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Minireview

Common structural motifs in small proteins and domains

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Abstract The high frequency of occurrence of the definite folding units in unrelated proteins and the fact that many small proteins are merely composed of the folding units indicate that these units can fold into unique structures per se and can be nuclei or 'ready building blocks' in protein folding.

Key words: Common fold; Protein folding; Structure comparison

1. Introduction

The information obtained by comparative analysis of the known protein structures is of particular value in understanding their architecture and the principles that govern the polypeptide chain folding. Structural comparisons of unrelated proteins are most important since the structural similarity between them suggests that some physical principles, rather than the evolutionary divergence or functional convergence of proteins, are the basis of the similarity. This paper demonstrates different levels of structural similarities between small proteins and domains. The structural role of the commonly occurring folding units is emphasized.

In globular proteins, the polypeptide chain is multiply folded upon itself, and elements of secondary structure that are close together along the sequence have a strong tendency to be in close contact in the three-dimensional structure [1]. Very often α-helices and/or β-strands adjacent along the chain form a few well-defined types of super-secondary structures or folding units. Some of them, such as β-α-β-α-β- and β-α-β-units [2,3], abcd-units [4], α-α-corners [5], β-β-corners [6], 3β-corners [7] and a few complex super-secondary structures involving triple-strand β-sheets [8], are of particular value in protein folding and prediction since they have a unique handedness (see Fig. 1). This appears to be an intrinsic property of the polypeptide chain which does not depend on the sequence. Another important feature of these folding units is that representatives of each given type have a unique overall fold independent of whether they occur in related or unrelated proteins. The high frequency of occurrence of the folding units in different proteins may be a result of relative stability of such folds. On the other hand, these folding units are composed of secondary structure elements adjacent along the polypeptide chain, which can associate rapidly to form compact folds.

2. Description of the recurring structural motifs

Fig. 1 represents structural motifs having a unique handedness which occur frequently within small proteins and domains. The upper row shows variants of the abcd-unit which differ from one another in the conformation of region c that can be β-structural, α-helical or irregular. Each variant of the abcd-unit can have the opposite direction of the polypeptide chain as compared with that shown in Fig. 1. There are also some more complex variants of the abcd-unit [4,8,9]. The variant of the abcd-unit having the α-helical conformation of segment c was observed to occur frequently within $\alpha + \beta$ folds and called the single split $\beta\alpha\beta$ motif [10]. Despite the differences, all the abcd-units have a common overall fold of the polypeptide chain. Very often two α-helices adjacent along the sequence form a unique structure called the α-α-corner. Examples of these structures were initially found in two protein families, 'E-F-hands' in the calcium-binding proteins [11] and 'helix-turn-helix' motifs in the DNA-binding proteins (for a review, see [12]). It was shown later that α-α-corners are widespread in unrelated proteins and occur practically always in one form independent of the length and conformation of the interhelical connection [5]. This form of the α-α-corner was initially defined as right-handed since the two-dimensional swirl of the polypeptide chain was right-turned (it is shown by an arrow in Fig. 1). In three dimensions, the polypeptide chain of the commonly occurring α-α-corner forms nearly a turn of a left-handed superhelix. β-β-hairpins can be right- and left-turned depending on whether the second β-strand runs on the right or left relative to the first one, when viewed from the same side. Similarly, triple-strand β-sheets having an up-and-down topology can exist in two forms, as S-like and Z-like β-sheets. It is of interest that one form of these structures is selected if they are folded into more complex three-dimensional structures themselves or included into super-secondary structures of higher order. If a β-β-hairpin forms a strongly twisted and coiled structure or folds into a β-β-corner, it is practically always right-turned, when viewed from the concave side [6]. Commonly occurring β-β-corners are right-handed, i.e. the strands, when passing from one layer to the other, rotate in the right-handed direction about an imaginary axis. All the 3β-corners observed in proteins are right-handed and can be considered as formed by Z-like β-sheets when viewed from the concave sides [7,8]. The super-secondary structures shown in the bottom row of Fig. 1 involve S-like β-sheets when viewed from inside [8]. These structures can be represented as right-handed β-S-β-, β-S-α-and α-S-α-superhelices if the S-like β-sheet is replaced by one imaginary strand in each case.

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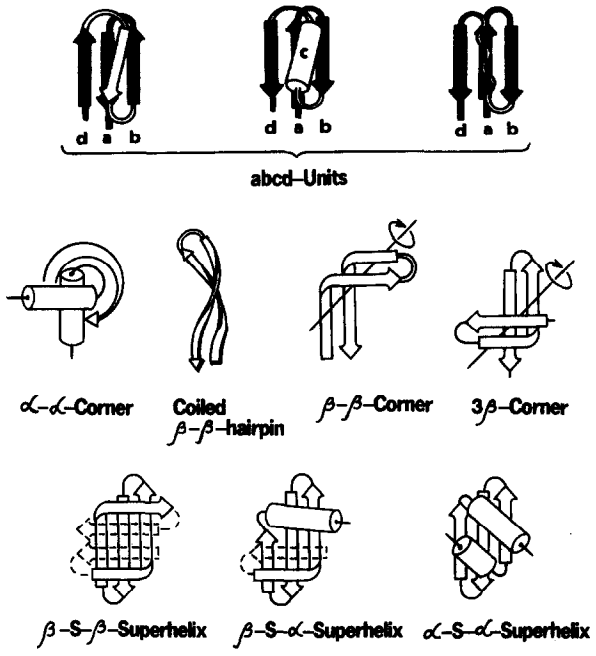

Fig. 1. Schematic representation of the commonly occurring folding units in small proteins and domains. β-strands are shown as arrows and α-helices as cylinders.

3. Small proteins and domains containing abcd-units

Small protein structures containing abcd-units are presented in Fig. 2. For a better comparison, the structures are arranged in a similar orientation, and strands a, b and d of the abcd-units are labelled. As seen, similarity between these proteins and domains is not limited by the presence of the commonly occurring abcd-unit. Some of them have larger common folds. For example, the overall folds of Kazal type inhibitors and ferredoxin are very similar, except for the polypeptide chain direction and conformations of segments joined to strand a. The protein structures shown in the upper row contain abcd-units having regions c in irregular conformations. The abcd-units of the second row have regions c in extended conformations and those of the third row have regions c in α-helical conformations. There are two abcd-units in hevein and WGA domains. One is labelled in the figure and the other is composed of strands b and a shared with the first abcd-unit, an α-helix in region c and the C-terminal strand. The protein structures represented in the fourth row can be considered as complex variants of the abcd-unit. Protein G, ubiquitin and heterocyst ferredoxin have quite similar overall folds except for structures of loop cd and the region that follows strand d. They may also be considered as proteins containing complex or modified abcd-units in which there is an additional β-strand between strands a and d.

In three upper rows, the molecules and domains are situated in such a way that each structure located on the right can be obtained by a stepwise addition of the corresponding structural segments to the abcd-unit shown on the left. Examples of such an analysis have been described earlier [4,5,7,9]. It looks likely that the abcd-unit is a core of each structure around which the remainder of the molecule or domain is folded. Some proteins and domains are merely composed of the abcd-unit. All this taken together suggests that the abcd-unit represents a stable kind of fold. The high frequency of occurrence of the abcd-units in unrelated proteins also supports this idea. Apparently, the abcd-unit can adopt its unique structure independently and relatively rapidly at a first step of protein folding. The remaining part of a protein molecule appears to fold around it.

4. Structural motifs in small proteins and domains with orthogonal packings of α-helices

The α-α-corner is one of the main 'building blocks' in small proteins and domains with orthogonal packings of α-helices (see Fig. 3). There are also more complex common folds in these proteins. Each of them can be represented as a combination of α-α-corners and α-α-hairpins and can be obtained by a stepwise addition of α-helices to the α-α-corner [5]. Levels of structural similarity between proteins of this class can be easily observed in Fig. 3. Monomers of some small proteins and some small domains are practically composed of the α-α-corner. The monomer structure of the DNA-binding domain of the transcription factor Max [57] can be considered as a distorted α-α-corner. The structures of the Arc repressor monomer [58] and the GAL-4 DNA-binding domain [59–60] consist of α-α-corners and small 'tails'. The met repressor monomer has a similar structure with longer 'tails' [61]. It is of interest that both the E3/E1p-binding domain and its synthetic analog have the same structure [62] which can be represented as a left-handed corner-corner superhelix similar to that of papain, G-peptidase and endochitinase (Fig. 3). The structured region of the binding domain, comprising 33 residues, represents an exceptionally short amino acid sequence with defined tertiary structure that has no disulphide bond, ligand or cofactor to stabilize the fold [62]. All these data suggest that the sequence coding for the α-α-corner can fold into the unique structure itself and the α-α-corner can be a nucleus in folding of larger proteins. This is also supported by the fact that α-α-corners have a definite sequence pattern of key hydrophobic, hydrophilic and glycine residues, irrespective of whether they occur in homologous or non-homologous proteins [5,9].

5. Small proteins and domains consisting of β-β-hairpins and β-β-corners

The upper row in Fig. 4 shows examples of protein structures composed of two β-β-hairpins. Structural similarity between the growth factors has been observed earlier [73,74]. The analysis described here highlights some details of these structures. An important feature of these proteins is that they contain one (TNF-R55 domain, NGF and TGF-β2) or two (PDGF-BB) strongly twisted and coiled β-β-hairpins. These β-β-hairpins are right-turned, when viewed from the concave sides. The structure of the N-terminal half of NGF can be considered as a right-handed β-β-corner with a long loop. The C-terminal coiled β-β-hairpin is packed into a concavity formed by this β-β-corner. The N-terminal β-β-hairpin of TGF-β2 is moderately twisted and coiled and also right-turned, when viewed from the concave side. It is possible to suggest that the N- and C-terminal halves of these proteins are folded into unique structures independent of each other, and their association results in the formation of final structures. The structure of FKBP can be represented as two distorted β-β-corners connected by an

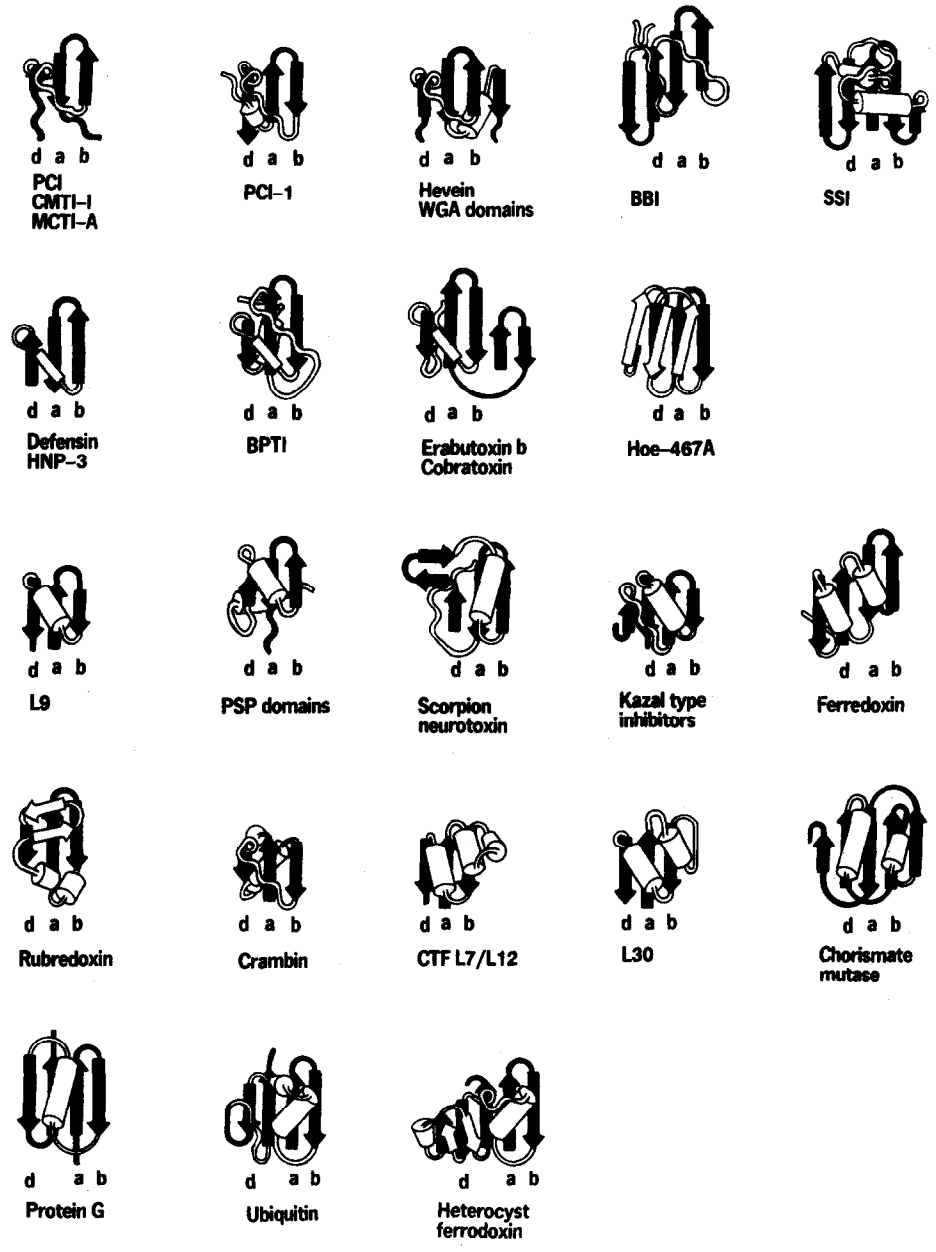

Fig. 2. Schematic representation of small proteins and domains containing abcd-units. β-strands are shown as arrows and α-helices as cylinders. Directions of the arrows coincide with those from the N- to C-ends. For clarity, strands a, b and d are labelled. The structural information was taken from the following papers: PCI, carboxypeptidase A unhibitor from potatoes [13]; CMTI-I, trypsin inhibitor from squash seeds [14]; MCTI-A, trypsin inhibitor of the squash family [15]; PCI-1, polypeptide chymotrypsin inhibitor-1 [16]; hevein [17]; WGA, wheat germ agglutinin [18]; BBI, Bowman-Birk type protease inhibitor [19]; SSI, *Streptomyces* subtilisin inhibitor [20]; defensin HNP-3 [21]; BPTI, bovine pancreatic trypsin inhibitor [22]; erabutoxin b [23]; cobratoxin [24]; Hoe-467A, α-amylase inhibitor Hoe-467A [25]; L9, ribosomal protein L9 [26]; PSP, porcine pancreatic spasmolytic polypeptide [27]; scorpion neurotoxin [28]; Kazal type inhibitors (see, e.g. [29–30]; ferredoxin (see, e.g. [31]); rubredoxin from *Desulfovibrio desulfuricans* [32]; crambin [33]; CTF, C-terminal fragment of ribosomal protein L7/L12 [34]; L30, ribosomal protein L30 [35]; chorismate mutase [36]; protein G [37]; ubiquitin [38]; heterocyst ferredoxin [39].

α-helix and packed so that one β-β-corner is situated in the concavity of the other and vice versa. The overall fold of the repeating structural motif called the trefoil unit [75] and observed in interleukin-1β and 1α, fibroblast growth factors and Kunitz-type inhibitors resembles that of the β-β-corner, but its central part forms a strongly twisted and coiled β-β-hairpin. Nevertheless, the N- and C-terminal β-strands form a right-turned β-β-hairpin (when viewed from the concave side or from a hydrophobic core) if the central part including the coiled hairpin and a short α-helix is considered as a long loop. Each domain of the above mentioned proteins is formed from 3 trefoil units. The structure of SLPI domains clearly demonstrates that the coiled β-β-hairpin is a core around which the remainder of the domain is folded. Most likely, this coiled hairpin is formed earlier than the remaining part of the domain during protein folding.

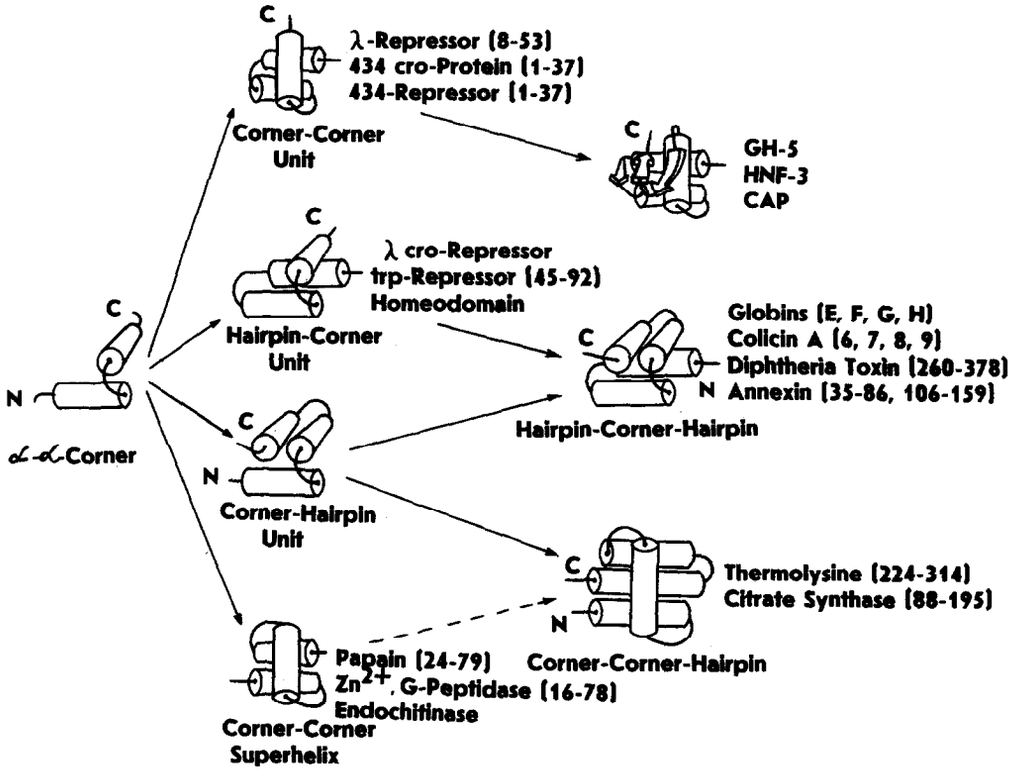

Fig. 3. Recurring structural motifs in molecules and domains with the orthogonal packing of α-helices. The structural information has been taken from the following papers: λ-repressor [40]; phage 434 cro-protein [41]; phage 434 repressor [42]; cro-repressor from bacteriophage λ [43]; trp-repressor [44]; engrailed homeodomain [45]; papain [46]; G-peptidase [47]; endochitinase [48]; GH-5, globular domain of histone H5 [49]; HNF-3, hepatocyte nuclear factor-3 [50]; CAP, catabolite gene activator protein [51]; colicin A [52]; diphtheria toxin [53]; annexin [54]; thermolysine [55]; citrate synthase [56].

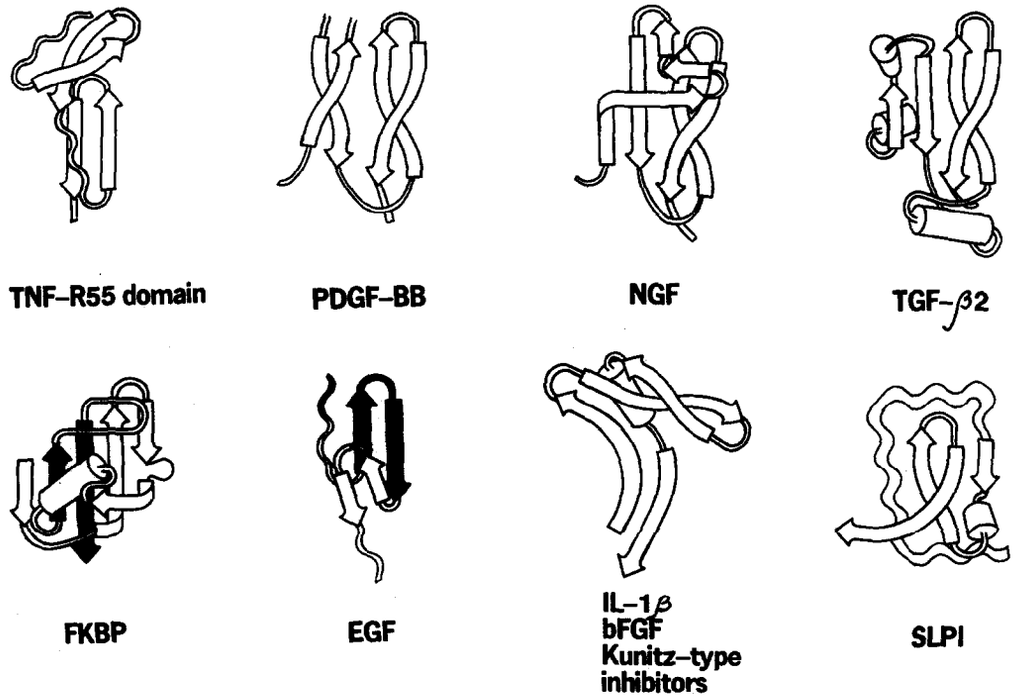

Fig. 4. Some small proteins and domains composed of β-β-hairpins and β-β-corners. TNF-R55 domain, the extracellular domain of the human 55 kd tumor necrosis factor receptor [63]; PDGF-BB, human platelet-derived growth factor BB [64]; NGF, nerve growth factor [65]; TGF-β2, human transforming growth factor β2 [66]; FKBP, FK506-binding protein [67]; EGF, human epidermal growth factor [68]; IL-1β, human interleukin-1β [69]; bFGF, human basic fibroblast growth factor [70]; Kunitz-type inhibitors (see, e.g. [71]); SLPI, human secretory leukocyte protease inhibitor domain [72].

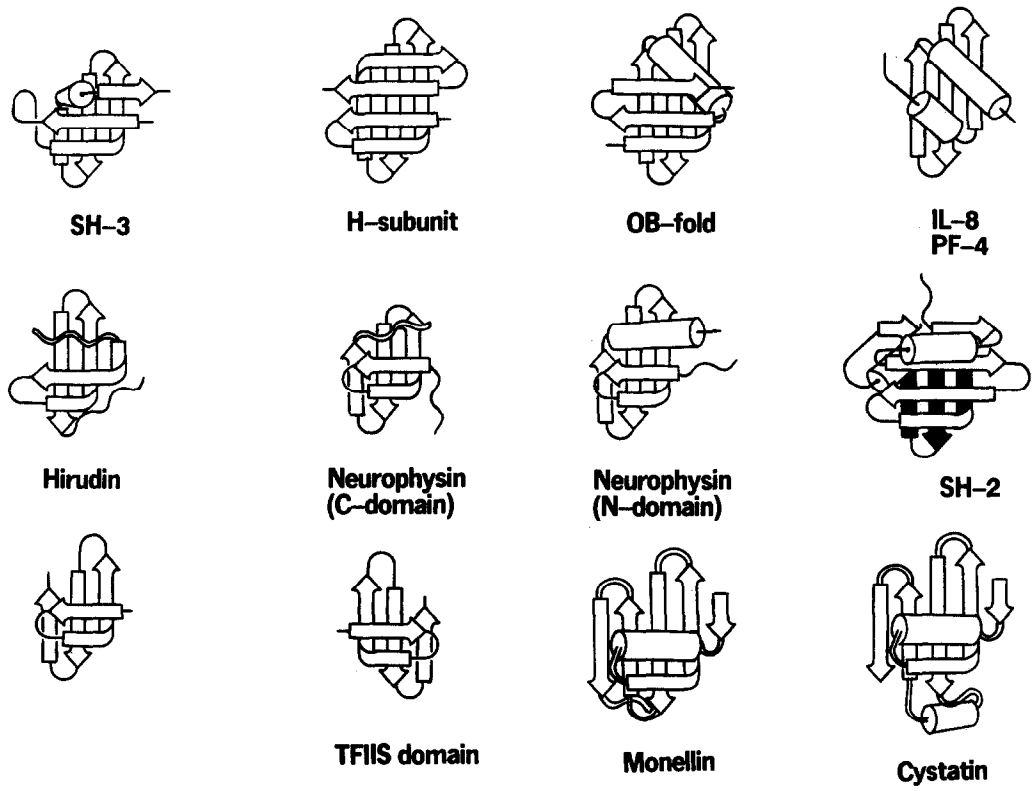

Fig. 5. Examples of protein molecules and domains with the predominantly orthogonal packing of β-sheets and α-helices. SH-3, a Src-homology 3 domain [76]; H-subunit of the photosynthetic reaction centre from *Rhodopseudomonas viridis* [77]; OB-fold [78]; IL-8, interleukin 8 [79]; PF-4, platelet factor 4 [80]; Hirudin [81]; neurophysin [82]; SH-2, Src-homology-2 domain [83]; TFIIS, eukaryotic transcriptional elongation factor TFIIS [84]; monellin, single-chain monellin [85]; cystatin, chicken egg white cystatin [86].

6. small molecules and domains containing S-like β-sheets and/or 3β-corners

The upper row in Fig. 5 represents protein folds that involve S-like β-sheets, the β-S-β-superhelix in SH-3 and H-subunit, the β-S-α-superhelix in the OB-fold, and the α-S-α-superhelix in IL-8 and PF-4. The OB-fold occurs in nuclease S, enterotoxin, verotoxin and other proteins [78]. The overall fold of the N- and C-terminal domains of neurophysin is rather similar to the OB-fold, as the N-domain also contains the right-handed β-S-α-superhelix and the C-domain has a similar superhelix with an irregular region instead of the α-helix. In fact, these examples show different variants of packing of other β-strands relative to the β-S-α-superhelix. All the structures shown in the second row of Fig. 5 as well as the SH-3 and H-subunit contain a right-handed 3β-corner. Hirudin is merely composed of a 3β-corner and irregular 'tails'. The structures of the other proteins can be obtained by a stepwise addition of β-strands and α-helices to 3β-corners as described in [7]. The TFIIS domain has a left-handed 3β-corner and is the only exception found so far. Its 'mirror-symmetrical' analog shown on the left has a fold that occurs in the SH-3, H-subunit, neurophysin domains and SH-2. This kind of fold also occurs in single-chains monellin and cystatin but has an α-helix instead of the first β-strand. As seen, cystatin and single-chain monellin share a common fold but have different functions. In addition to the structural similarity between monellin and cystatin, there are similarities in their sequences [87]. This suggests that the proteins have diverged from a common ancester.

7. Discussion

Thus, small proteins and domains contain a restricted set of structural motifs. They can be grouped into several structural families depending on the commonly occurring structural motif found in each family. There are many examples of small proteins sharing larger common folds (levels of structural similarity between proteins of each family can be easily observed in Figs. 2–5). Analysis shows that structural similarity is observed between both homologous and non-homologous proteins. The high frequency of occurrence of the structural motifs in unrelated proteins appears to be due to the relative stability of these kinds of folds. The structural motifs described here have unique structures themselves and some of them can be a core around which the remainder of the molecule or domain is folded. All this taken together supports the hypothesis suggested earlier [4–8] that these motifs can fold independently of the remaining part of the protein and can be nuclei and/or a 'ready building blocks' in protein folding. The fact that many small proteins and domains are merely composed of the motifs also supports this idea.

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