynamics (MD) simulations of in total 3 μs length. In atomic detail, comparative analyses of the trajectories revealed that Leu33 is involved in stabilizing interactions connecting the PSI domain in the head region of integrin and the nearby EGF-I and EGF-II domains in the leg region of the β-subunit. The absence of this network of interactions in the Pro33 variant destabilizes the β-subunit. The resulting local instability percolates through the structure and leads to the system being globally less stable; this fosters a heightened activatability. In good agreement with experimental observations, these findings explain how the fine-tuned conformational equilibrium of the integrin can be allosterically influenced by a distant mutation.

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