Transcriptomics: Open Access
ISSN: 2329-8936
Appavu, Transcriptomics 2016, 4:1
http://dx.doi.org/10.4172/2329-8936.1000e116
Editorial
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Expanding the Loop Segments in β-hairpin Nonapeptides in Protein Folding and Biological Functions

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Editorial

Analysis of β-hairpins in proteins, have revealed several examples of antiparallel β-strands connected by short linking segments, which contain more than two residues [1-6].The design of synthetic peptide hairpins formed with central two residue turns has been facilitated by the ease with which specific types of β-turn structures can be generated in short peptides. Earlier work in this laboratory has addressed the question of expanding the central connecting loop in designed peptide β-hairpins. (Figure 1) schematically compares the two residue and three residue β-hairpins. Successful expansion of the loop region has been achieved using a centrally positioned ^{D}Pro-^{L}Pro-^{D}Ala segment. A detailed NMR study of the nonapeptide Boc-Leu-Phe-Val-^{D}Pro-^{L}Pro-^{D}Ala-Leu-Phe-Val-OMe revealed that registered antiparallel strands are formed in solution. The hairpin facilitating three residue turn requires the ^{D}Ala residue to adopt an α_L conformation (φ ~60°, ψ ~30°) [2-7]. When the residue at position (6) was replaced by ^{L}Ala, the nonapeptide yielded a two residue hairpin structure with the ^{D}Pro-^{L}Pro segment forming a type-II′ β-turn. The ^{L}Ala(6) residue is now incorporated into the C-terminus segment, with "slipped" strand registry. The significant conformational transitions were appeared replacing the ^{D}Ala(6) to Gly(6), and ^{L}Ala(6) in the protein secondary structure conformation. This conformation, referred to as a "slipped hairpin" structure, together with the three residue hairpin is illustrated in Figure 1. Inspection of the structures shown in Figure 1 suggests the two conformations are clearly distinguishable, if the aromatic ring orientations are considered. Thus, in addition to cross-strand nuclear over hauser effects (NOEs) and delineation of NH bonded groups, aromatic proton chemical shifts may prove to be a convenient diagnostic for the conformations present in this class of designed nonapeptides. The Editorial describes a systematic analysis of peptides in which the residue at position 6 is varied in the sequence Boc-Leu-Phe-Val-^{D}Pro-^{L}Pro-Yyy-Leu-Phe-Val-OMe. Studies on related peptides in which ^{L}Pro(5) is substituted by Aib and ^{L}Ala are also reported in this laboratory [5-7]. NOE effect clearly reveals the replacement of Xxx and Yyy positions L, and D Amino Acids yield a mixed population of three residue β-hairpins and two residue β-hairpins stabilization of Aromatic-Aromatic interactions.

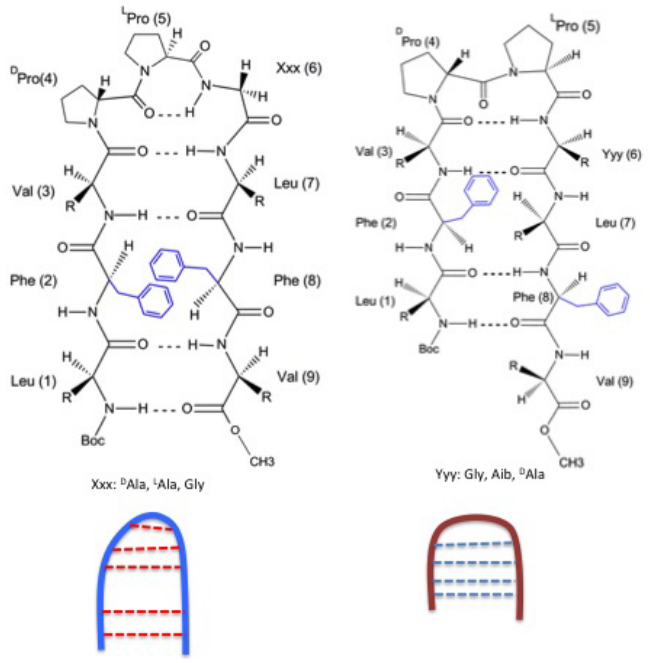

Figure 1: Schematic representation of the three residue *β*-hairpin (left), and two residue "slipped" *β*-hairpin structure (right) in nona peptide sequences. Note the difference in orientation of the phenylalanine (Phe) side chains in the two distinct conformations.

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Received January 28, 2016; **Accepted** February 18, 2016; **Published** February 23, 2016

Citation: Appavu R (2016) Expanding the Loop Segments in β-hairpin Nonapeptides in Protein Folding and Biological Functions. Transcriptomics 4: e116. doi:10.4172/2329-8936.1000e116