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In Silico Molecular Interaction Analysis Of Type I Collagen Telopeptides With Cyclodextrins

Bioinformatics

KEYWORDS : Homology modeling; Telopeptide; Cyclodextrin; Type I collagen

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ABSTRACT

Type I Collagen is the extracellular matrix protein of skin, tendon, bone etc. The proteomic feature of the collagen is of triple helical form, but the ends are capped by short peptide extensions, called Telopeptides, which are non-helical in nature. Normally telopeptides of collagen denatures at 35°C, but in the presence of α, β and γ cyclodextrins the denaturation can be prevented until 40°C. Increasing concentration of cyclodextrin resulted in aggregation of the protein. Further, cyclodextrin imparts high level of thermal stability to collagen with shrinkage temperature of collagen. It was known that the hydrophobic amino acids play an important role in the fibril formation of collagen. . In this current study , Type I Collagen telopeptide chains were modeled using modeler software also docked with α, β and γ cyclodextrins.

INTRODUCTION

Collagen is a group of naturally occurring proteins. Collagen is a natural polymer and the primary component of cartilage, ligaments, bone, tendon, and teeth [1]. It controls the strength and elasticity of the skin as well- and it is involved in the development of tissue. It is the main component of connective tissue, and is the most abundant protein in mammals, making up about 25% to 35% of the whole-body protein content [2]. There are more than 25 types of collagen, but 80 – 90 percent of the collagen in the body. To date, 28 collagen types have been identified; with types I, II, III, V and XI involved in forming fibrillar structures.

N-telopeptide is involved in directing the linear arrangement of the collagen molecules, whereas the carbonyl-terminal may have a more prominent role in directing lateral alignment [3]. Also, the self assembly of type I collagen involves the N-telopeptide domain of the monomer crosslinking with the helical region of a second monomer in an endothermic entropy driven process. The process of fibril formation may be triggered by conformational changes in the extra helical peptides that promote intermolecular association [4, 5]. Proteolytically modified collagen monomers, treated to remove only the telopeptide regions, form structurally defective fibrils [6]. In addition, excition of telopeptides leads to changes in the lag period, as seen in thermally induced fibrillogenesis experiments suggesting that significant events involving the telopeptides take place during the lag phase. These data imply that the nonhelical ends of collagen may be involved in fibril formation whose role is not yet clear [7, 8].Hence, elucidating the pathway of the fibril formation of collagen is of considerable significance as it is also the subject of the present investigation. This is to be done by exploiting one of the properties of cyclodextrin, wherein, it encapsulates the hydrophobic molecules [9]. Thus, the cyclodextrins when allowed to interact with collagen are expected to engulf the hydrophobic amino acid residues present at the non-helical ends of the protein. Here conformational changes are expected and hence the changes the fibrils formed are to be determined.

Telopeptide of α-I collagen (I) and α-II collagen (I) have been modeled using Modeller9V7. Appropriate templates have been selected using blastP [10]. Modeller9v7 is a computer program that models three-dimensional structures of proteins and their assemblies by satisfaction of spatial restraints [11]. Modeled telopeptides have validated with SAVES server .It provides the user with an expert-system consultation about the accuracy of a macromolecular structure model, diagnosing local problems and enabling their correction.

MATERIALS AND METHODS

Retrieval of target sequence from database

The Protein sequence of Collagen α -I (I) and Collagen α -II(I) was retrieved from SWISSPROT database [12] using unique accession number P02452 and P08123respectively. Collagen α -I(I) is on length of 1464aa with N-terminal propeptide has 161aa and C-terminal propeptide with 246aa also N- terminal Telopeptide has17aa and C-terminal Telopeptide with 26aa. Similarly Collagen α -II(I) is on length of 1366aa with N-terminal propeptide has 79aa and C-terminal propeptide with 247aa also N- terminal Telopeptide has 11aa and C-terminal Telopeptide with 15aa.Both collagen is in nature of triple helical and the domain region covers same range of about 1014aa.

Template selection mode for telopeptides

Selection of appropriate template for unpredicted structure is more curated process in theoretical protein modeling studies. Templates for Collagen telopeptide identified using the PDBsumdatabase [13]. Collagen α -I (I) of human with N-terminal telopeptide and C-terminal telopeptide sequence is "QLSYGYDEKSTGGISVP" and "SAGFD FSFLPQPPQEKAHDGGRYYRA" .On the same way Collagen α -II(I) of human with N-terminal telopeptide and C-terminal telopeptide sequence is "QYDGKGUGLGP" and "RGDKGEPGEKGPRGL" respectively.

Theoretical modeling and validation of telopeptides

In the structural proteomics domain, homology modeling plays a vital role to resolve the unresolved protein or peptides. Initially it begins from homologous selection of templates using a sequence-sequence alignment mode followed by structure-sequence alignment, finally with modeling and superimposition of template and query. After modeling, the peptides or proteins it was validated in SAVES, server of check the peptide quality [14].

Molecular docking

Docking of receptor and ligand plays an imperative role in rational based drug designing. Auto Dock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. AutoDock 4 is free and is available under the GNU General Public License. In this current study Docking studies were carried out using the program Auto dock 4 Collagen α -I (I) and Collagen α -II(I) telopeptides with α , β and γ cyclodextrins.

RESULTS AND DISSCISION

Template Structure-query sequence alignment

Modeller9v7 was used for modeling the query sequence with

appropriate target template sequence. N-Telopeptide of Collagen α -I (I) shares 78.3% sequence identity with the Chain A, Hypothetical Protein from pyrofurisus pfu consists of 293 amino acids, (PDB Id: 1NNH) with the maximum score and maximum query coverage is considered in selecting the template. C-Telopeptide of Collagen α -I (I) matches with high sequence identity of 73.5% by Chain A of Crystal structure of the collagen Triple helix with (PDB Id: 1K6F) consists of 29 amino acids. Similarly for N-Telopeptide of Collagen α -II(I) shares 71% of identity with its target sequence , Crystal structure of the Human brd2 second bromodomain (PDB Id: 2E3K) chain:R consists of 13 amino acids . Whereas C--Telopeptide of Collagen α -II (I) matches with high sequence identity of 57.1% by Chain A of Solution structure of Collagen heterotrimer with (PDB Id: 2KLW) consists of 31 amino acids. Modelled telopeptides of Collagen α -I (I) and Collagen α -II(I) is given in figure 1.

Validation

Validation of modeled protein is important to prove the quality of the protein or peptide. As per ramachandran plot, stereochemical quality of a peptide structure was analyzed residue-by-residue geometry and found that all the four peptides are in favorable allowed region with cent percent. In addition, the Zscore are better and favor the quality of the peptides.

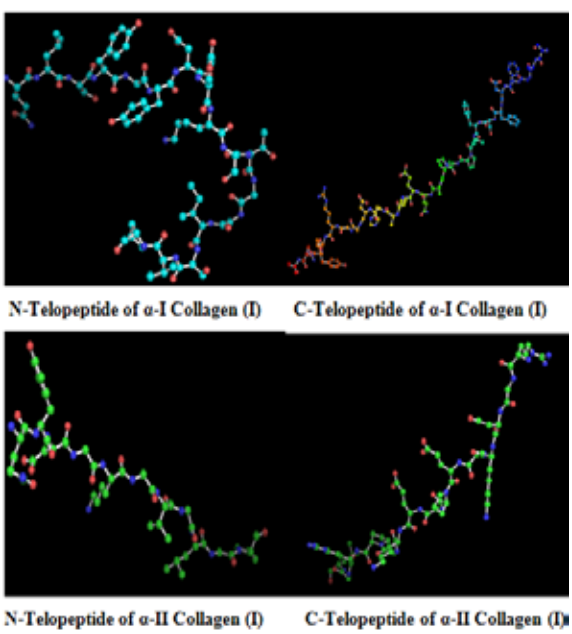

Figure 1: Modelled telopeptides of Collagen α -I (I) and Collagen α -II(I)

Receptor-ligand Interaction

Docking studies were carried out for Collagen α (I), Collagen α (II) telopeptides with α, β cyclodextrins. Favorable interaction energies were found when docked each telopeptide with α, β, γ cyclodextrins. Grids were laid over a three-dimensional cubic box where the telopeptide occupied the center of the box. In order to get the best interaction, torsion angles of the rotatable bonds were identified for each ligand. It ranked followed by the docking various conformations based on ranges of energy, lowest (best) to highest. For each run there were 10 docked conformations .Foreach of which hydrogens are added and among, Out of 10 conformation there was only one with minimum binding energy, which was considered as the best run for receptor-ligand interaction. Binding Energy is the sum of the intermolecular Energy, the torsional energy and the Internal energy. Figure 2 shows sample docked interaction representation of Collagen α -I (I) C-Telopeptide with β-Cyclodextrin .similarly N-Telopeptide of Collagen α -I(I) and Collagen α -II(I) were docked with α, β and γ Cyclodextrins. as same as C-Telopeptide of Collagen α -I(I) and Collagen α -II(I) were docked with α, β and γ Cyclodextrins .The interaction between Collagen α -I(I) and Collagen α -II(I) with α, β and γ Cyclodextrins was found for each dock and Interaction details are given in (Table 1)

Table 1: Collagen and cyclodextrin interaction analysis

Collagen	Cyclo Dextrin	Interactions	Binding Energy (kcal /mol)
α1 N ter	A	Tyr6,Glu8, Tyr4	-6.59
	B	Tyr4,Glu8	-9.15
	Γ	Gln14, Pro12	-8.89
α2 N ter	A	Gly8,Lys10, Gly11	-6.61
	B	Asp3,Lys4, Gly5	-8.25
	Γ	Tyr4,Glu8	-5.88
α1 C ter	A	Gln11,Leu9, Lys5,Glu15, Gln14,Pro12	-7.51
	B	Leu9,Gln11, Phe8,Pro10, Lys5	-9.21
	Γ	Gln14, Pro12	-7.10
α2 C ter	A	Gln1,Glu4, Tyr2,Lys5	-6.93
	B	Gly6,Lys5, Leu9	-9.22
	Γ	Gly6,Lys5	-6.58

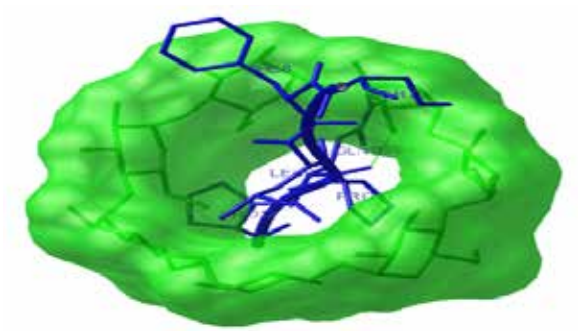

Figure 2: Collagen α -I (I) C-Telopeptide with β - Cyclodextrin

CONCLUSION

Hence from this current study it is very clear theoretical modelled Collagen α -I(I) C-terminal with α cyclodextrin and Collagen α -I(I) C-terminal with β cyclodextrin shows each five hydrogen bonding sites which have the maximum interactions. The literature states that Type I collagen has four cross linking sites, one in each telopeptide and two others at the sites in the triple helical domain at the 87th and 930th residue. The present work aims at engulfing the Lysine residue with cyclodextrins, so that, when the Lysine is engulfed with cyclodextrins, the shrinkage temperature of the protein will be increased.

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