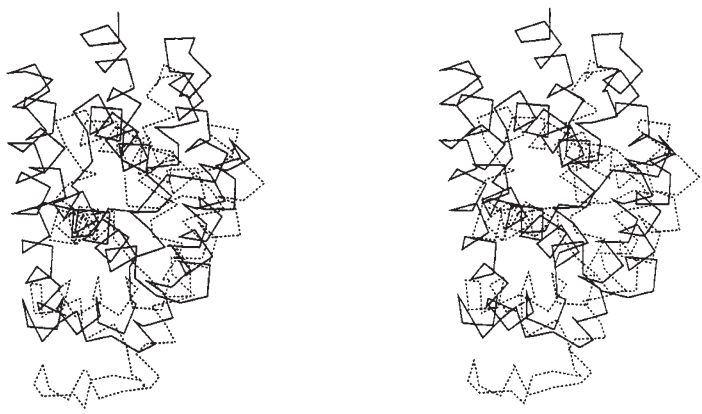


Globin fold in a bacterial toxin

SIR — We have developed an algorithm for protein-structure comparison by alignment of distance matrices¹ and have performed an all-against-all comparison of more than 150 different protein tertiary structures in the Protein Data Bank. As a result, we have made the startling discovery that the membrane-insertion domain of the bacterial toxin colicin A (ref. 2) closely resembles the globin fold: six α -helices (and one turn of 3_{10} -helix) are arranged similarly in space, the packing between the helices is similar as well as the sequential order in which the chain threads through the helices (Fig. 1). The domain of colicin A thus joins the structural class that so far has consisted of the globin and phycocyanin families.

Despite similar folds, the three protein families (globins, phycocyanins and colicin A) lack significant sequence similarity, bind different cofactors (or none), and are involved in very different biological functions (oxygen transport,

FIG. 2 Stereo view of superimposed $C\alpha$ traces of colicin A and myoglobin (shown dashed). The amino terminus of myoglobin is at the upper right, that of colicin A at the lower left.



photosynthesis, ionophoric activity). The fact that globins and phycocyanins are no longer structurally unique clearly calls for a re-evaluation of their proposed evolutionary kinship³. A structural analysis shows that colicin A is as similar to either globins or phycocyanins as they are to each other, both in terms of overall topography of the fold and in terms of side-chain packing (Fig. 2).

Colicin A kills sensitive cells by forming pores in the cytoplasmic membrane. The part of colicin A that has been solved crystallographically² is a proteolytically cleaved carboxy-terminal fragment (residues 389–592), which is water soluble and has ionophoric properties similar to those of the entire protein. Interestingly, the membrane-pore-forming unit, comprising helices 5–9 (ref. 4) or 3–9 (ref. 2), is essentially identical to the globin-like domain (helices 4–9). In addition, recent spectroscopic results (J. H. Lakey *et al.*, manuscript submitted) show that this unit remains closely packed on membrane insertion rather than opening up like an umbrella as initially suggested². Bacteria could have acquired this domain by adapting a gene fragment of some, as yet unidentified, protein with the globin fold.

A substantial fraction of known protein structures can be described in terms

of a relatively small set of folding motifs, such as helical bundles, β -barrels and the like. Our finding establishes the three-on-three helical sandwich of the globin fold as one such prototypic motif used by proteins in various functional contexts.

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HIV tropism

SIR — Nara *et al.* point out¹ that cell surface factors other than CD4 influence HIV-1 tropism *in vitro*, but it has been known for some years that HIV-1 isolates that vary in genetic composition replicate at different rates in transformed CD4⁺ cell lines and in primary cells (reviewed in refs 2–4). All *in vitro* experimental systems, of course, require careful interpretation.

The underlying reasons for the apparent correlation between the sensitivity of HIV-1 isolates to neutralization by soluble CD4 (sCD4) and the ability of these isolates to replicate in transformed T cells are imperfectly understood. Nara *et al.* emphasize the effect of the target cell on the sCD4-sensitivity of HIV-1, but fail to note reports that document the importance of viral factors^{5–7}. The data of Nara *et al.* are derived from studies using HIV-1 IIIB, which is a highly adapted virus, so it is potentially misleading to draw general inferences from studies with this virus. Cell line-adapted HIV isolates such as IIIB or RF are up to 1,000-fold more sensitive to sCD4 neutralization than primary viruses, irrespective of whether peripheral blood mononuclear cells or cell lines are used to monitor their replication^{5–7}.

HIV-1 did not evolve to resist neutralization by sCD4, but it may well have

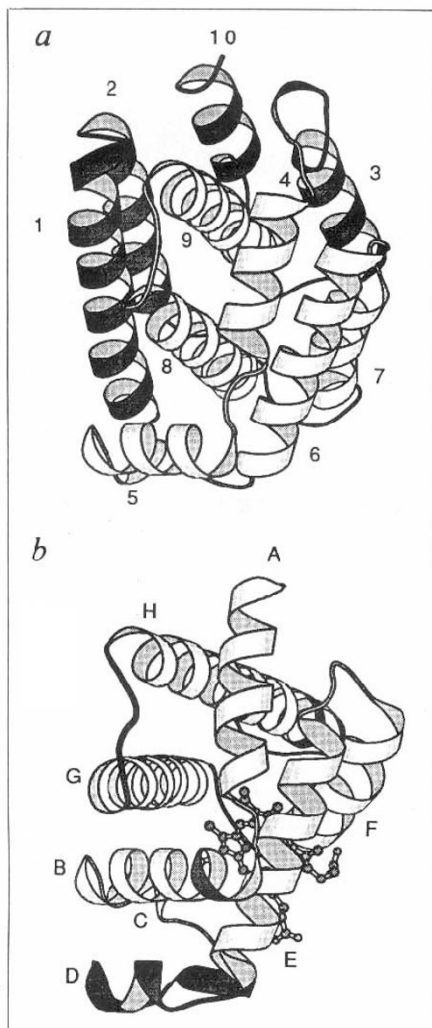


FIG. 1 Ribbon diagrams⁵ of *a*, the carboxy-terminal fragment of colicin A (Protein Data Bank entry 1COL) and *b*, myoglobin (Protein Data Bank entry 1PMB). The common core has lighter shading. The equivalent α -helices in colicin A and globins, respectively, are helix 4 = A, 5 = B, 6 = E, 7 = F, 8 = G and 9 = H. The ribbon diagrams highlight the similar overall fold of the common core, in spite of small shifts in the relative orientations of some of the helix pairs. The structural alignment method¹ picks up 112 structurally equivalent residues between colicin A and myoglobin, which in rigid-body superimposition give a root mean square deviation of $C\alpha$ positions of 3.2 Å. The equivalent segments follow (1COL/1PMB): A73–A89/A4–A20, A90–A109/A24–A43, A110–A128/A61–A79, A129–A135/A81–A87, A136–A145/A89–A98, A149–A166/A99–A116, A167–A187/A123–A143.