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Review Article
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Fundamental of Secondary Structures in Peptide Based Synthetic Nanovaccine Development

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Abstract

The peptides vaccines are composed of the twenty genetically coded amino acids generally exist as an ensemble of different conformational states in solution. The induction of folded conformations in short peptide vaccine sequences may be achieved by the incorporation of stereochemically constrained non-coded amino acids. The aim of this review briefly provides basic understanding of method of vaccine development.

Keywords: Peptide; Homologation; Immunotherapy

Introduction

A large body of work emanating from Appavu et al. and elsewhere has explored the utility of α, α-dialkylated amino acids as inducers of well folded conformations in small peptides [1,2]. α-Aminoisobutyric acid (Aib) has been the most widely used residue, with its helix forming propensity being first suggested on the basis conformational energy calculations [3,4]. Since the appearance of the first crystal structures of Aib containing peptides in the 1970's, a very large body of experimental work has firmly established the tendency of Aib residues to promote helical conformations [5-7]. The studies have reinforced the view that restricting conformational choices at specific residues in polypeptide chains may be a viable strategy for stabilizing well defined structures, even in short peptides [8]. The incorporation of Aib residues has permitted the crystallization and structure determination of synthetic helical peptides of length between 18-20 residues [5,9,10]. The β-turn, an internally hydrogen bonded structure involving two central residues, is a common structural feature in short peptides and is an important determinant of chain folding in proteins [7,11]. The proline residue, is the only coded amino acid in which rotation about the N-C^{α} bond (φ) is limited (φ~-60° ± 20° for ^{L}Pro) by the constraint of side chain backbone cyclization, as a consequences of pyrrolidine ring formation. Pro is often found at the i+1 position in β-turns. The enantiomer ^{D}Pro provides an opportunity to stabilize "mirror image" β-turn conformations. An early analysis of protein structures by Thornton and co-workers [12], subsequently expanded by other groups [13], has established the tendency of β-hairpins in proteins to contain type-I′ and II′ β-turn structures, both of which are energetically unfavourable for the chiral L-aminoacids. Necessarily, the achiral Gly residue is often found in these turn segments. The design of peptide β-hairpins has been facilitated by the recognition that the use of the ^{D}Pro residue at the i+1 position, strongly favors formation of prime turns (type-II′ and type-I′). Since, the first demonstration of this design principle in the mid 1990's [6,7], a large number of studies have appeared employing ^{D}Pro-Xxx segments as nucleators of β-hairpin conformations [14]. The area of peptide design has been dramatically influenced in recent years, by therecognition that backbone expanded homologated amino acid residues (β, γ residues) can be used to generate unprecedented folded conformations in short peptides [5,6]. Early successes in these area were achieved using chiral β-residues obtained from the α-aminoacids by Arndt-Eistert homologation and by the use of cyclic residues in which torsional freedom about the C^{α}-C^{β} (θ) bond was restricted. The exploding literature on β and γ-peptides has been extensively reviewed [15]. More recent work has explored the possibility of using β, and γ residues containing gem-dialkyl substituents, which should in principle, restrict conformational freedom about the single bonds, flanking the tetra substituted "C" atom. This principle has been most effectively demonstrated in the case of the β, β-disubstituted γ aminoacid residue, gabapentin (1-aminomethylcyclohexaneacetic acid) [1].The brief view of this review pave the way of conformational properties of short peptides containing Aib, ^{D}Pro-Xxx segments, D peptide and geminally disubstituted β-aminoacids are significant role in vaccine adjuvant development.

Conformation Directing Effects of Aib Residues

The reduction in stereochemically accessible conformational space upon alkylation at the C^{α} atom was originally demonstrated by Ramachandran and co-workers in their seminal paper, which appeared nearly fifty years ago. A comparison of the Ramachandran maps for Gly and Ala residues reveals the dramatic reduction in the extent of conformational space that is free of unfavorable van der Waals contacts. Clearly, replacement of a hydrogen atom by a methyl group at the C^{α} position limits the range of conformational possibilities. Addition of a second alkyl group at the C^{α} atom, as in the case of Aib, must necessarily further diminish the range of sterically allowed conformations. Ramachandran and Chandrasekaran (1972) recognized that the allowed regions of φ, ψ space for the Aib residue, can be readily estimated by considering only the regions of overlap of the Ramachandran maps for ^{L}Ala and ^{D}Ala residues. (Figure 1a) illustrates, the regions of overlap, which suggested that Aib residues are largely constrained to adopt conformations lying in the right (α_R) and left (α_L) handed helical regions of φ, ψ space. Conformational energy calculations confirmed that helical conformations are indeed most favorable for the Aib residue [6]. The first crystal structures of acyclic Aib containing peptides determined in the late 1970's, firmly established the ability of Aib residues to promote helical folding even in short peptides [16]. Subsequent crystal structure determination of a very large number of Aib containing peptides confirmed, the overwhelming

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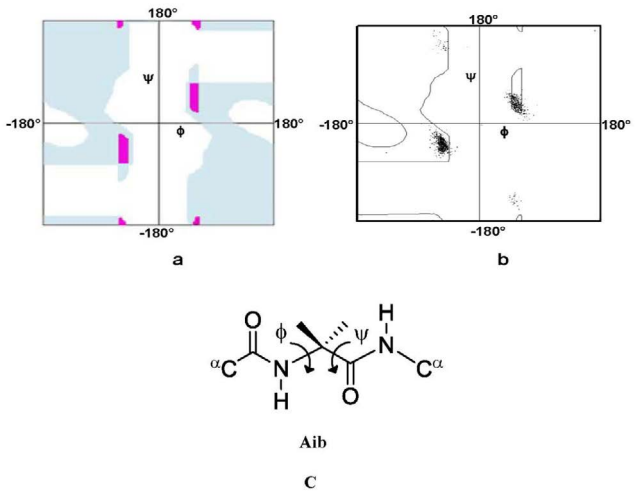

Figure 1: (a) Overlap of the Ramachandran map for amino acids LAla and DAla. The overlap region which is shaded is allowed for Aib. (b) Cluster plot for crystallographically determined conformations for 1430 Aib residues. (c) Definition of torsion angles for the Aib residue [8].

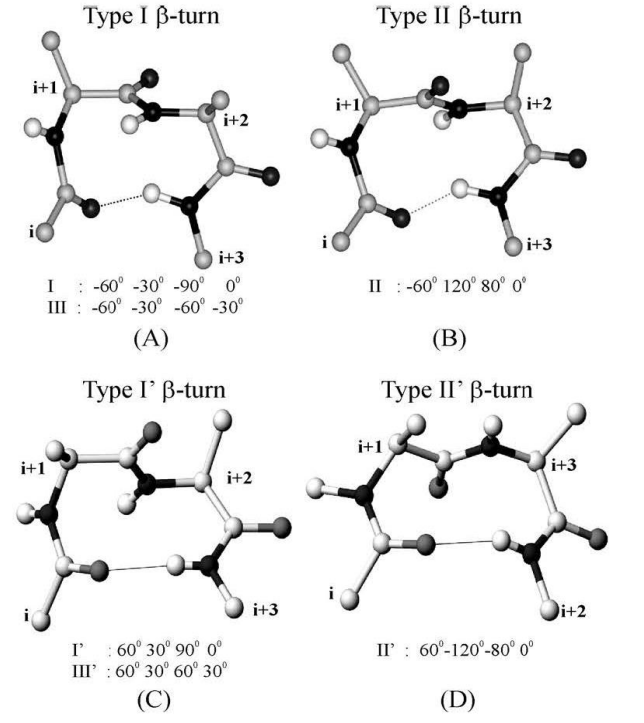

Figure 2: Classification of β-turns. (a) Type-I β-turn. (b) Type-II β-turn. (c) Type-I′ β-turn. (d) Type-II′ β-turn [11].

preference for conformations lying in the helical regions of φ, ψ space [17,18]. (Figure 1b) shows a cluster plot of experimentally determined φ, ψ values for Aib residues. Since, the Aib residue is achiral, both right and left handed helical conformations are energetically favourable, with the result that the Aib residues favour φ, ψ values of ± 60° ± 30°, ± 30° ± 30°. Consequently, Aib residues can occupy both i+1 and i+2 positions in the type-I/III β-turns or type-I′/III′ β-turns [11], and the i+2 position in type-II/II′ β-turns (For a definition of the torsion angles at the i+1 and i+2 residues in β-turns (Figure 2). Continuous helical structures are generated by successive type-I/III or I′/III′ β-turns. It may be noted that for the purposes of this discussion a distinction is not made between type-I and III β-turns, since they only differ slightly in φ, ψ value at the i+2 position. When Aib residues are inserted as guests into all L-amino acid sequences, right handed helical structures (φ~60°, ψ~30°) are favored. In principle, insertion of an Aib-^{D}Xxx segment into a host all "L" sequence can nucleate type-I′ β-turns, which in turn may facilitate β-hairpin formation, with registered interstrand hydrogen bonds stabilizing the folded conformations [2]. Figure 3 illustrates these situations. The above discussion suggests that insertion of Aib-Xxx segments into the centre of a host, all L-amino acid residue sequence can result in dramatically different situations, depending upon the nature of the Xxx residue. If the Xxx residue, is an "L" residue, the central segment is likely to favour type-I/III β-turn conformations, with the Aib residue adopting φ, ψ values in the right handed helical (α_R) region of φ, ψ space. In this case, a centrally nucleated 3_{10} helical turn serves to propogate a right handed helical structure in the peptide. If Xxx, is a D-residue type I′/III′ turns are favoured, which then facilitate hairpin formation. In this case, both the Aib and Xxx residues adopt φ, ψ values, in the *left handed* helical (α_L) region of φ, ψ space. The octapeptides, Boc-Leu-Phe-Val-Aib-^{D}Ala-Leu-Phe-Val-OMe, and Boc-Leu-Val-Val-Aib-^{D}Pro-Leu-Val-Val-OMeprovide examples, where hairpin formation is successfully stabilized by centrally positioned Aib-Xxx segments [1,4-7]. Figure 3 schematically illustrates the relationship between β-turn type and the nature of the secondary structure that may be facilitated by a centrally positioned turn segment. However, examples of D-residues adopting right handed helical (α_R) conformations, when placed in host L-amino acid sequences have also been reported in peptide crystal structures. For example, the peptides Boc-Leu-Aib-Val-Ala-Leu-Aib-Val-^{D}Ala-^{D}Leu-Aib-OMe, and Boc-Leu-Aib-Val-Ala-Leu-Aib-Val-^{D}Ala-^{D}Leu-Aib-Leu-Aib-Val-OMe adopt continuous right handed helical conformations, with the D-residues adopting torsion angles φ~-50°, ψ~-60°. It should be noted that α_L conformations are

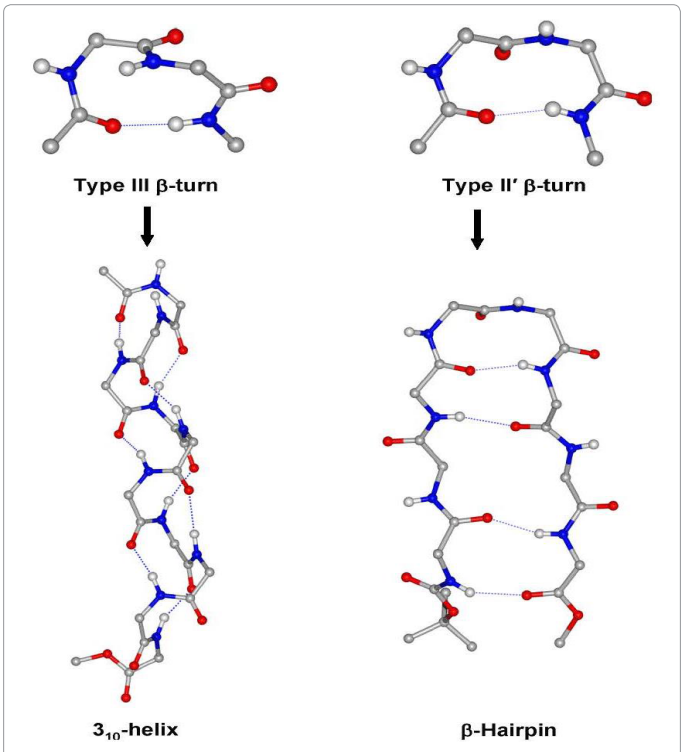

Figure 3: Isolated single type-III and type-II′ β-turns facilitate peptide folding into a 310-helix and a β-hairpin [12].

generally favored for D-residues, but the difference in the energy is relatively small, 1kcalmol^{-} [14]. These observations suggest that Aib-^{D}Xxx segments, may provide a means for studying conformational switching between helical and hairpin structures in designed peptides [13].

Conclusions

The current scenario of secondary structure based peptide vaccine development is important for immunotherapy for both infectious and non-infectious diseases. The torsion angle of vaccines design enhances the antibody production to fight against infections. In the future, the described peptide vaccines are highly potential for HPV Vaccine development technology.

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