A FOUR-HELICAL SUPER-SECONDARY STRUCTURE

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Summary: A stable structure, composed of four roughly parallel α-helices, has been observed in hemerythrin, tobacco mosaic virus protein and tyrosyl-tRNA synthetase. Since the latter two interact with RNA, it is conjectured for these strucutres that the four-helical arrangement provides a common role.

The increasing number of known protein structures has made possible the recognition of recurring stable arrangements of secondary structural elements. For instance, Rao and Rossmann (1) showed the occurrence of a β-strand - α-helix - β-strand - α-helix - β-strand structure common to flavodoxin and lactate dehydrogenase, which was termed a "super-secondary structure." More recently, Levitt and Chothia (2) have suggested that there are four basic structural patterns. Furthermore, at least 20 different protein structures have been analyzed to show that the β-strand - α-helix - β-strand arrangement has almost invariably the same hand (3,4).

Recurring structural themes have resulted in considerable controversy regarding the divergent or convergent nature of their evolution (5-9). The divergent concept has been strengthened by observing a common functional property (10) which appears to require conservation of the domain structure (11), such as the calcium binding protein (12) or the polysaccharide binding fold (13). The binding site in these domains involves only a small portion of the total structure; yet the entire structure is apparently required to maintain the functional integrity of the site. Alternatively, the convergent argument is supported by recognizing the possibility of only a limited variety of interactions betweeen secondary

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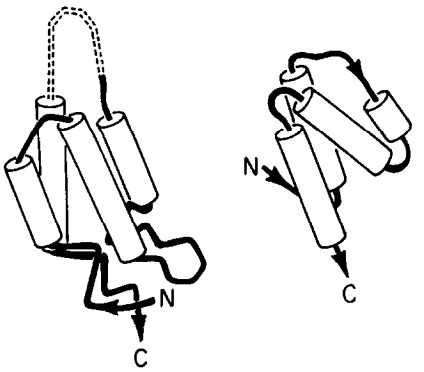

Figure 1

Diagrammatic representation of the secondary and tertiary structures in TMV protein (left) and the third domain in tyrosyl-tRNA synthetase (right).

structural elements (14,15). Strong topological homology without apparent functional correlation is exemplified by the structural similarity of superoxide dismutase and the immunoglobulin domain (16).

The structure of tyrosyl-tRNA synthetase has recently been described by Irwin et al. (17). It is apparent that the structure has three distinct, spatially separated, domains. The first is involved in subunit-subunit contact. The central domain is the familiar β-α-β type structure so frequently associated with nucleotide binding. Indeed, the ATP site does occur in the standard manner at one end of the sheet, although the topology is not that typically found in dehydrogenases (5,6). This suggests that a nucleotide binding domain is possibly determined by the interrelationship of secondary structural elements without reference to their connectivity. The maintenance of the topological requirement seems likely for proteins that have diverged from a common ancestor as appears to be the case for some dehydrogenases.

The third structural domain of tyrosyl-tRNA synthetase is composed of four essentially parallel helices. A similar arrangement of secondary structural elements has been found for tobacco mosaic virus (TMV) disk

protein (18) and hemerythrin (19,20). The similarity of TMV protein and hemerythrin has been previously observed (A. C. Bloomer and W. A. Hendrickson, private communication). The correspondence of the last domain of the synthetase and TMV protein is striking apart from the direction in which the synthetase chain has been traced (Figure 1). That is, the arrangement of secondary structural elements is similar although their connectivity is different. The correlation of the TMV protein structure and the third domain of synthetase is particularly salient as both possess three parallel helices and one cocked at about 35° (± 15°). This angle of cross-over between α-helices corresponds roughly to the 20° predicted by Crick (14). However, in hemerythrin there are two pairs of parallel helices.

It has been shown that RNA binds to the disordered loop region in TMV protein, illustrated as a dashed line in Figure 1 (18,21). In view of this function of TMV protein, it is conceivable that a similar function occurs in the corresponding domain of the synthetase.

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