Multiscale Modeling of Collagen IV Network: Insights into the Structural Basis of Pathologies

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Abstract: Collagen type IV is the primary component of the protein network in metazoan basement membranes. The supramolecular basis of the structure is a triple-helical unit with cross-linking domains (NC1 and 7S) at both termini. In the basement membrane, these building blocks form a cross-linked two-dimensional network, capable of supporting cellular attachment and proliferation. A better understanding of factors affecting the formation of such a stable network would help towards understanding debilitating pathologies associated with the basement membrane, e.g., Alport's syndrome. In this study, we utilized atomistic and coarse grain models for the network of Collagen type IV. For the atomistic model, a 2D network was simulated, composed of collagen triple helices. The mechanical properties were studied, including the introduction of crosslinks. For the coarse-grained model, we first focused on the building blocks, with biomimetic sticky termini, and then simulated the formation of membrane-like structures from these building blocks. The combination of these complementary approaches (coarse-grained and atomistic modeling) enabled us to decipher crucial stages of collagen type IV network formation and how certain mutations can negatively affect the assembly process. The model was validated with experimentation on peptide-based model systems as well as with morphological characterization of the assembled structures via microscopy. Our multi-scale (nm to μm) model of the collagen type IV network should help us understand the effects of protein-density, cross-link strength, mutation in the primary sequence, chain flexibility, and mechanical stimuli on the morphology and the integrity of the network.