Structure & Prediction of Protein Structure

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Subject: Principles of Drug Discovery

Introduction to Proteins

- Vital for cellular function
- Roles: Enzymes, signaling, structural, molecular machines
- Function is dictated by 3D structure

Structure of Proteins

- Proteins are made of 20 amino acids
- Peptide bonds form the backbone
- Folding stabilized by noncovalent bonds

Protein Folding Forces

- Electrostatic attractions
- Hydrogen bonds
- Van der Waals forces
- Hydrophobic clustering drives core folding

Levels of Protein Structure

- Primary: Amino acid sequence
- Secondary: Alpha helix, Beta sheet
- Tertiary: 3D folding
- Quaternary: Multi-subunit arrangement

Protein Domains and Folds

- Domains fold independently
- Types: All , All , +, /
- Examples: Myoglobin, SOD, Triosephosphate isomerase

Supersecondary Structures (Motifs)

- Beta hairpin, Helix-turn-helix
- Zinc finger, Greek key, EF-hand
- Structural building blocks

Dihedral Angles & Ramachandran Plot

- Phi (), Psi (), Omega ()
- Ramachandran plot: Allowed conformations
- Glycine and Proline exceptions

Turns and Loops in Proteins

- Turns: Short, reverse direction
- Loops: Longer, irregular
- Found on surface, aid interactions

Computational Prediction Methods

- Homology Modeling
- Protein Threading
- Ab Initio (de novo) Prediction

Homology Modeling Steps

- Template selection
- Sequence alignment
- Backbone & side chain modeling
- Model optimization and verification

Protein Threading Overview

- Fit sequence to known folds
- Used when low sequence identity
- Scoring and template match
- Tools: I-TASSER, PHYRE2

X-ray Crystallography

- Steps: Crystallization, X-ray exposure, data collection, phase solving
- Generates electron density map
- Builds atomic 3D structure

NMR Spectroscopy for Structure

- Works in solution
- Uses NOESY, COSY, TOCSY
- Determines interatomic distances
- Suitable for non-crystallizable proteins

Conclusion & Applications

- Protein structure defines function
- Crucial in drug discovery
- Both experimental and computational methods provide insight

References

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- Alberts et al. Molecular Biology of the Cell
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- Majumder, Statistical Modelling for Bioinformatics