High-Resolution Three-Dimensional Structure of Collagen Fibrils and Its Role in Vertebrate Skeletal Biomineralization

ZHIJUN XU[1], YANG YANG[2], WEILONG ZHAO[1], ZIQIU WANG[1], WILLIAM LANDIS[1], QIANG CUI[3] AND NITA SAHAI

[1]Dept. of Polymer Science, University of Akron, OH 44325 zxu@uakron.edu, wz24@zips.uakron.edu, zw10@zips.uakron.edu, wlandis@uakron.edu, sahai@akron.edu

[2]Department Chemistry and Biochemistry, Rowan Univ., Glassboro, NJ 08028 yangy@rowan.edu

[3]Department of Chemistry, University of Wisconsin-Madison, WI 53706 cui@chem.wisc.edu

Bone, dentin and calcified avian tendon are examples of calcium phosphate (apatitic) biomineralization. These tissues consist of collagen protein, non-stoichiometric apatite, non collagenous proteins and small molecules. The importance of the three-dimensional (3-D) self-assembled structure of type I collagen has been long recognized in controlling intrafibrillar calcium phosphate (Ca-P) nucleation in specific "hole" zones. The two-dimensional stucture was determined six decades ago by Transmission Electron Microscopy, but because of a lack of the 3-D structure, the Å to nanometer-scale mechanisms of Ca-P nucleation remain unknown. A major advance in the field was the recent determination of the low-resolution 3-D structure of collagen fibrils by synchrotron X-Ray Diffraction. However, this structure provided only the positions of the carbon atoms in the collagen molecule backbone. The location and orienation of amino acid side chains as well as the high-resolution positions of the backbone carbon atoms themselves could not be determined experimentally. Further, conventional molecular dynamics methods have been unable to represent Ca-P (or other ionic biominerals, such as $CaCO_3$) nucleation accurately.

Based on the low-resolution XRD structure of collagen and high-resolution structure of short collagen-mimic peptides, we used state-of-the-art molecular dynamics modeling methods to optimize the entire 3-D self-assembled fibril structure at high-resolution from the atomic (Å) to the fibril (100s of nm) length-scale, and in the presence of hydrating waters, Na^+ and Cl^-. The charged sidechains of amino acid residues in the collagen molecules were found to be oriented into the fibril "hole" zones, thus, attracting Ca^{2+} and phosphate ions. The high-resolution 3-D structure of collagen provides, for the first time, a structural basis for Ca-P nucleation in the hole zones.