**Structural biomechanics of platelet-driven clot contraction**

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Blood clot contraction plays an important role in prevention of bleeding and in thrombotic disorders. We found that activated platelets bend and shorten individual fibrin fibers via their filopodia that undergo sequential extension and retraction, as if pulling hand-over-hand. Platelets also induce compaction of fibrin fibers into platelet-attached agglomerates. As a result of simultaneous pulling on multiple, closely-set fibrin fibers, platelets pull themselves closer to each other and form secondary clusters larger than the initial aggregates. Contracting platelets actively remodel a fibrin network by increasing its density followed by enhanced clot stiffness. Kinetic analysis of the time course of structural and mechanical transitions revealed a multiphasic behavior with at least three distinct phases that differ in duration and rate constants. All the observed changes were reduced or abrogated in the presence of specific inhibitors of non-muscle myosin IIA (blebbistatin) and the platelet integrin αIIbβIII (abciximab), indicating that actomyosin-driven cell contractility and integrin-fibrin mediated platelet-fibrin interactions are crucial for contraction of blood clots. Finally, blood clot contraction was found to be a spatially non-uniform process with faster compression of the clot edge and a delayed deformation of the clot interior. Altogether, the results provide a quantitative structural basis for the mechanobiology of clot contraction at various spatial scales from a single cell/single fiber level up to the network and macroscopic levels. Our results obtained on platelet-induced contraction of the filamentous fibrin network are of fundamental importance because they provide a foundation for understanding dynamic and complex biomechanical interplay between non-muscle cells and fibrous extracellular matrices of various compositions.