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COMPUTATIONAL ANALYSIS OF TYPE I COLLAGEN AND PROLYL HYDROXYLASE INTERACTIONS: IMPLICATIONS FOR OSTEOGENESIS IMPERFECTA THERAPEUTIC TARGETS

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ABSTRACT

Background: Osteogenesis Imperfecta (OI), or "brittle bone disease," is a rare hereditary connective tissue disorder characterized by an increased risk of fractures due to impaired bone mineralization. Type I collagen is the primary structural protein in bone, and mutations in the **COL1A1** and **COL1A**2 genes account for approximately 90% of OI cases. The enzyme **Prolyl Hydroxylase 2 (PHD2/EGLN1)** plays a crucial role in collagen post-translational modifications, influencing its structural integrity and function. **Objective:** To analyze the molecular interactions between Type I collagen and Prolyl Hydroxylase 2 (PHD2) using **in silico** approaches to identify potential therapeutic targets for OI. **Methods:** A computational

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framework was employed to study the structural properties of key proteins involved in bone mineralization. Three-dimensional protein structures were retrieved from the **Protein Data Bank (PDB),** and molecular docking simulations were performed using **GRAMM**. Structural validation was conducted via **Ramachandran plot analysis, MolProbity geometric evaluation**, and hydrophobicity assessments. Interaction interfaces were analyzed using **SPPIDER and PISA** software to evaluate **Interface Surface Area (ISA) and Hydrophobicity Index (HPI). Results:** Structural analysis confirmed that **7CWK (Type I collagen) and 7Q5V (PHD2) displayed a robust molecular interaction (ISA = 658 Å², HPI = 0.81 ± 0.89)**, suggesting a stable binding interface with significant hydrophobic characteristics. A second Type I collagen model, **8K4W**, demonstrated an even greater interaction with 7Q5V **(ISA = 1123 Å², HPI = 0.90 ± 0.74)**, indicating a stronger potential binding affinity. **Conclusion:** These findings validate the selected protein structures and provide insights into their molecular interactions. This computational approach enhances our understanding of OI pathophysiology and could aid in developing therapeutic strategies targeting collagen stability and enzymatic regulation.

KEYWORDS: Osteogenesis Imperfecta; Silico Analysis; Type I Collagen; Prolyl Hydroxylase 2; Protein-Protein Interaction.

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ANÁLISIS COMPUTACIONAL DE LAS INTERACCIONES ENTRE EL COLÁGENO TIPO I Y LA PROLIL HIDROXILASA: IMPLICACIONES PARA LOS OBJETIVOS TERAPÉUTICOS DE LA OSTEOGÉNESIS IMPERFECTA

RESUMEN

Antecedentes: La osteogénesis imperfecta (OI), o "enfermedad de los huesos de cristal", es un trastorno hereditario poco frecuente del tejido conectivo que se caracteriza por un mayor riesgo de fracturas debido a una mineralización ósea deficiente. El colágeno tipo I es la principal proteína estructural del hueso, y las mutaciones en los genes **COL1A1 y COL1A2** representan aproximadamente el 90 % de los casos de OI. La enzima **Prolil Hidroxilasa 2 (PHD2/EGLN1)** desempeña un papel crucial en las modificaciones postraduccionales del colágeno, influyendo en su integridad estructural y función. **Objetivo:** Analizar las interacciones moleculares entre el colágeno tipo I y la prolil hidroxilasa 2 (PHD2) mediante métodos **in silico** para identificar posibles dianas terapéuticas para la OI. **Métodos:** Se empleó un marco computacional para estudiar las propiedades estructurales de proteínas clave implicadas en la mineralización ósea. Se obtuvieron estructuras proteicas tridimensionales del **Banco de Datos de Proteínas (PDB)** y se realizaron simulaciones de acoplamiento molecular con **GRAMM**. La validación estructural se realizó mediante análisis de gráficos de **Ramachandran, evaluación geométrica de MolProbity** y evaluaciones de hidrofobicidad. Las interfaces de interacción se analizaron utilizando el software **SPPIDER y PISA** para evaluar el **Área Superficial de la Interfaz (ISA)** y el **Índice de Hidrofobicidad (HPI)**. **Resultados:** El análisis estructural confirmó que **7CWK (colágeno tipo I) y 7Q5V (PHD2) mostraron una interacción**

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molecular robusta (ISA = 658 Å², HPI = 0,81 ± 0,89), lo que sugiere una interfaz de unión estable con características hidrofóbicas significativas. Un segundo modelo de colágeno tipo I, 8K4W, demostró una **interacción aún mayor con 7Q5V (ISA = 1123 Å², HPI = 0,90 ± 0,74)**, lo que indica una afinidad de unión potencial más fuerte. **Conclusión:** Estos hallazgos validan las estructuras proteicas seleccionadas y brindan información sobre sus interacciones moleculares. Este enfoque computacional mejora nuestra comprensión de la fisiopatología de la OI y podría ayudar a desarrollar estrategias terapéuticas dirigidas a la estabilidad del colágeno y la regulación enzimática.

PALABRAS CLAVE: Osteogénesis Imperfecta; Análisis Silico; Colágeno Tipo I; Prolil Hidroxilasa 2; Interacción Proteína-Proteína.

INTRODUCTION

Osteogenesis Imperfecta (OI) is a Mendelian inherited connective tissue disorder primarily characterized by bone fragility, recurrent fractures, and skeletal deformities. These clinical manifestations result from defects in type I collagen, the principal component of the extracellular matrix, which plays a critical role in bone mineralization and structural integrity (Subramanian et al., 2024).

Mutations in the COL1A1 and COL1A2 genes impair collagen synthesis and stability, leading to various phenotypic presentations classified into fifteen subtypes (Unger et al., 2023). Among these, Type I OI, the most common form, is an autosomal dominant disorder that results in quantitatively

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reduced but structurally normal collagen. Conversely, Type II OI, the most severe form, is often perinatally lethal and associated with gross collagen malformations.

Beyond structural abnormalities, collagen dysfunction disrupts its interactions with regulatory proteins, including osteocalcin, osteonectin, and fibroblast growth factors (FGFs), which modulate bone mineralization. The HIF signaling pathway, regulated by Prolyl Hydroxylase 2 (PHD2/EGLN1), has been linked to collagen post-translational modifications, particularly in hydroxylation events that enhance its structural fidelity and mineral-binding capacity (Christenson et al., 1997).

Current treatments for OI, such as bisphosphonates, calcium, and vitamin D supplementation, primarily focus on mitigating bone fragility rather than addressing its underlying molecular pathogenesis. Given this gap, an in-silico analysis of collagen-PHD2 interactions may uncover potential therapeutic targets that could modulate collagen stability and improve bone strength (Carvalho et al., 2024).

Thus, this study aims to investigate the molecular interactions between Type I collagen (7CWK and 8K4W) and PHD2 (7Q5V) using computational docking techniques to define novel therapeutic strategies for OI.

2. Methods

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2.1 Selection of Proteins and Structural Data Retrieval

A computational framework was employed to investigate proteins crucial for bone mineralization, focusing on their association with Osteogenesis Imperfecta (OI). Three key proteins were selected based on their structural and functional relevance:

- Type I Collagen (PDB IDs: 7CWK and 8K4W)
- Prolyl Hydroxylase 2 (PDB ID: 7Q5V)

These three-dimensional crystal structures were retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org/), ensuring high-resolution datasets for molecular modeling. Each structure was validated for structural integrity, atomic coordinates, and crystallographic quality, following established criteria (Christenson et al., 1997; Subramanian et al., 2024).

2.2 Protein Structure Analysis and Validation

To ensure accuracy in structural modeling, the selected PDB files underwent geometric validation and stereochemical assessment:

1. Ramachandran Plot Analysis – Performed using MolProbity, evaluating the ϕ (phi) and ψ (psi) backbone torsion angles to confirm that residues fall within allowed conformational regions.
2. Chirality and Tetrahedral Geometry Evaluation – Checked for chirality errors and tetrahedral distortions that could compromise molecular docking accuracy.

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3. Side-chain Conformation and Rotamer Favorability – Assessed via rotamer analysis to ensure that side-chain orientations align with energetically stable conformations.
4. Backbone Geometry Optimization – Verified peptide bond angles, bond lengths, and steric clashes to refine molecular accuracy.

2.3 Molecular Docking and Interaction Predictions

Molecular docking was performed to predict potential binding sites and assess interaction stability between Type I collagen and Prolyl Hydroxylase 2 (PHD2):

- Protein-protein docking was conducted using GRAMM (Global Range Molecular Matching), an empirical docking algorithm optimized for rigid-body molecular interactions (https://vakserlab.ku.edu/gramm.php).
- The docking simulations generated multiple binding poses, which were ranked based on interaction energy, spatial fit, and biological relevance.

2.4 Molecular Interaction and Interface Analysis

To further evaluate interaction strength and stability, docking outputs were analyzed using:

1. SPPIDER (Solvent-Accessible Protein-Protein Interface Detector)

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- Calculated Interface Surface Area (ISA), which measures the contact area between protein complexes.
- Identified critical binding residues and analyzed interaction specificity.

2. PISA (Protein Interfaces, Surfaces, and Assemblies)
   - Assessed hydrophobic and hydrophilic interactions at the binding interface.
   - Determined binding free energy and interface stability.

Additionally, the Hydrophobicity Index (HPI) was calculated to determine interface hydrophobicity, which correlates with binding affinity and structural stability (Gavva et al., 2023).

2.5 Computational Tools and Software Utilized

The following computational tools were employed for structural visualization, data analysis, and molecular simulations:

- MolProbity (http://molprobity.biochem.duke.edu/) – Structural validation and quality assessment.
- Python Molecular Viewer (PMV) – Molecular visualization and interactive modeling.
- UCSF Chimera (https://www.cgl.ucsf.edu/chimera/) – 3D rendering of protein

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structures and complex formation analysis.

- Swiss-Pdb Viewer (https://spdbv.vital-it.ch/) – Comparative visualization of molecular conformations.

All computational analyses were performed following best practices for in silico structural studies to ensure reproducibility and accuracy (Yang et al., 2022).

3. Results and Discussion

3.1 Structural Validation of Selected Proteins

To ensure the accuracy of the selected PDB structures, a comprehensive validation analysis was performed. The Ramachandran plot assessment confirmed that nearly all residues were in allowed and favored regions, indicating a reliable conformation (Table 1). Chirality checks revealed no tetrahedral geometry errors, indicating the correct stereochemical orientation of all structures.

Table 1. Ramachandran Plot Analysis for Selected Proteins

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Protein Code	Favored Regions (%)	Allowed Regions (%)	Outliers (%)
7CWK	100.0% (59/59)	100.0% (59/59)	0.00%
8K4W	100.0% (263/263)	100.0% (263/263)	0.00%
7Q5V	97.7% (303/310)	100.0% (310/310)	0.00%

These results confirm that the selected type I collagen and PHD2 structures are suitable for molecular docking and interaction analysis.

3.2 Protein-Protein Interaction Analysis

Molecular docking between Type I collagen (7CWK, 8K4W) and Prolyl Hydroxylase 2 (7Q5V) revealed strong and stable interactions, as quantified by Interface Surface Area (ISA) and Hydrophobicity Index (HPI).

3.2.1 Interaction Between 7CWK and 7Q5V

- ISA = 658 Å², indicating a moderate interaction surface, which is significant for protein-protein complexes.
- HPI = 0.81 ± 0.89, suggesting a predominantly hydrophobic interface.
- Interacting Residues: P1, G3, P4, G6, P7, G9, Q10, G12, E13, R14, G15, F16, G18, P19, G21, P22, G24, P25, G27.

A larger ISA generally correlates with greater binding stability in protein-protein interactions. The hydrophobic nature of the

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interface further reinforces its potential biological relevance in collagen modification pathways (Yang et al., 2022).

3.2.2 Interaction Between 8K4W and 7Q5V

- ISA = 1123 Å², a substantially larger interaction surface, suggesting greater binding stability than the 7CWK-PHD2 complex.
- HPI = 0.90 ± 0.74, indicating a highly hydrophobic interface.
- Interacting Residues: Q239, L240, V241, S242, K244, I251, R252, W258, D277, R281, N293, G294, R295, T296, Y310, R312, H313, V314, D315, P317, N318, D320, R322, R370, F391, R396, A399, K400, Y403.

The significantly higher ISA and HPI values suggest that the 8K4W-PHD2 complex is more stable than 7CWK-PHD2, likely due to increased binding contacts and a more hydrophobic environment.

3.3 Structural Implications for Osteogenesis Imperfecta Therapy

The observed interactions suggest that PHD2 plays a critical role in collagen stability via post-translational hydroxylation. Given that mutations in COL1A1 and COL1A2 interfere with collagen integrity, targeted interventions aimed at modulating PHD2 activity may be beneficial in OI patients.

Moreover, the differences in ISA and HPI between the two collagen models (7CWK vs. 8K4W) highlight potential structural variations that could influence therapeutic strategies. Future drug design could leverage these insights to develop small

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molecules that enhance PHD2-mediated collagen stabilization.

3.4 Limitations and Future Directions

While in silico analysis provides valuable insights, certain limitations must be considered:

1. Computational models rely on static protein conformations, whereas biological interactions occur in dynamic environments.
2. Experimental validation (e.g., in vitro or in vivo studies) is required to confirm the functional relevance of these interactions.
3. Mutational analysis could further elucidate the impact of OI-associated genetic variants on collagen-PHD2 binding efficiency.

Future studies should integrate molecular dynamics simulations to evaluate the flexibility and stability of these complexes under physiological conditions.

4. Conclusion

This study provides a computational analysis of Type I collagen (7CWK and 8K4W) interactions with Prolyl Hydroxylase 2 (7Q5V), offering insights into potential therapeutic targets for Osteogenesis Imperfecta (OI). The findings demonstrate that both Type I collagen models interact with PHD2, but 8K4W exhibits a larger interface surface area (ISA = 1123 Å²) and a higher hydrophobicity index (HPI = 0.90 ± 0.74), indicating a stronger and potentially more stable interaction. Structural validation confirmed the accuracy of the

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PDB models, reinforcing their reliability for in silico analysis. The role of PHD2 in collagen post-translational modifications suggests a possible therapeutic approach targeting enzymatic regulation to enhance collagen stability in OI patients.

These findings contribute to a better understanding of collagen-protein interactions and open new possibilities for targeted therapies. However, further experimental validation is necessary to confirm the biological relevance of these molecular interactions, including in vitro and in vivo studies. Additionally, molecular dynamics simulations should be incorporated to evaluate the stability and conformational flexibility of these complexes under physiological conditions.

The insights provided by this study may serve as a foundation for future drug discovery efforts, particularly in developing small molecules that modulate PHD2 activity to improve collagen stability in OI patients.

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