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Mechanistic Basis for the Binding of RGD- and AGDV-Peptides to the Platelet Integrin αIIbβ3

Kononova O., Litvinov R., Blokhin D., Klochkov V., Weisel J., Bennett J., Barsegov V.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 American Chemical Society. Binding of soluble fibrinogen to the activated conformation of the integrin αIIbβ3 is required for platelet aggregation and is mediated exclusively by the C-terminal AGDV-containing dodecapeptide (γC-12) sequence of the fibrinogen γ chain. However, peptides containing the Arg-Gly-Asp (RGD) sequences located in two places in the fibrinogen Aα chain inhibit soluble fibrinogen binding to αIIbβ3 and make substantial contributions to αIIbβ3 binding when fibrinogen is immobilized and when it is converted to fibrin. Here, we employed optical trap-based nanomechanical measurements and computational molecular modeling to determine the kinet ics, energetics, and structural details of cyclic RGDFK (cRGDFK) and γC-12 binding to αIIbβ3. Docking analysis revealed that NMR-determined solution structures of cRGDFK and γC-12 bind to both the open and closed αIIbβ3 conformers at the interface between the αIIb β-propeller domain and the β3 βI domain. The nanomechanical measurements revealed that cRGDFK binds to αIIbβ3 at least as tightly as γC-12. A subsequent analysis of molecular force profiles and the number of peptide−αIIbβ3 binding contacts revealed that both peptides form stable bimolecular complexes with αIIbβ3 that dissociate in the 60-120 pN range. The Gibbs free energy profiles of the αIIbβ3-peptide complexes revealed that the overall stability of the αIIbβ3-cRGDFK complex was comparable with that of the αIIbβ3−γC-12 complex. Thus, these results provide a mechanistic explanation for previous observations that RGD- and AGDV-containing peptides are both potent inhibitors of the αIIbβ3-fibrinogen interactions and are consistent with the observation that RGD motifs, in addition to AGDV, support interaction of αIIbβ3 with immobilized fibrinogen and fibrin.

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