JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2026.2693643

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The multifaceted nature of mollusk shell proteins: a complex interplay of protein sequence, function, and biomineralization

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ABSTRACT

Mollusk shell formation represents a complex biomineralization process governed by diverse shell proteins, yet their sequence–structure–function relationships remain incompletely understood. We have presented a comprehensive bioinformatic synthesis of 210 shell-associated proteins from 30 molluscan species to delineate compositional, structural, regulatory and evolutionary principles underlying shell formation. Primary sequence analyses revealed highly biased amino acid compositions characterized by a predominance of hydrophilic residues, enrichment of glycine-, aspartate- and serine-rich regions, and reduced nonpolar content. Nearly 65% of proteins were either highly acidic or highly basic, aligning with the prevailing view that charged macromolecules influence calcium carbonate nucleation. Repetitive low-complexity motifs, extensive post-translational modification sites and secretory signals were widespread, supporting extracellular matrix localization and functional adaptability. Structural predictions indicated limited secondary structure and extensive intrinsic disorder, with almost three-quarters of proteins classified as partially or completely disordered. Quantitative analyses demonstrated strong coupling between intrinsic disorder and regulatory motif enrichment, suggesting that these proteins primarily act as flexible, multivalent scaffolds rather than rigid structural components. Charge–hydropathy profiling and aggregation analyses further highlighted diverse structural strategies associated with biomineralization and matrix assembly. The nacrein protein family, examined as a representative case, showed a conserved carbonic anhydrase catalytic core combined with lineage-specific flexible regions, illustrating how structural conservation and disorder-driven adaptability facilitate carbonate regulation and shell microstructure diversification. This integrative framework supports a model in which mollusk shell proteins function as disorder-rich, post-translationally regulated biomolecular networks orchestrating mineral nucleation, crystal growth and shell morphogenesis.

KEY POINTS

- Mollusk shell matrix proteins exhibit strong compositional bias, widespread intrinsic disorder and limited secondary structure, distinguishing them from typical globular proteins and underpinning their biomineralization roles.
- Both acidic and basic shell proteins contribute to calcium carbonate nucleation and shell formation
- Extensive post-translational modifications, secretory signals and binding domains indicate that shell proteins function as extracellular, regulatory and multivalent interaction networks.
- Intrinsic disorder is strongly coupled with regulatory motif enrichment, supporting a model in which shell proteins act as flexible scaffolds coordinating mineral nucleation, crystal growth and matrix assembly.
- Evolutionary and structural analyses, including the nacrein case study, reveal conserved catalytic cores combined with lineage-specific flexible regions, highlighting adaptive strategies shaping mollusk shell diversity.

ARTICLE HISTORY

Received 26 May 2026
Accepted 17 June 2026

KEYWORDS

Mollusk; shell formation; biomineralization; intrinsically disordered proteins; bioinformatics

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/07391102.2026.2693643.

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