Atomic structure of fibrin protofibrils

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Fibrin polymerization starts when fibrinogen is proteolytically converted to monomeric fibrin, which self-assembles to form double-stranded oligomers. The oligomers continue to grow longitudinally until they reach a critical length of about 0.5-0.8 µm consisting of ~20-25 fibrin monomers, now called protofibrils. Protofibrils aggregate laterally to form thicker fibers arranged into a branched fibrin network. Determination of atomic structures of short-lived fibrin oligomers and protofibrils cannot be accomplished by X-ray crystallography because of the unstable nature of these highly heterogeneous intermediate supramolecular assemblies. Yet, atomic-level structure of fibrin oligomers is necessary to elucidate the mechanisms of formation and properties of fibrin polymers, which determine the integrity and viscoelasticity of blood clots and thrombi. We combined multiscale modeling in silico with atomic force microscopy (AFM) imaging to reconstruct complete atomic models of double-stranded fibrin protofibrils with γ-γ crosslinking, A:a and B:b knob-hole bonds, and αC regions – all important structural determinants not resolved crystallographically (see Figure). Structures of fibrin oligomers and protofibrils containing up to 19 monomers were successfully validated by quantitative comparison with high-resolution AFM images. We characterized the protofibril twisting, bending, kinking, and dissociation of A:a knob-hole bonds, and calculated hydrodynamic parameters of fibrin oligomers. Atomic structures of protofibrils provide a basis to understand the submolecular mechanisms of the early stages of fibrin polymerization.

Figure. A representative equilibrium structure observed during coarse-grained simulations of FP10/9 with a kink in the α-helical coiled-coils (magnified in inset).
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