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β-Helix core packing within the triple-stranded oligomerization domain of the P22 tailspike

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Abstract

A right-handed parallel β-helix of 400 residues in 13 tightly packed coils is a major motif of the chains forming the trimeric P22 tailspike adhesin. The β-helix domains of three identical subunits are side-by-side in the trimer and make predominantly hydrophilic inter-subunit contacts (Steinbacher S et al., 1994, *Science 265*:383–386). After the 13th coil the three individual β-helices terminate and the chains wrap around each other to form three interdigitated β-sheets organized into the walls of a triangular prism. The β-strands then separate and form antiparallel β-sheets, but still defining a triangular prism in which each side is a β-sheet from a different subunit (Seckler R, 1998, *J Struct Biol 122*:216–222). The subunit interfaces are buried in the triangular core of the prism, which is densely packed with hydrophobic side chains from the three β-sheets. Examination of this structure reveals that its packed core maintains the same pattern of interior packing found in the left-handed β-helix, a single-chain structure. This packing is maintained in both the interdigitated parallel region of the prism and the following antiparallel sheet section. This oligomerization motif for the tailspike β-helices presumably contributes to the very high thermal and detergent stability that is a property of the native tailspike adhesin.

Keywords: β-helix; β-sheet; oligomerization; prism; stability; tailspike

The interfaces between the subunits of a large number of oligomeric proteins include significant numbers of salt bridges and hydrogen bonds and generally differ from the hydrophobic cores of the individual subunits (Miller, 1989; Janin & Chothia, 1990). In contrast, the α-helical fibrous proteins, including the collagens and coiled coils, have extended interfaces between their polypeptide chains that bury hydrophobic residues and are critical for their stability (Branden & Tooze, 1998). Another type of subunit–subunit interaction is the mixed β-sheet with at least one strand from two or more polypeptide chains. Examples include the arc repressor of phage P22 (Breg et al., 1990), actin-binding gelation factor (McCoy et al., 1999), and the serum protein transthyretin (Hamilton et al., 1993). Interchain β-strand interactions are also found in the assembly complex formed between the FimH adhesin of *Escherichia coli* and the exposed hydrophobic core of the periplasmic FimC chaperone (Choudhury et al., 1999). Recent structural models of protein assembly and aggregation reactions incorporate repetitive interchain β-sheet formation, or 3D-domain swapping (Schlunegger et al., 1997), as the mechanism driving oligomerization. These models include donor strand complementation in pilin assembly, the loop-sheet polymerization of α1-antitrypsin and other serpins (Lomas, 1996), and fibrillogenesis of transthyretin and other amyloidogenic proteins (Blake & Serpell, 1996).

The parallel β-helix fold

A distinctive β-sheet motif is the parallel β-helix fold first reported by Yoder et al. (1993) for pectate lyase C, a plant pathogen virulence factor. In this fold, β-strands pack and coil processively like a coiled spring. The buried hydrophobic cores of β-helix domains are extended, rather than globular, and are characterized by distinctive stacks of side chains that occur at equivalent positions in successive rungs, or turns, of the β-helix (Raetz & Roderick, 1995; Yoder & Jurnak, 1995; Pickersgill et al., 1998a). Cupped stacking of buried aliphatic and aromatic side chains is observed, as are stacks of buried polar residues—most notably the six-residue asparagine ladder in pectate lyase C (Yoder et al., 1993).

More recent crystal structures have revealed additional right-handed β-helices as well as left-handed parallel β-helix folds. Right-handed β-helix (RβH) domains are represented by virulence factors, adhesins, and enzymes from diverse prokaryotes and some

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Abbreviations: LβH, left-handed β-helix; RβH, right-handed β-helix; THDP, tetrahydrodipicolinate N-succinyltransferase.

eukaryotes. Examples include tailspike of *Salmonella typhimurium* phage P22 (Steinbacher et al., 1994), pectin lyase A of the plant pathogen *Aspergillus niger* (Mayans et al., 1997), and virulence factor P.69 pertactin of the whooping cough pathogen *Bordetella pertussis* (Emsley et al., 1996), chondroitinase B of *Flavobacterium heparinium* (Huang et al., 1999,) and polygalacturonase of *Erwinia carotovora* (Pickersgill et al., 1998b). Left-handed β-helix (LβH) domains have been found in proteins of the hexapeptide repeat family such as THDP succinyltransferase of *Mycobacterium bovis* (Beaman et al., 1997), UDP-*N*-acetylglucosamine acyltransferase of *E. coli* (Raetz & Roderick, 1995), and acyltransferase from *Pseudomonas aeruginosa* (Beaman et al., 1998). A carbonic anhydrase from the archaeon *Methanosarcina thermophila* provides another example of a left-handed parallel β-helix (Kisker et al., 1996).

All LβH proteins crystallized to date are trimers. In contrast, RβH domains have been found in monomeric proteins, with one exception, the P22 tailspike protein. The tailspike protein is a homotrimer of 666-residue subunits (Fig. 1B) (Sauer et al., 1982). The native tailspike protein is extremely stable: it is trypsin-resistant, SDS-resistant, and has a melting temperature of 88 °C (Sargent et al., 1988; Sturtevant et al., 1989; Thomas et al., 1990; Chen & King, 1991; Mitraki et al., 1991). Residues 143–540 in each subunit form a RβH domain of 13 coils and 3 extended loops. Each subunit binds O-antigen, a component of the host lipopolysaccharide, in a groove on the surface of each RβH (Steinbacher et al., 1996). At the C-terminal end of the RβH domain, the tailspike subunits wrap around each other and form an intertwined β-sheet domain (Fig. 1B,D) (Steinbacher et al., 1994), which Seckler (1998) has termed a triple β-helix. The chains in the intertwined region then separate again and form three single β-sheets (residues 541–619) extending beyond the intertwined region toward the C-terminus (Fig. 1A,B). A final β-sheet forms the C-terminal caudal fin domain (residues 620–666) of each subunit.

The C-terminal triple β-helix and β-sheet structure will be referred to here as a triangular β-sheet prism. It differs from the β-prism motif (Shimizu & Morikawa, 1996; Wright, 1997; Bourne et al., 1999) defined as having the beta strands parallel to the long axis of the resulting domain.

A distinctive feature of the tailspike folding pathway (Fig. 2) is the presence of a partially folded trimeric intermediate, termed the protrimer, in which the chains are associated but not fully folded (Goldenberg & King, 1982). The β-helix domains of the subunits appear to form in a partially folded single-chain intermediate [I] (Fig. 2) prior to subunit association (Brunschier et al., 1993; Danner & Seckler, 1993). The protrimer presumably represents the intermediate in which the interdigitated prism forms. The single-chain intermediate [I] is the critical intermediate at the junction between the productive folding pathway and the nonproductive pathway to the aggregated inclusion body state (Fig. 2, bottom). A partially melted single-chain conformation, denoted [I*] in Figure 2, is believed to be the inclusion body precursor that self-associates into soluble aggregation intermediates (Speed et al., 1995). These species may be stabilized through interchain β-sheet contacts involving β-strands that are normally buried and protected within the subunit β-helix domains. Temperature-sensitive folding (tsf) mutations, which further destabilize the already thermolabile intermediate [I], are restricted to the parallel β-helix domain (Haase-Pettingell & King, 1988, 1997).

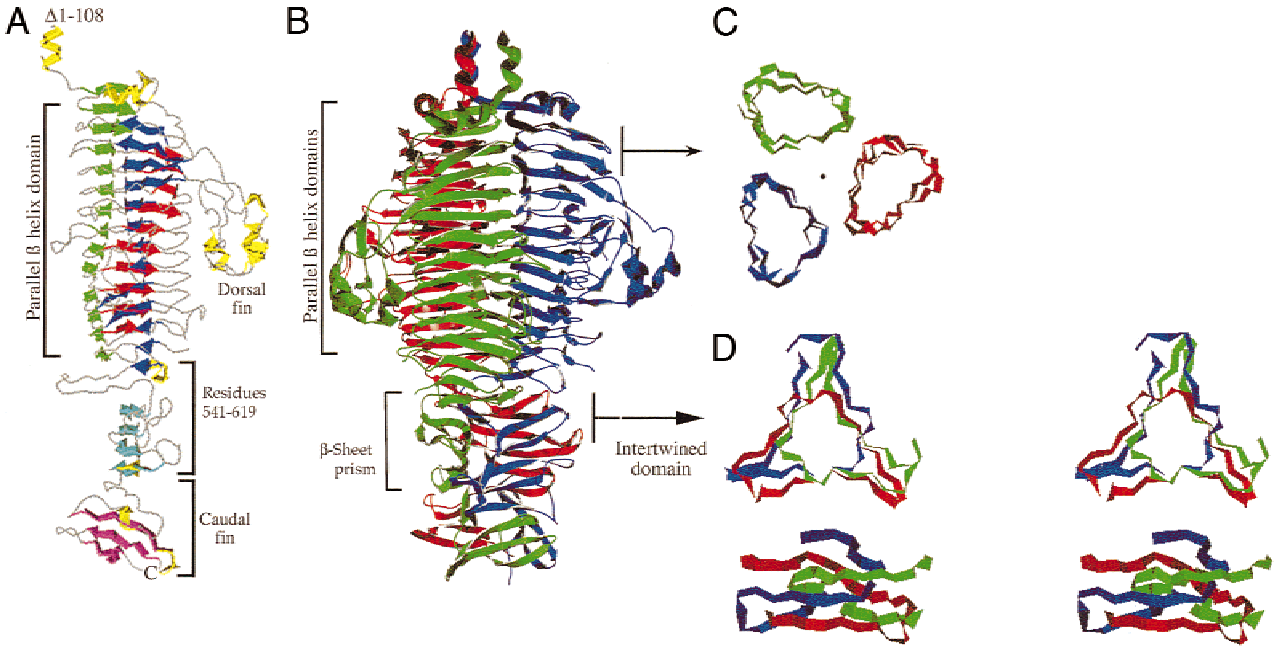

Fig. 1. Ribbon diagram of the P22 tailspike protein at 2 Å resolution (residues 109–666) (Steinbacher et al., 1994). **A:** Tailspike subunit with the N-terminus at the top and the C-terminus at the bottom. Coiled yellow arrows indicate α-helices, and the other colored arrows show the locations of five β-sheets. **B:** Native tailspike trimer in same orientation as subunit in **A**. The subunits are colored separately. **C:** Axial view of residues 143–197 showing the subunit β-helix domains. **D:** Stereo views of the intertwined domain (residues 538–564). Top, axial view; bottom, side view. Coordinates from the Protein Data Bank (1tsp) (Abola et al., 1987).

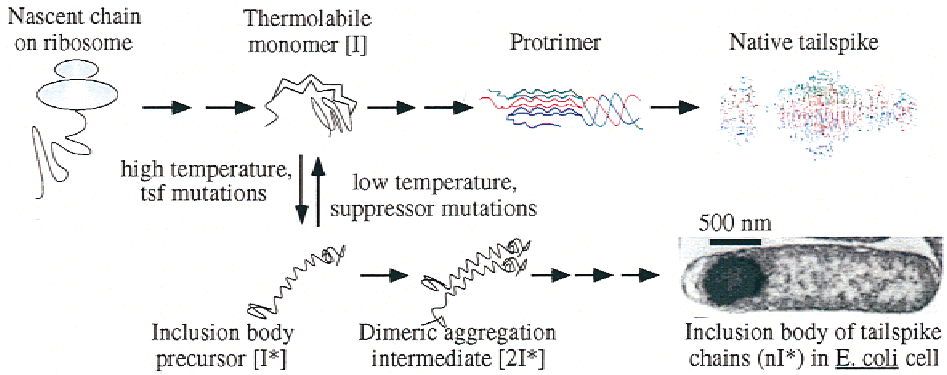

Fig. 2. Competing tailspike folding and inclusion body pathways. A thermolabile single-chain intermediate [I] associates into the protrimer in which the chains are associated but not fully folded. The intertwined oligomerization domain presumably forms in this species. The protrimer is stabilized by transient interchain disulfide bonds, but these are reduced in the formation of the mature thermostable trimer (Robinson & King, 1997). As the temperature of folding increases, [I] fails to reach the protrimer stage and transforms to the misfolded single-chain species denoted [I*], which is the inclusion body precursor. This off-pathway conformation predominates at high temperature or in the presence of tsf mutations, which destabilize the β-helix in the single-chain [I] intermediate. Self-association of [I*] into soluble multimers leads ultimately to the formation of insoluble aggregates or inclusion bodies. Reproduced from Betts and King (1999) with permission.

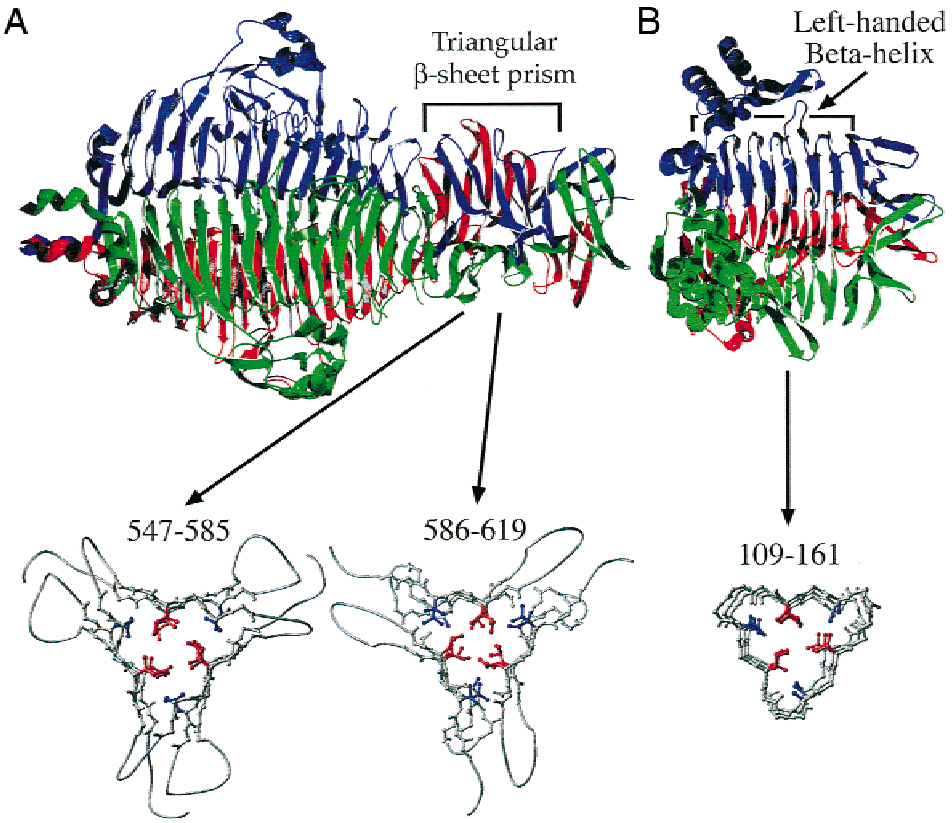

Fig. 3. Comparison of the tailspike three-stranded triangular β-prism and a left-handed β-helix (LβH) domain from THDP succinyltransferase (Beaman et al., 1997). **A:** Ribbon diagram of residues 109–666 of the P22 tailspike trimer with the three amino-termini at left and three carboxyl-termini at right. The two cross sections are through the triangular β-sheet prism domain. The central side-chain stacks are in red and the corner stacks are in blue. **B:** Ribbon diagram of THDP succinyltransferase trimer of LβH subunits (residues 102–233). The amino-termini of the three LβH domains are to the left. A cross section through one of the subunits is shown below. The central side-chain stacks are red and the corner stacks are blue. The images were prepared with Swiss-PDB Viewer (Guex & Peitsch, 1997).

In contrast to [I] and [I*], the protrimer intermediate is not prone to misfolding and self-association reactions, at least not under physiological conditions (Brunschier et al., 1993; Betts & King, 1998). Some of the stability of the protrimer may derive from its transient interchain disulfide bonds, which are reduced in the transition to the native tailspike (Robinson & King, 1997). The conversion of the protrimer to the native trimer conformation through the wrapping around of the chains confers higher stability to the mature tailspike trimer despite the absence of disulfide bonds in this native state. The interdigitated β-sheet prism would thus appear to be a key component of the stability of the mature tailspike trimer.

Hydrophobic cores of the left-handed β-helix

In the course of exploring the contacts in the three-chain interdigitated region of the tailspike protein, we observed that the pattern of secondary structure and hydrophobic core packing was identical to that of a single-chain LβH domain. A side-by-side comparison of the tailspike triangular β-sheet prism and the LβH of THDP succinyltransferase is shown in Figure 3.

In both LβH and RβH domains, the polypeptide backbone coils alternate between β-strands and turns, while the interior side chains form stacks of hydrophobic residues packing the protein core. The β-strands run perpendicular to the long axis of the molecule. Occasionally, the coils are interrupted by extended loops in the turns between the β-strands. In LβH proteins, each coil forms an almost perfect equilateral triangle made up of three tandem repeats of a six residue motif: two residues in a β-strand followed by four residues in a left-handed 120° turn (Fig. 3B, bottom). In the hydrophobic core, there are central stacks of predominantly bulky hydrophobic residues (I,V) and corner stacks of generally smaller residues (A, T). The central stack side chains are shown in red in Figures 3 and 4, and the corner stack side chains are shown in blue.

Unlike the repetitive structure and sequence of LβH domains, RβH domains exhibit more variety (Jenkins et al., 1998). Each coil of a RβH domain traces the rough outline of a kidney bean and includes 3–4 β-strands. Two of the β-strands form a β-sandwich. Currently far more common, the three-stranded coils have an ideal length of 22 residues (Heffron et al., 1998). Both three- and four-stranded RβH coils show limited sequence conservation, even when comparing coil sequences from the same protein.

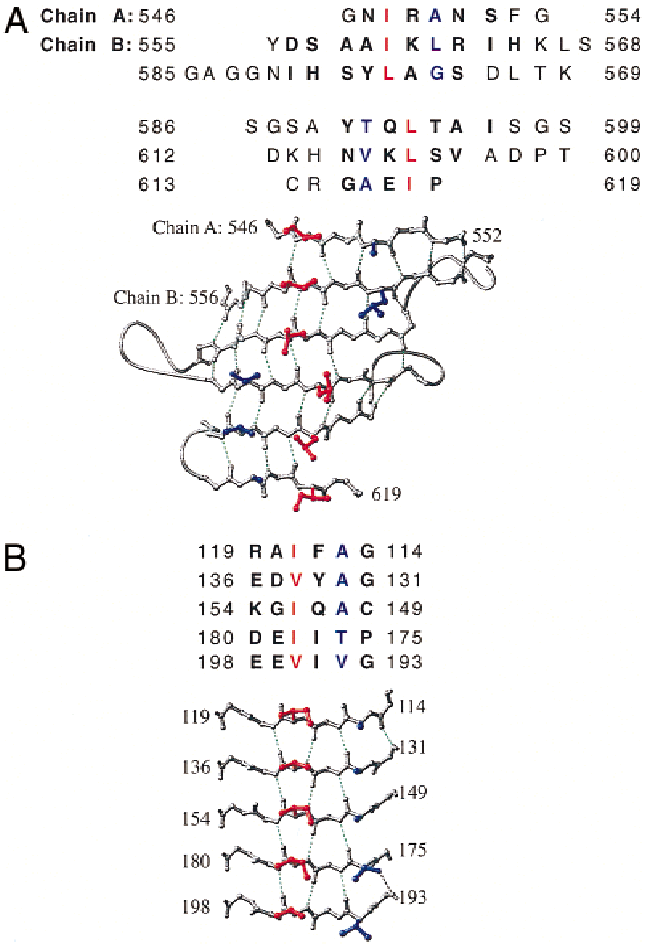

Fig. 4. Structure-based sequence alignments of β-sheet elements within the tailspike triangular β-sheet prism (**A**) and the LβH of THDP succinyltransferase (**B**). The residues in bold are involved in main-chain hydrogen bonds (green dashed lines). The central side-chain stacks are red and the corner stacks are blue. **A:** The backbones of two tailspike polypeptide chains are shown (residues 547 to 552 of Chain A and residues 556 to 619 of Chain B). Residues I548, I560, and L577 form one central stack and L592, L606, and I618 form a second central stack. Note that the second central stack is offset relative the first. This shift causes the small-residue stack to switch positions from right of the central stack in the diagram (A550, L562, and G574) to left of the central stack (T591, V608, and A616). **B:** Stack of five hexapeptide repeats from one side of a THDP succinyltransferase subunit. Color coding as above. The images were prepared with Swiss-PDB Viewer (Guex & Peitsch, 1997).

Identical hydrophobic cores of the tailspike β-helix multichain domain

Residues 541–619 of the three tailspike chains interact to form a triangular prism with a complex β-sheet fold. Axial views of two contiguous stacks of three such triangles are shown side-by-side in Figure 3A (bottom). This core packing in the interdigitated region is propagated into the β-sheet prism region formed by the three C-terminal antiparallel β-sheets. The β-strands on each side of the β-prism hydrogen bond to the β-strand of the triangle above and below them in the stack. Thus, in this region each side of the triangular prism is a seven-stranded β-sheet. The hydrogen bonding pattern of strands 2–7 of this mixed β-sheet are shown in Figure 4A. The first two β-strands of each sheet are parallel and come from two different subunits. Strands 3–7 are from the same subunit and are oriented in an antiparallel fashion. The presence of a mixed parallel/antiparallel β-sheet is in contrast to the typical LβH domain, in which the β-sheets are all parallel (Fig. 4B). However, the positioning of β-sheets in an equilateral triangle is identical.

The hydrophobic core of the triangular prism is characterized by extensive subunit–subunit contacts in the triangular space between the polypeptide backbones. The central core of the structure is filled by three side-chain stacks of Leu and Ile (red side chains in Figs. 3A, 4A). The three corners of the triangle are filled in by mixed stacks of Gly, Ala, Val, and Leu (blue side chains). Residues participating in the core stacks and the corner stacks are located two residues apart in each β-strand. As the tailspike polypeptide backbone threads through the prism structure, loops and turns of varying length result in irregular spacing of stacked side chains in

the amino acid sequence. The combination of variable loop and turn lengths and the intertwined structure would clearly make predicting a triangular β-sheet prism from sequence information alone highly problematic.

The triangular β-sheet prism as a motif for protein oligomerization and stabilization

Pickersgill et al. (1998a) have argued that the widely distributed RβH domains evolved from a common ancestor. It seems reasonable that the intertwined tailspike prism may have evolved by mutations that induced three-dimensional domain swapping, or strand-swapping, between ancestral β-helix monomers. In this scenario, the tailspike β-sheet prism represents an auxiliary oligomerization and stabilization domain.

Built on a hydrophobic core previously only seen in single-chain structures, the ability of this domain to bring together chains in a novel manner could be exploited as an oligomerization domain. A pathological expression of oligomerization through β-strand interactions are amyloid fibrils. Lazo and Downing (1998) recently proposed that the RβH fold (as seen in the main body of the tailspike protein) might serve as a structural motif for amyloid protofibrils. The β-sheet prism provides a natural model for incorporating multiple chains into a highly stable β-sheet structure.

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