Experimental Support for the "Hydrophobic Zipper" Hypothesis

In a recent report (1), we described the kinetics of folding of the all-β sheet protein interleukin-1β (IL-1β) with the use of nuclear magnetic resonance (NMR), far-ultraviolet dichroism, and fluorescence spectroscopy. The deuterium/hydrogen exchange method has demonstrated that intermediates with a stable hydrogen-bonded secondary structure were only formed on the second time scale. Subsequent closer inspection of those parts of the IL-1β structure that are involved in these folding intermediates revealed clustering of hydrophobic residues, in particular, leucines. The five strands (Fig. 1) of the 12-stranded structure, which were detected in the NMR experiment (1), constitute the major site of early-forming hydrogen bonds. Within the symmetrical "trefoil" structure (2), they comprise hairpin 2 (strands 6 and 7) and parts of the adjacent barrel strands 5, 8, and 9. The locations of the major hydrophobic residues are also revealed (Fig. 1).

Our experimental data are similar to a recent theoretical model proposed by Dill et al. (3) that has been termed the "hydrophobic zipper" model of protein folding. In the initiation of folding, hydrophobic side chain pairs that are closely positioned in the sequence are brought together by a limited conformational search, with subsequent pairing of other pairs, one after another, like the zipping of a zipper. In IL-1β, the initial zipper would be made up from strands 6 and 7, with the other strands arranged around these. The location and distribution of hydrophobic side chains in this region of the protein structure add support to this notion (Fig. 2). The zipper-like arrangement of Leu61, Leu62, Leu63, and Cys71, running from right to left (Fig. 2), is most striking.

Angela M. Gronenborn
C. Marius Clore
Laboratory of Chemical Physics,
National Institute of Diabetes and
Dietetic and Kidney Diseases,
National Institutes of Health,
Bethesda, MD 20892

REFERENCES

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