Molecular Dynamics Structural Analysis of Calcium Phosphate Clusters Nucleated in Collagen Fibril Hole Zones

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The nucleation of amorphous or crystalline biomineral phases, modulated by bioorganic molecules, is an important early step in understanding the molecular-level mechanisms of biomineralization. Amorphous precursors nuclei in the solid or in the liquid phase for calcium phosphate (Ca-P, apatitic) and calcium carbonate (calcite, aragonite) have been proposed in the literature. In the present study, we examined the structure of Ca-P clusters formed in the hole zones of collagen fibrils using molecular dynamics (MD) simulations of collagen structure and Ca-P nucleation.

The high-resolution three-dimensional self-assembled structure of collagen molecules within fibrils was optimized with explicit water solvation and the presence of Na^+ and Cl^-. Application of the Hamiltonian Replica exchange MD run over simuations run over long simulation periods (20 ns) allowed more accurate determination of nucleation in the collagen fibril "hole" zones compared to conventional MD simulations. As expected, Ca-P cluster sizes (~1.3 nm and 1.6 nm) in the hole zones depended on the initial concentration of Ca^{2+} and phosphate ions in the aqueous solution. The clusters were larger and stable over longer simulation times than clusters formed in the control sytem of aqueous solutions in the absence of collagen. Furthermore, the density of water in the hole zone was less than that of bulk water. In the clusters formed in the hole zones, Ca^{2+} ions formed equilateral triangles of ~1.6 Å side-length and circumference ~ 17.8-18.6 Å. The triangles were stablized by phosphate ions bridging pairs of Ca^{2+}. These structural features are similar to those found on the (001) face of hydroxyapatite and octacalcium phosphate. It may be inferred conservatively from these calculations that the self-assembled collagen fibril structure is sufficient to promote intrafibrillar nucleation of Ca-P clusters within hole zones. However, the results can not be taken to imply either direct nucleation of apatite/OCP or of amorphous precursor phases *in vivo*; nor can the results be used to unequivocally exclude the role of non-collagenous proteins or other biomolecules in nucleation, because the modifying molecules were not accounted for in the present simulations.