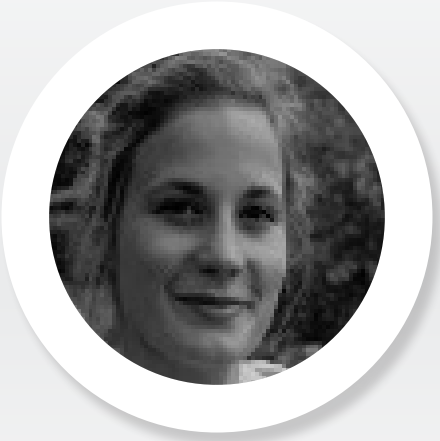
Una Janke, Pharm Anal Acta 2019, Volume:10
DOI: 10.4172/2153-2435-C2-048



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Conformational dynamics of integrin alpha IIb beta 3 and its relation to changes in protein structure

The transmembrane protein integrin alpha IIb beta 3 (αIIbβ3) is involved in hemostasis, wound healing and clot formation. Intracellular as well as extracellular signals can cause inside-out or outside-in signaling, which leads to atleast three different conformations: the bent (resting) state; the intermediate extended form; and the ligand-occupied active state. The conformational dynamics of the overall structure of αIIbβ3 during the activation process is possibly related to changes in protein secondary structure, which has not been studied until now in a membrane environment (e.g. liposomes). Moreover, αIIbβ3 is related to the autoimmune disease immune thrombocytopenia, where potential external triggers influence the antigenicity of the integrin by changing the protein structure. In this study, we determined the drug-induced activation of αIIbβ3 and the relation to the structure of this protein reconstituted into liposomes. The combination of activation assays and the biophysical tools quartz crystal microbalance, surface plasmon resonance and circular dichroism spectroscopy show binding of the conformation-specific antibody PAC-1 (which recognizes the active integrin) to αIIbβ3-treated with clinically relevant drugs (e.g. quinine). However, insignificant changes in protein secondary structure were found. Molecular dynamics simulation (MDS) studies confirmed a globular hinge motion in the ectodomain of the integrin with minor changes in protein secondary structure. Our biophysical setup in combination with MDS can be applied to study transmembrane proteins under different conditions in a biomimetic system.

Biography

Una Janke has studied Human Biology at the University of Greifswald, with the main focus on Immunology. Currently, she is a PhD student in the group of Prof. Mihaela Delcea at the Institute of Biochemistry and uses biophysical tools to investigate the impact of mutations and environmental factors (e.g. ions, drugs) on activation and immunogenicity of platelet receptor integrin αIIbβ3.

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