Fibrinogen, monomeric and polymeric fibrin differentially interact with the platelet integrin αIIbβ3

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Differences in the efficacy of αIIbβ3 antagonists with regard to fibrinogen-mediated platelet aggregation versus contraction of the fibrin-platelet meshwork suggest that the interaction of αIIbβ3 with fibrinogen and fibrin is different. Using optical trap-based force spectroscopy, we compared the probability, strength, and specificity of the interactions of purified integrin αIIbβ3 with monomeric and polymeric fibrin versus fibrinogen. Rupture force histograms for αIIbβ3-fibrinogen interactions could be segregated into moderate (20-60 pN) and strong (>60 pN) interactions. Monomeric fibrin displayed a similar force profile but with a higher cumulative binding probability and a greater binding strength. αIIbβ3-fibrin interactions were also less sensitive to inhibition by αIIbβ3 antagonists, suggesting that they had different binding specificity. Both fibrinogen and fibrin interactions with αIIbβ3 were partially inhibited by RGD-containing peptides, suggesting the existence of common RGD-containing binding motifs. Polymeric fibrin displayed a rupture force profile similar to fibrinogen and monomeric fibrin with moderate and strong forces that peaked at 70-80 pN. αIIbβ3 antagonists, cycloRGD-peptide, and the γC-dodecapeptide each produced a sharp drop in the medium-to-high force range. We found that the kinetic parameters of interactions indicate the existence of low- and high-affinity bound states and that the mechanical stability of the bimolecular αIIbβ3-ligand complexes had the following order: fibrin polymer>fibrin monomer>fibrinogen. These quantitative differences reflect the distinct specificity and molecular mechanisms of αIIbβ3-mediated reactions, implying that targeting platelet interactions with fibrin could increase the therapeutic indices of antithrombotic agents by focusing on the destabilization of forming thrombi rather than the prevention of platelet aggregation.

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