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Helical assemblies: Structure determinants

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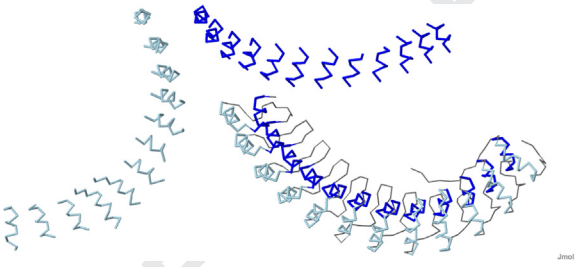
HIGHLIGHTS

- Pocket geometry of α-helix contributes to chirality and curvature of the helical assembly.
- Orientation of helical edges determines direction of the assembly and influences curvature of the assembly.
- Amino acid composition of α-helix determines its pocket geometry.

GRAPHICAL ABSTRACT



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ABSTRACT

Protein structural motifs such as helical assemblies and α/β barrels combine secondary structure elements with various types of interactions. Helix–helix interfaces of assemblies – Ankyrin, ARM/HEAT, PUM, LRR, and TPR repeats – exhibit unique amino acid composition and patterns of interactions that correlate with curvature of solenoids, surface geometry and mutual orientation of the helical edges. Inner rows of ankyrin, ARM/HEAT, and PUM-HD repeats utilize edges $(i-1, i)$ and $(i+1, i+2)$ for the interaction of the given α-helix with preceding and following helices correspondingly, whereas outer rows of these proteins and LRR repeats invert this pattern and utilize edges $(i-1, i)$ and $(i-3, i-2)$. Arrangement of contacts observed in protein ligands that bind helical assemblies has to mimic the assembly pattern to provide the same curvature as a determinant of binding specificity. These characteristics are important for understanding fold recognition, specificity of protein–protein interactions, and design of new drugs and materials.

1. Introduction

Helical assemblies are essential modules of many cellular processes that regulate events of transcription, sensory transduction, development, recognition, and communication (Andrade et al., 2001; deWit et al., 2011; Blatch and Lassle, 1999; Sawyer et al., 2013). As mediators of protein–protein interactions and cell signaling, helical structures provide a basis for our understanding of many pathologies such as mental, degenerative and immune system diseases, cancer, and inflammation (Utreras et al., 2013; Lishko et al., 2007; Sanders et al., 2014; Holzer and Izzo, 2014; Latorre et al., 2009). Many helix bundles have been shown to be vital for the development of drugs against influenza, obesity/diabetes, hepatitis C virus and other diseases (Schnell and Chou, 2008; Berardi et al., 2011; OuYang et al., 2013). Designed repeat proteins have the ability to bind their specific targets and provide drug candidates for future treatments (Stumpp et al., 2008; Abil et al., 2014). Structure of the helical assembly can contain one or more rows of stacked helices that form a solenoid, a helix of helices. Each type of the repeat – Ankyrin, ARM/HEAT, Pumilio homology domain (PUM-HD), leucine rich repeat (LRR), or

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tetratricopeptide (TPR) – exhibits unique properties, characteristic amino acid composition (Andrade et al., 2001; deWit et al., 2011; Blatch and Lassle, 1999; Sawyer et al., 2013), and groups of consensus sequences (Mosavi et al., 2002; Gaudet, 2008).

The structure of the α-helix organizes the protein backbone in a specific hydrogen bonding pattern (Pauling et al., 1951). Arrangements and energetics of interactions of α-helices, β-sheets, and loops have been extensively studied with model peptides (Chou et al., 1988, 1989, 1990a, 1990b) and proteins including 8α/8β barrels (Chou and Carlacci, 1991), α-helix bundles (Carlacci, 1990b, 1990c, 1991; Carlacci and Maggiora., 1991; Chou et al., 1992a, 1992b), leucine zippers (Chou, 1992), and globins (Gerritsen et al., 1985). Packing of secondary structure elements "knobs into holes" (Crick, 1953), complementarity of interacting surfaces (Chothia et al., 1981), hydrogen bonding and van der Waals interactions contribute to specificity and stability of protein molecules and energy of hydrophobic and electrostatic interactions (Scheraga et al., 1982; Schulz and Schirmer, 1982; Chou et al., 1983, 1984; Carlacci, 1990a, 1991). Formation of pathogenic β-sheet aggregates from α-helix prion proteins demonstrates polypeptide chain conformational transitions under various conditions (Zhou, 2011b; Zhou and Huang, 2013). The hydrophobic and hydrophilic environment of α-helices is one of the major factors influencing their structural properties (Chou et al., 1997). The distribution of amino acids at the helical surfaces of leucine zipper dimeric molecular complexes clearly shows clustering of hydrophobic residues at interface positions **a** and **d** and hydrophilic residues at the interface with solvent (Chou et al., 1990a, 1997, 2011; Zhou, 2011a). As an α-helix binds more ligands, hydrophobic patches expand so that adjacent edges become involved in helix–helix interactions. In membrane helices or helices surrounded by other secondary structure elements, all edges are hydrophobic since they are not exposed to polar solvent. Hydrophobic interactions determined by specific amino acid combinations are important structural determinants of these oligomers.

Amino acid combinations characteristic for each type of helix–helix interface and arrangement of α-helices in proteins show good correlation (Kurochkina, 2008; Kurochkina and Choekyi, 2011). Specific combinations at particular helical edges are important for the shape of the assembly as was previously shown for 8α/8β TIM-barrel proteins and 4-α-helix subunits of tobacco mosaic virus (Kurochkina, 2010). In the present work, we demonstrate that arrangement of amino acids at the helical edges and specific amino acid combinations of helix–helix interfaces can distinguish one type of helical assembly from another. Inner rows of ankyrin, ARM/HEAT, and PUM-HD repeats utilize edges $(i-1, i)$ and $(i+1, i+2)$ for the interaction of the given α-helix with preceding and following helices, respectively, whereas outer rows of these proteins and LRR repeats invert this pattern and utilize edges $(i-1, i)$ and $(i-3, i-2)$. The reason that this inversion of contacts leads to the change in handedness of the assembly can be explained by the geometry of the helical surface and mutual orientation of the helical edges. Each of the two different contact patterns corresponds to a unique helix arrangement. The new approach elaborated can be used to address mechanisms of action of protein molecules, prediction of specific protein–protein interactions, fold recognition, and design of drugs, nanostructures and nanomaterials.

2. Results

2.1. Solenoid structures and patterns of interactions

Each peptide group comprises two amino acids joined by a peptide bond. The surface of an α-helix is shaped by planes containing peptide groups of hydrogen-bonded residues. A helical edge that contains Cα atoms of the two consecutive amino acids together with all atoms located between α-carbons forms such a plane. An edge can be designated by two consecutive C_α atoms, for example, $(i, i+1)$ or $(i+1, i+2)$ (Fig. 1A). Edges and peptide planes are important for determining both the α-helix shape and recognition of binding surfaces by secondary structure elements. The helix–helix interface is formed by amino acids located mainly at the conserved core positions **a** and **d** and less conserved but more exposed positions **e** and **g** in leucine zipper nomenclature (Kohn et al., 1977). Each type of the repeats assembly has a repeat unit: a pair of α-helices and a β-hairpin (ankyrin), two (HEAT, TPR) or three (ARM) α-helices, or α-helix and β-strand (LRR) stacked so that they form one or two rows of α-helices (Fig. 1B and C). In the ankyrin repeat molecules, each inner row helix (A) forms an antiparallel interface with outer row helix (B) and two parallel interfaces, one with preceding (A′) and one with following (A″) helices. As a result, AB, AA′, and AA″ interfaces are observed in the inner row, and BB′ and BB″ interfaces in the outer row (Fig. 1C). A similar arrangement of helices is present in PUM and ARM/HEAT repeats but they differ in the number of repeats per helical turn, interhelical angles, and structure of the repeat unit. In ARM/HEAT repeats, B helices form an inner (concave) row whereas A helices form an outer (convex) row. In the LRR repeat unit, outer row helices wrap around an inner row β-sheet and a second row of helices (Fig. 1B). Although outer rows of ankyrin, ARM/HEAT, PUM, and LRR repeats have a similar organization (Fig. 1B and C), the direction of the assembly is opposite to that of inner rows. These two types of assemblies cannot be superimposed. The difference in the outline of each assembly can be clearly seen if positions **a** of the row helices of the two assembly types are shown in the same coordinate system (Fig. 1D). This coordinate system is selected so that the α-carbon of amino acid at position **a** is at the origin, the peptide group between residue at position **a** and residue at position **g** preceding **a** is in *XZ* plane, vector from C_α at position **g** to C_β at position **a** is parallel to the *X* axis, and the negative end of the *Y*-axis points toward the interacting helix (Kurochkina, 2008). Coordinates of each row of helices are transformed so that position **a** of the N-terminal helix interface with the following helix is at the origin, and peptide group of the residues at positions **g** and **a** is in *XZ* plane. All consecutive helices of the row will follow in the negative *Y* direction. We can see that inner and outer rows follow opposite *X* axis directions.

Assignment of positions **a**, **d**, **e**, and **g** to each helix–helix interface (Fig. 1E) reveals that contacts of the central helix with three surrounding helices follow a particular pattern that is repeated at each ankyrin unit. This pattern differs from the pattern of other helix–helix interfaces. For instance, parallel interfaces of the TIM-barrel proteins utilize edges $(i, i+1)$ and $(i+5, i+6)$ to contact the preceding and following helices (Kurochkina, 2010), whereas the inner rows of ankyrin repeats use $(i-1, i)$ and $(i+1, i+2)$.

This same pattern of contacts is observed at the helix–helix interfaces of the inner rows of ARM/HEAT and PUM-HD assemblies. However, in the outer rows of these proteins and LRR repeats, the pattern of contacts is inverted: edges $(i-1, i)$ and $(i-3, i-2)$ are involved in contacts of the central helix with the preceding and following helices. How does this inversion result in the change of the direction of the solenoid producing two types of assemblies that cannot be superimposed?

2.2. Pocket geometry and chirality

If we draw a plane perpendicular to the peptide group plane of the residues $(i-1, i)$, we can see that the edges $(i-3, i-2)$ and $(i+1, i+2)$ are mirror images of each other (Fig. 1A). Conserved feature of any α-helix is that angle of the edge $(i-3, i-2)$ with the peptide

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