



IIT Guwahati

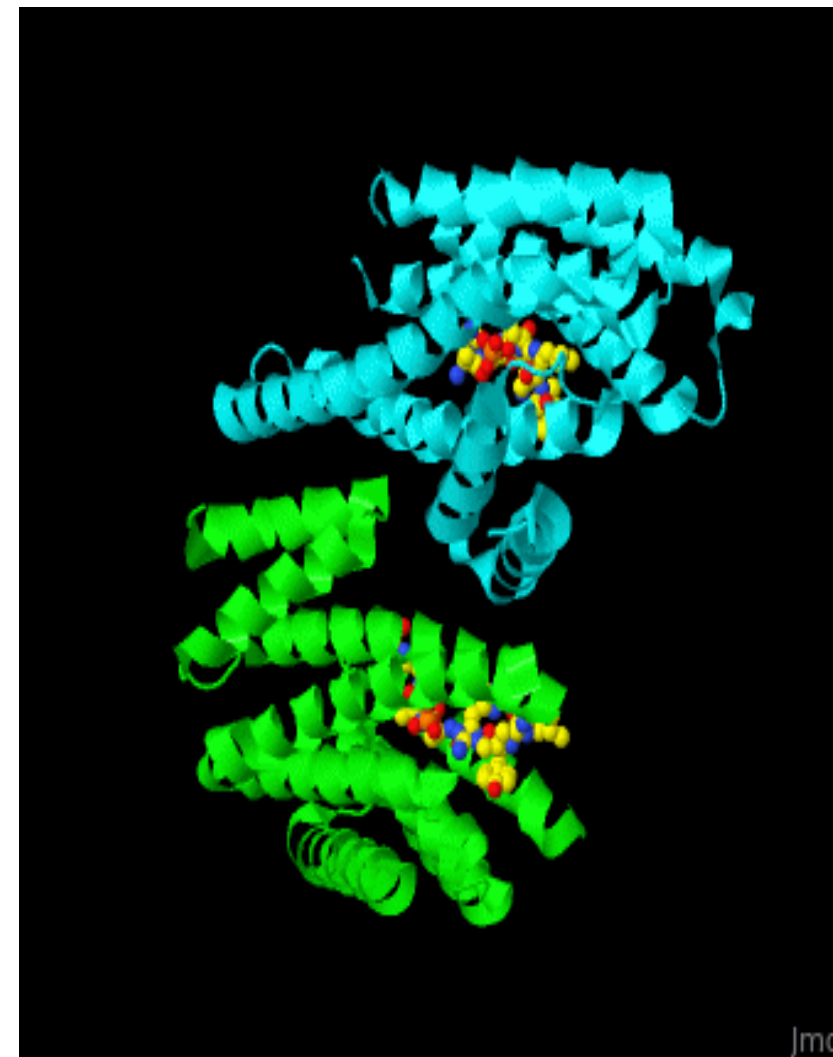
Lecture 12

Course BT 631

Protein Structure function and Crystallography

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Structural Motifs: Super-secondary structures

Motifs are super-secondary structures formed by regular secondary structure elements like α -helix and β -Sheet and irregular structures like turns and loops.

Motifs are evolutionary and conserved in nature.

Super secondary structures can be regarded as intermediates between Secondary and Tertiary structure.

Types of Motifs

A) **Helix** super-secondary structures

1. Helix-turn-helix (HtH)
2. Helix-loop-helix (HLH)
3. Helix-hairpin-helix (HhH)
4. Helix corner (α - α corner) (Hc)

B) **Sheet** super-secondary structures

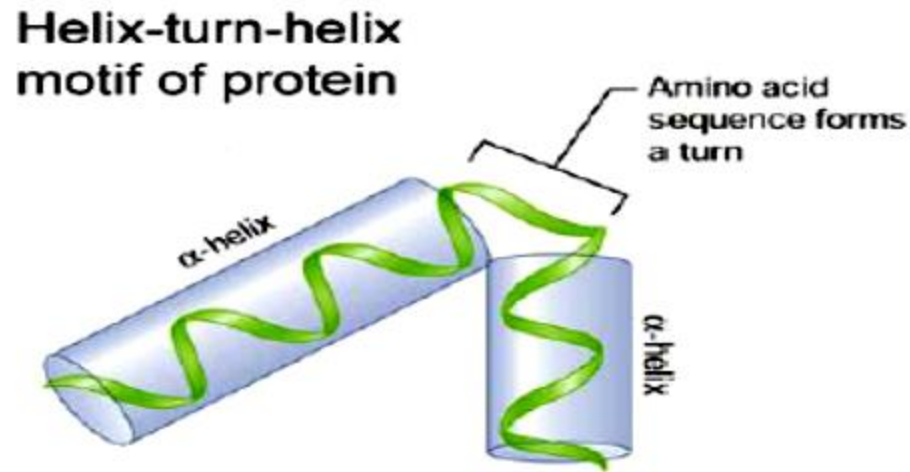
1. Beta corner (β - β corner)
2. Greek key motif
3. Beta Jelly Roll

C) **Mix** super-secondary structures

1. Beta-alpha-beta (β - α - β)
2. Rossmann fold

A) Helix super-secondary structures

1. **Helix-turn-Helix:** The Helix-turn-helix (HtH) is a major structural motif observed in proteins capable of binding DNA e.g. CAP and λ repressor (Cro). It consists of **Two** segments of alpha helix separated by a short irregular region or "turn". The **one** helix contributes to DNA recognition (called recognition helix) and **the second** helix stabilizes the interaction between protein and DNA.



Proteins having this motif are generally involved in cell proliferation, establishment of DNA structure, developmental regulation, maintenance of **circadian rhythms**, movement of DNA, regulation of a myriad of bacterial operons and initiation of transcription itself.

Circadian rhythms are physical, mental, and behavioral changes that follow a 24-hour cycle.

A) Helix super-secondary structures

2. *Helix-Loop-Helix*: In HLH, in general, one helix is smaller and due to the flexibility of the loop, undergoes dimerization by folding and packing against another helix. The larger helix typically contains the DNA-binding regions.



- A basic helix-loop-helix (HLH) is a protein structural motif that characterizes a family of transcription factors.
- Transcription factors having HLH motif are dimeric, each with one helix containing basic amino acid residues that facilitates DNA binding.

A) Helix super-secondary structures

2. *Helix-Loop-Helix*:

HLH proteins typically bind to a consensus sequence called an **E-box** (CACGTG).

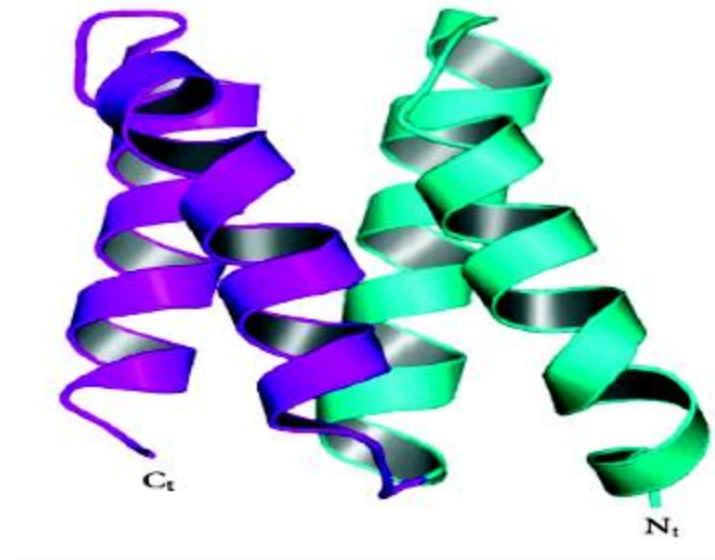
E-box (enhancer box) is a DNA sequence found in eukaryotes that acts as a protein-binding site and that regulates gene expression in neurons, muscles and other tissues

Transcription factors containing a HLH motif are

- i) MyoD, Myf5 (Skeletal Muscle)
- ii) Pho4 (Yeast)

A) Helix super-secondary structures

3. *Helix-hairpin-Helix*: The helix-hairpin-helix (HhH) motif is similar to, the helix-turn-helix (HtH) and the helix-loop-helix (HLH) motifs, but is distinct. **In HhH motif, the second helix does not protrude from protein surface and therefore cannot lie in the major groove of DNA.**



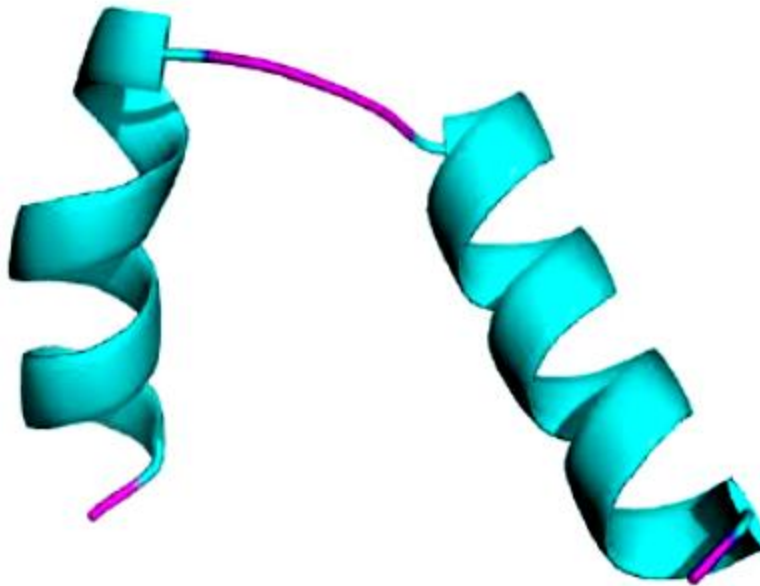
- DNA-binding proteins with a HhH structural motif are involved in *non-sequence-specific DNA binding* that occurs via formation of H-bonds between **protein backbone Nitrogen** and **DNA phosphate groups**.
- Proteins containing HhH motif are 5'-exonuclease domain of prokaryotic DNA polymerase, T4 RNaseH and some viral exonucleases.

A) Helix super-secondary structures

4. Helix corner (α - α corner)

Short loop regions connecting helices which are roughly perpendicular to one another are referred to as α - α corner.

e.g. a) *calcium binding motif* and
b) *Leucine Zipper Motif*.

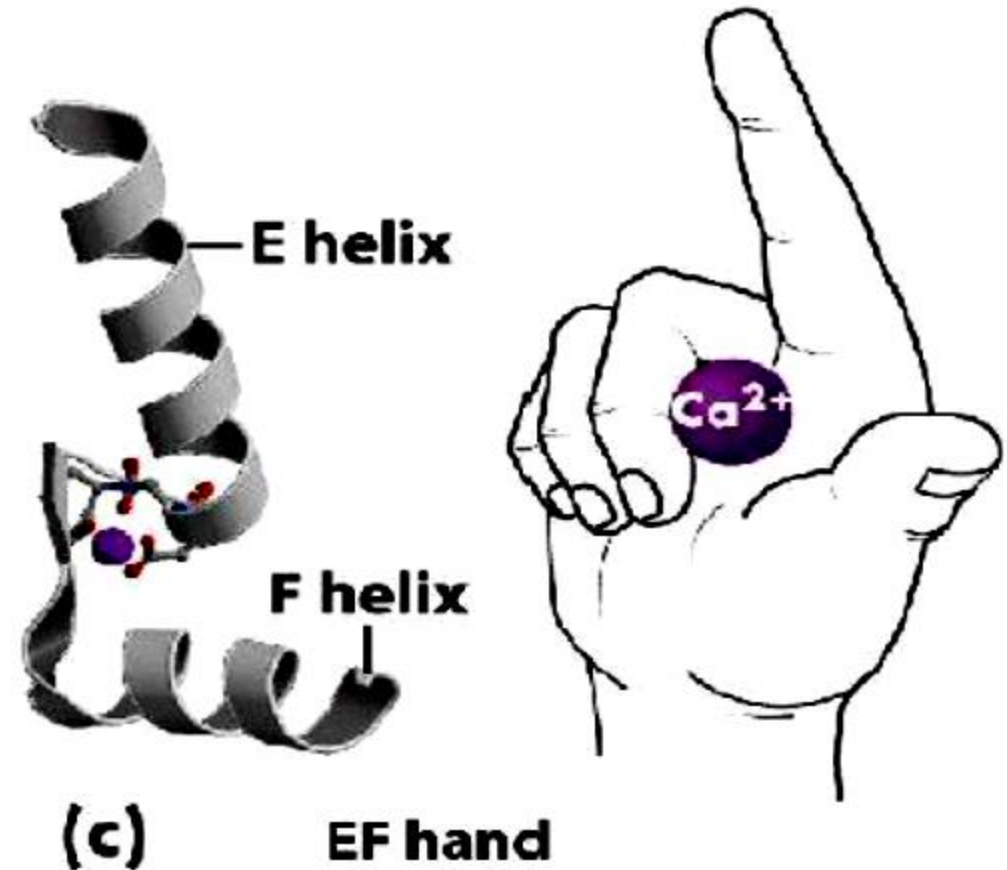


A) Helix super-secondary structures

4. Helix corner (α - α corner)

a) The calcium binding motif (EF-hand)

- The motif comprises two α helices, E and F, which flank a loop of 12 contiguous residues.
- Five (5) of the loop residues are **Calcium ion** binding ligands. Their side chains contain an oxygen atom and preferably is Asp or Glu.
- Residue 6 of the loop is glycine because the side chain of any other residue would disturb the structure of the motif.
- Finally, a number of side chains form a hydrophobic core between the helices and thus must be hydrophobic.

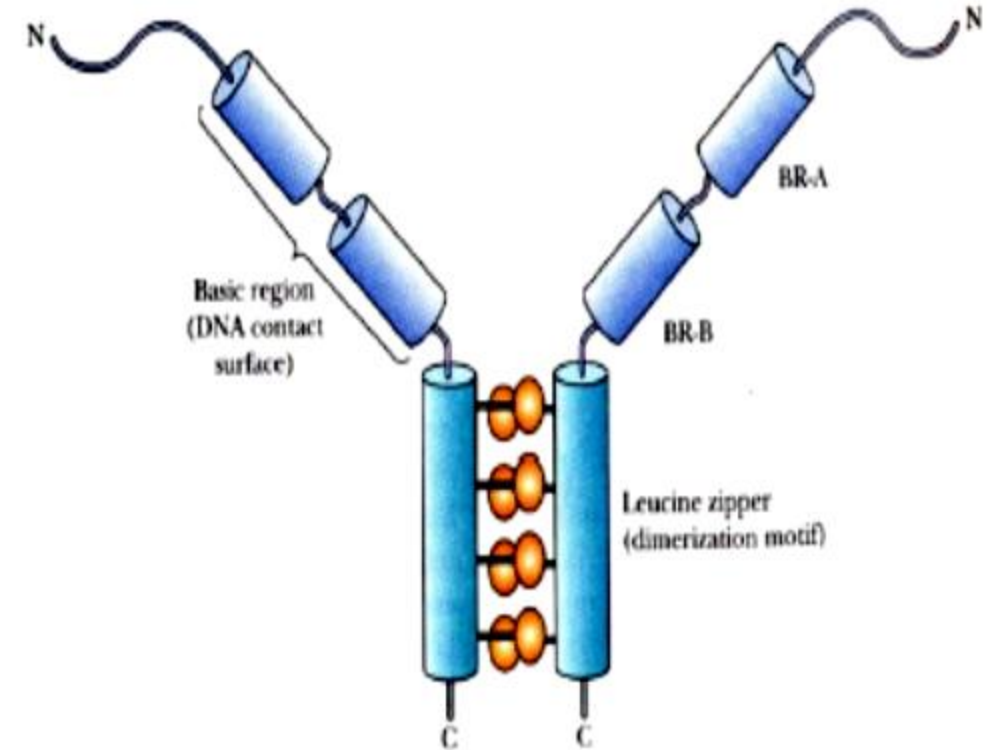


A) Helix super-secondary structures

4. Helix corner (α - α corner)

b) Leucine Zipper Motif

- Proteins of this type form homo-or hetero-dimers.
- Two α -helices, one from each monomer, form a **coiled-coil structure at one end due to hydrophobic interactions between leucine** that extend from one side of each helix.
- Beyond (i.e. above) the dimerization interface the alpha helices diverge, allowing them to fit into the major groove of the DNA double helix.
- The dimerization partner determines DNA binding affinity and specificity.
- Stability is achieved by efficiently burying the hydrophobic Leucine residues.



Found in fibrinogen (essential in blood coagulation), DNA binding protein (GCN4, AP1), structural proteins (spectrin), muscle protein myosin.